ADVISORY COUNCIL ON ALZHEIMER'S RESEARCH, CARE, AND SERVICES

Public Comments from Advisory Council Meeting, February 2026

List of Comments

Comments and questions, or alerts to broken links, should be sent to napa@hhs.gov.

PLEASE NOTE: The Public Comments included here are not an endorsement of the views or information by National Alzheimer's Project Act, its Advisory Council members, the Administration or the federal agencies involved in this project.

C. Krebs | 2-11-2026

PhysiciansCommittee for Responsible Medicine PCRM.ORG

5100 Wisconsin Ave. NW, Suite 400 • Washington, DC 20016 • Tel: 202-686-2210 • Fax: 202-686-2216 • pcrm@pcrm.org

February 11, 2026

Re: **Prioritizing Human-Based Approaches in Alzheimer's Research**; Written Comment on the February 9, 2026 Meeting of the Advisory Council on Alzheimer's Research, Care, and Services

Sent via email to maria-theresa.okafor@hhs.gov and napa@hhs.gov

Dear members of the Advisory Council on Alzheimer's Research, Care, and Services,

On behalf of the Physicians Committee for Responsible Medicine, a 501(c)(3) nonprofit organization supported by nearly one million members and supporters worldwide working for effective, efficient, and ethical medical research and product testing, thank you for the opportunity to comment on this meeting.

The National Institutes of Health (NIH) has been increasingly supporting human-based, nonanimal research approaches, including new approach methodologies (NAMs), in place of animal-based methods. In April 2025, the NIH announced an initiative to expand innovative, human-based science while reducing animal use in research, and

detailed actions to deliver this, including the establishment of the Office of Research Innovation, Validation, and Application.[1] The initiative is already being implemented across institutes, centers, and offices, including in strategic plans[2] and new funding opportunities.[3] It builds on agency efforts like the Complement Animal Research in Experimentation (Complement-ARIE) program—which seeks to advance a comprehensive and diverse array of NAMs and increase their acceptance and use and appreciation of their value[4]—as well as the National Center for Advancing Translational Sciences Tissue Chip Projects & Initiatives.[5]

The FDA is investing millions of dollars towards expediting NAMs into regulatory use in place of animals, including through its ISTAND program,[6] collaborating with industry and academic partners, and updating guidance to streamline nonanimal preclinical

[1] National Institutes of Health. NIH to prioritize human-based research technologies. April 29, 2025. Accessed January 14, 2026. https://www.nih.gov/nih-prioritize-human-based-research-technologies
[2] E.g., National Institutes of Health Office of Research Infrastructure Programs. Strategic Plan Infrastructure for Innovation Fiscal Years 2026-2030. Accessed Feb 10, 2026. https://orip.nih.gov/sites/default/files/ORIP-Strat-Plan-Final-11-25-2025-508-updated-compressed.pdf
[3] E.g., National Institutes of Health. Expired RFA-AG-26-014: Aging Mammalian Tissues In Vitro (R21 Clinical Trial Not Allowed). Accessed Feb 10, 2026. https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-26-014.html
[4] National Institutes of Health Common Fund. Complement Animal Research In Experimentation (Complement-ARIE) Program. Accessed February 10, 2026. https://commonfund.nih.gov/complementarie
[5] National Center for Advancing Translational Sciences. Tissue Chip Projects & Initiatives. January 16, 2026. Accessed February 10, 2026. https://ncats.nih.gov/research/research-activities/tissue-chip/projects
[6] Food and Drug Administration. Innovative Science and Technology Approaches for New Drugs (ISTAND) Program. Accessed February 10, 2026. https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-program

testing. The new FDA commissioner announced that the agency would phase out animal use in favor of human-relevant methods,[7] on the heels of the reintroduction of the FDA Modernization Act 3.0[8] aimed at actively encouraging and facilitating the qualification and widespread use of human-specific NAMs in the testing of new drugs.[9]

These initiatives, plans, and announcements will improve clinical translation and spare animal lives. In this respect, we are greatly encouraged by progress being made in research into dementias, particularly Alzheimer's disease (AD), in line with these federal initiatives. We especially note and applaud efforts involving the National Institute on Aging and the National Institute of Neurodegenerative Disorders and Stroke. These include workshops[10] with diverse expertise highlighting challenges and opportunities in this field, and seeking "clinically meaningful"[11] change in human drug trials for AD and related dementias (ADRD).

However, a major goal of the National Plan to Address Alzheimer's disease—to prevent and effectively treat AD by 2025—has failed, and may well be some years away. In conjunction with long-term translational failures, this stark fact underlines the urgent need for a transition to more clinically translational methods of research. **We therefore recommend that federal support for ADRD—including research strategies, programs, infrastructure, and funding opportunities—shift from animal use toward human-based approaches in line with federal priorities.** To aid in this alignment, below we have summarized some of the many areas where human-based methods are already being used to investigate ADRD. We encourage the NIH to explore these approaches for future investment, and we encourage the Advisory Council on Alzheimer's Research, Care, and Services to become familiar with them.

The Physicians Committee has expertise in many areas of research and the application of NAMs. We therefore appreciate your attention to our comments, and would welcome the opportunity for further dialogue and to support the Advisory Council in any way to advance its support of human-based research methods and the replacement of animal use in research.

Sincerely,

Jarrod Bailey, PhD, FOCAE
Director of Medical Research
Physicians Committee for Responsible Medicine

[7] Food and Drug Administration. FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs. April 20, 2025. Accessed February 10, 2026. https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs

[8] FDA Modernization Act 3.0., S.355, 119th Congress (2025-2026).

[9] Carratt SA, Zuch de Zafra CL, Oziolor E et al. An industry perspective on the FDA Modernization Act 2.0/3.0: potential next steps for sponsors to reduce animal use in drug development. *Toxicological Sciences* 2024; 203:28-34. https://doi.org/10.1093/toxsci/kfae122

[10] E.g., National Institute on Aging. Workshop: 3-D In Vitro Tissue Systems for Research on Aging. July 29-30, 2024. Accessed February 10, 2026. https://www.nia.nih.gov/research/dab/workshops/workshop-3-d-vitro-tissue-systems-research-aging

[11] National Institute on Aging. Clinically Meaningful Outcomes in AD/ADRD Trials. March 12-14, 2024. Accessed February 10, 2026. https://www.nia.nih.gov/research/dbsr/workshops/clinically-meaningful-outcomes-ad-adrd-trials

Brain organoids are derived from induced pluripotent stem cells (iPSCs), isolated from healthy individuals or people with neurological conditions and diseases. They are scalable experimental systems able to model complex clinical phenotypes and interindividual variability that is infeasible to engineer into animals,[12] as well as higher-order brain complexity, such as inter-region circuitry.[13] They have recently been shown to replicate key features of learning and memory, including synapse formation, functional connectivity, and input-specific synaptic plasticity,[14] and are frequently used in the modelling of neurodegenerative diseases, including AD and Parkinson's disease (PD).

Organoids derived from AD patients accumulate beta-amyloid plaques and tau tangles that are hallmarks of the disease.[15] Cerebral organoids model the development and architecture of human neuronal tissues in a manner "unparalleled" by 2D cultures and animal approaches.[16] Neuropathogenesis-chips measure functional changes via real-time human-specific electrophysiology, as well as identify new drug candidates via effects on neuropathophysiological features.[17] Complex human stem-cell based "vascularized neuroimmune" models have been validated via multiple pathologies and biomarkers, including reduction of amyloid burden upon treatment with the drug lecanemab, approved in 2023.[15]

With regard to Parkinson's disease (PD) and related dementia: Organoids derived from PD patients also exhibit phenotypes and pathologies seen in patients, including the accumulation of α-synuclein in Lewy bodies and loss of dopaminergic neurons.[18] Human midbrain organoids and assembloids are facilitating the human-specific analysis of how alpha-synuclein pathology spreads from the hindbrain to the midbrain and dysregulates synapses, improving understanding of Parkinson's progression and aiding in the screening of new therapies.[19] They are also being used to study mitochondrial dysfunction[20] and to test new therapeutic approaches.[21] PD

[12] Faravelli I, Antón-Bolaños N, Brown JR, et al. Brain Organoids: Tools for Understanding the Uniqueness and Individual Variability of the Human Brain. *Annual Rev Genomics and Human Genetics*. 2025;26:299-320. https://doi.org/10.1146/annurev-genom-111522-014009

[13] Maisumu G, Willerth S, Nestor MW, et al. Brain organoids: building higher-order complexity and neural circuitry models. *Trends in Biotechnology*. 2025;43(7):1583-1598. https://doi.org/10.1016/j.tibtech.2025.02.009

[14] Alam El Din D-M, Moenkemoeller L, Loeffler A, et al. Human neural organoid microphysiological systems show the building blocks necessary for basic learning and memory. *Communications Biol*. 2025;8. https://doi.org/10.1038/s42003-025-08632-5

[15] Ji Y, Chen X, Wang Z, et al. Alzheimer's disease patient brain extracts induce multiple pathologies in novel vascularized neuroimmune organoids for disease modeling and drug discovery. *Molecular psychiatry*. **30**, 4558–4575 (2025). https://doi.org/10.1038/s41380-025-03041-w

[16] Sreenivasamurthy S, Laul M, Zhao N, et al. Current progress of cerebral organoids for modelling Alzheimer's disease origins and mechanisms. *Bioeng Transl Med*. 2022;8(2). https://doi.org/10.1002/btm2.10378

[17] 11 Amartumur S, Nguyen H, Huynh T, et al. Neuropathogenesis-on-chips for neurodegenerative diseases. *Nat Commun*. 2024;15(1):2219. https://doi.org/10.1038/s41467-024-46554-8

[18] Frattini E, Faustini G, Lopez G, et al. Lewy pathology formation in patient-derived GBA1 Parkinson's disease midbrain organoids. *Brain*. 2025;148(4):1242-1257. https://doi.org/10.1093/brain/awae365; Kim H, Kang S, Cho B, et al. Parkinson's Disease Modeling Using Directly Converted 3D Induced Dopaminergic Neuron Organoids and Assembloids. *Adv Sci. (Weinh).* 2025;12(14):e2412548. https://doi.org/10.1002/advs.202412548; Becerra-Calixto A, Mukherjee A, Ramirez S, et al. Lewy Body-like Pathology and Loss of Dopaminergic Neurons in Midbrain Organoids Derived from Familial Parkinson's Disease Patient. *Cells*. 2023;12(4):625. https://doi.org/10.3390/cells12040625

[19] Gomez-Giro G, Frangenberg D, Vega D, et al. **α**-Synuclein Pathology Spreads in a Midbrain-Hindbrain Assembloid Model. *Adv Sci (Weinh)*. 2025;12(20):e2409040. https://doi.org/10.1002/advs.202409040

[20] Sabaté Soler S, Rosety I, Giro G, et al. Released mitochondrial DNA and neurofilament light chain as Parkinson's disease phenotypes in patient-specific midbrain assembloids. *bioRxiv*. 2025. https://doi.org/10.1101/2025.03.28.645921

[21] Qin S, Gao J, Ding M, et al. Parkinson's disease in a dish: The emerging role of organoids in research and therapy. *Organoid Research*. 2025;1(2):025040006. https://doi.org/10.36922/OR025040006

organoids are constantly improving, for example, via the incorporation of additional cell types and vasculature networks.[22]

Brain microphysiological systems (MPS) are augmenting brain organoid research. These so-called brain-chips often show multiple genomic and functional similarities with the human brain,[23] while also demonstrating greater clinical translation and superior prediction of the safety and efficacy of new drugs for neurological disorders.[24] Neurological drug development has had for some time one of the highest failure rates of any class of drugs in clinical trials at more than 94%.[25] Recently, it was proposed that MPS may be able to replicate targeted clinical trials of drugs in 50-100 patients—to identify subgroups that respond best to a new drug and those to whom it might be toxic—greatly improving likelihood of success and reducing costs and time to regulatory approval.[26] There are many areas of research in which brain MPS can accurately replicate human diseases and clinical responses, including blood-induced toxicity,[27] fungal invasion of the blood-brain barrier,[28] and transport of extracellular vesicles, nanocarriers, drugs, and antibodies.[29]

There is substantial evidence pointing towards the involvement of neuroinflammation in the neuropathogenesis underlying neurodegenerative diseases and dementias, and great progress has been made in the engineering of a human brain MPS to specifically model this in a human context. Neuroinflammation compromises the integrity of the blood brain barrier (BBB), which can further contribute to more neuroinflammation, neurotoxicity, and the accumulation of pathological proteins, all of which in turn exacerbate disease progression.

Human brain chips have been organotypic for some time, incorporating multiple cell types including endothelial-like cells, pericytes, glia, astrocytes, and cortical neurons. They maintain in vivo relevant permeability of the BBB and facilitate cell-cell interactions that mediate neuroinflammation. Their clinical mimicry is unprecedented and verified by transcriptomics, as well as functionally by the replication of multiple aspects of the inflammatory environment shown by glia activation, increased release of proinflammatory cytokines, and compromised barrier permeability. They permit investigation of the mechanistic understanding of intercellular interactions and complex BBB functions, and, like brain organoids, are being improved via

[22] Zimmermann A-S, Sabaté Soler S, Zagare A, et al. Vascularized midbrain assembloids show neuroinflammation and dopaminergic neuron vulnerability in Parkinson's Disease. *bioRxiv*. 2025. https://doi.org/10.1101/2025.08.06.668815
[23] Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. *Nat Rev Genet*. 2022;23(8):467-491. https://doi.org/10.1038/s41576-022-00466-9
[24] Balestri W, Sharma R, da Silva VA, et al. Modeling the neuroimmune system in Alzheimer's and Parkinson's diseases. *Journal of Neuroinflammation*. 2024;21(32). https://doi.org/10.1186/s12974-024-03024-8
[25] Thomas, DW, Chancellor D, Micklus A, et al. Clinical development success rates and contributing factors 2011-2020. Published online 2021. https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf
[26] Ingber DE. Challenges and opportunities for human Organ Chips in FDA assessments and pharma pipelines. *Cell Stem Cell*. Published online 2026:S1934-5909(25)004564. https://doi.org/10.1016/j.stem.2025.12.022
[27] Vatine GD, Varrile R, Workman MJ, et al. Human iPSC-Derived Blood-Brain Barrier Chips Enable Disease Modeling and Perosnalized Mecicine Applications. *Cell Stem Cell*. 2019;24(6):995-1005. https://doi.org/10.1016/j.stem.2019.05.011
[28] Kim J, Lee K-T, Lee JS, et al. Fungal brain infection modelled in a human-neurovascular-unit-on-a-chip with a functional blood-brain barrier. *Nature Biomedical Engineering*. 2021;5:830-846. https://doi.org/10.1038/s41551-021-00743-8
[29] Park T-E, Mustafaoglu N, Herland A, et al. Hypoxia-enhance Blood-Brain Barrier Chip recapitulates human barrier function and shuttling of drugs and antibodies. *Nature Communications.* 2019;10(2621). https://doi.org/10.1038/s41467-019-10588-0

the incorporation of perfusable vasculature.[30] A recent study circulated red blood cells and their exosomal cargo from young and old donors in vascular channels of human brain MPS, demonstrating age-associated differences in proteins involved in inflammation and synaptic dysregulation.[31]

MPS can also be used to replicate the neurovascular unit, providing controllable conditions via microfluidic technology to model responses to potential stem cell therapies,[32] drug delivery, and neuroinflammation-induced brain tube disruption and immune cell extravasation.[33] A recent study used human iPSCs from a patient with AD and a healthy individual to differentiate neurons, astrocytes, pericytes, microglia, and brain-like microvascular endothelial cells, and cultured them in an MPS model of the cortical neurovascular unit to investigate changes induced by AD-like pathology.[34]

Finally, the use of live brain-slice cultures, originating from biopsies from consenting patients undergoing surgery, is enabling the study of human brain reactions to toxic Alzheimer's associated proteins, and facilitating the testing of new therapies in a human-specific manner.[35]

[30] Nahon DM, Cuenca MV, van den Hil FE, et al. Self-assemling 3D vessel-on-chip model with hiPSC-derived astrocytes. *Stem Cell* Reports. 2024;19(7):946-956. https://doi.org/10.1016/j.stemcr.2024.05.006; Pediaditakis I, Kodella KR, Manatakis DV, et al. A microengineered Brain-Chip to model neuroinflammation in humans. *iScience*. 2022;25(8):104813. https://doi.org/10.1016/j.isci.2022.104813

[31] Mehta-Doshi A, Tsu BL, Sauceda C, et al. Age-dependent neuroinflammatory effects of red blood cells and their exosomes in a human brain-on-chip model. *Blood RCI red cells & iron*. 2026;2(1):100044. https://doi.org/10.1016/j.brci.2025.100044

[32] Lyu Z, Park J, Kim K-M, et al. A neurovascular-unit-on-a-chip for the evaluation of the restorative potential of stem cell therapies for ischaemic stroke. *Nature Biomedical Engineering*. 2021;5:847-863. https://doi.org/10.1038/s41551-021-00744-7

[33] Qiu B, Pompe S, Xenaki KT, et al. Generation of a perfusable three-dimensional human neurovascular chip to model brain drug delivery and immune cell extravasation. *Journal of Controlled Release*. 2025;387:114257.

https://doi.org/10.1016/j.jconrel.2025.114257
[34] Shen AN, Matazel KS, Gill WD, et al. Modeling neurovascular dysfunction in Alzheimer's disease using an isogenic brain-chip model. *Fluids and Barriers of the CNS*. 2026;23(1). https://doi.org/10.1186/s12987-025-00708-y
[35] McGeachan RI, Meftah S, Taylor LW, et al. Divergent actions of physiological and pathological amyloid-β on synapses in live human brain slice cultures. *Nat Commun*. 2025;16(1):3753. https://doi.org/10.1038/s41467-025-58879-z

---

J. Pierrat | 2-6-2026

My husband was diagnosed with behavioral variant frontotemporal degeneration at the young age of 55 after a harrowing diagnostic journey. I would like council members to understand the unique challenges of managing a loved one afflicted with this disease and with the behavioral variant in particular. FTD patients are often young (between 45-65) and in their prime earning years. The disease is often misdiagnosed and misunderstood, with many patients receiving an incorrect psychological diagnosis first. There are no treatments and no cure available for this terminal disease and there are limited options for managing care of these patients, particularly the young ones. Caregivers are left to witness progressive decline, along with the emotional, financial and social devastation the disease brings. All dementia is difficult and tragic, but behavioral variant FTD is the worst of the worst. Please help us end FTD.

Julia Pierrat

W. Smith | 1-30-2026

Thank you for the opportunity to speak today and for your continued leadership through the National Alzheimer's Project Act.

I'm here to bring attention to **CureGRN** and to a devastating but under-recognized cause of dementia: **GRN progranulin–related disease**.

Mutations in the **GRN gene** lead to progranulin deficiency, causing a highly aggressive, inherited form of **frontotemporal dementia**. This disease can strike across the adult lifespan—from people in their 40s and 50s during their working and caregiving years, to individuals in their 70's and 80's in their retirement and sunset years. Families are often misdiagnosed with Alzheimer's disease, psychiatric illness delaying appropriate care and compounding trauma.

Importantly, **progranulin deficiency is increasingly recognized across neurodegenerative disease**, with growing evidence of its relevance in subsets of **Alzheimer's and Parkinson's disease** as well.

What makes GRN-related disease especially important is that it is **genetically defined, biologically understood, and increasingly measurable**. Progranulin levels can be

quantified. genetic tests exist. And most importantly, **therapeutic strategies aimed at restoring progranulin are already in development**. With access to genetic counseling and testing, families now have a clear path to diagnosis, research participation, and targeted clinical trials.

CureGRN is a patient-driven community that unites families, researchers, clinicians, and industry to accelerate awareness, research, and treatment development for GRN-related disease. This work reflects exactly what NAPA was designed to support: **cross-disease collaboration, precision medicine, and inclusion of families living with genetic and non-Alzheimer's dementias**. We are the related dementia

As NAPA continues to shape the national dementia strategy, I urge you to explicitly include **genetic and non-Alzheimer's dementias**, such as GRN-related FTD, in research prioritization, funding, and public awareness efforts. Progress in rare, well-defined diseases often unlocks insights that benefit the broader dementia community.

Families affected by GRN disease are not rare in their suffering—but they are rare in visibility. With NAPA's leadership, that can change.

Thank you for your time and consideration.

Wanda Smith
Founder, CureGRN