Article

A Perspective: Challenges in Dementia Research

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Abstract: Although dementia is a common and devastating disease that has been studied intensely for more than 100 years, no effective disease modifying treatment has been found. At this impasse, new approaches are important. The purpose of this paper is to provide, in the context of current research, one clinician's perspective regarding important challenges in the field in the form of specific challenges. These challenges not only illustrate the scope of the problems inherent in finding treatments for dementia, but can also be specific targets to foster discussion, criticism and new research. One common theme is the need to transform research activities from small projects in individual laboratories/clinics to larger multinational projects, in which each clinician and researcher works as an integral part. This transformation will require collaboration between researchers, large corporations, regulatory/governmental authorities and the general population, as well as significant financial investments. However, the costs of transforming the approach are small in comparison with the cost of dementia.

Keywords: dementia; Alzheimer's disease; big data; neurophysiology; imaging; biomarkers

1. Introduction

A total of 115 years has passed since Alois Alzheimer [1] published his paper on dementia, in which he made the optimistic statement: "A histological examination will enable us to determine the characteristics of some of these cases. This process will gradually lead to a clinical distinction of specific illnesses". However, despite subsequent massive clinical and basic science research [2,3], it remains difficult to identify and diagnose dementia in the early stages, or to develop a disease modifying treatment.

Now is the time for novel approaches. Historically, new and exciting ideas have arisen out of attempts to answer seemingly simple challenges. For example, the X-prizes [4], Hilbert's 10 problems in mathematics [5], the structure of DNA [6] or the electromagnetic spectrum emitted by a heated object [7], have all generated completely novel and unexpectedly important developments.

The purpose of this paper is to propose, in the context of current knowledge, specific challenges regarding dementia that may stimulate controversy and specific research. Many elements of these challenges have already been addressed to some degree, but the full promise of each challenge cannot be met without integrating multiple techniques and ideas.

2. Specific Challenges

2.1. Challenge 1: Optimizing and Quantifying the Patient Evaluation

There are many types of dementia, which can have different etiologies, symptoms and prognosis [8,9]. The first step in analyzing dementia must be a widely available, comprehensive, yet concise assessment of each individual, which can be applied serially [10] in both cognitively healthy persons and patients with clear dementia. It must include multiple components including those listed below.

2.1.1. Quantification of Behavior

Improved Analysis of Standard Behavioral Testing

The evaluation for cognitive impairment begins at the behavioral level [11]. The problem is that cognitive tests are naturally dependent on many factors, such as age [12,13], race, gender, education, language [14], IQ and experience [15], as well as medical factors such as sleep [16,17], pain and many others. There are two solutions to this problem, one is to pick a test or set of tests and then study how its results change with all of these factors [18]. Although this a very reasonable approach, it is complex because the number of factors that influence test results, even in normal people, will be large and difficult to predict. This results in large test variances for individuals and reduces the precision of the assessment. A second solution is to start with a number of tests including quantitative psychophysical tests (that may be less dependent on education and language than traditional paper and pencil tests) [19,20] and use statistical techniques to find a limited combination of these test elements, which is minimally dependent on the factors that influence cognition in cognitively healthy people. This is not enough, however, because the ideal test should not only yield results that were similar in cognitively healthy people, but also be sensitive to the different phenotypes seen in cognitive disorders of differing etiology.

Data Mining/Extraction Techniques

Important techniques that might provide additional information not available in the standardized paper and pencil and psychophysical testing, are modern data mining techniques to extract features in a video [21] or audio recordings of individuals [22]. The use of data available in social media [23] could also provide important information.

Other Testing

Other important non-neuropsychological clinical tests that can provide insight into dementia involve eye movements [24,25], retinal function [26], gait [27], olfaction [28,29], taste [30] and hand movements [31].

2.1.2. General Medical Conditions

No assessment of dementia is complete without a knowledge of the patient's general medical conditions. This would have to include all elements of the traditional history and physical, as well as laboratory testing for common systemic conditions that could affect the brain such as vitamin B12, thyroid function, etc. The National Alzheimer's Coordinating Center's Uniform Data Set [32] contains additional data that is also important.

2.1.3. The Neurological Exam

A full description of the patient would also include the results of the general neurologic examination as it provides information on strength, sensation, gait, reflexes, and cranial nerves that are important. Many quantitative methods have been proposed to calculate this [33,34] and the selection of the optimal data variables is critical. At the present time, specific examinations are used for each disease. This approach is useful once the pathophysiology of a disease is clear but for dementia, a wider net must be cast.

2.1.4. Imaging

The results of brain imaging are critical to any full patient description. Clearly, MRI and/or CT images of the brain should be obtained if possible [35,36]. However, a comprehensive evaluation should include the possibility of obtaining perfusion imaging [37] as well as CT angiogram and MR angiogram images [38] and metabolic PET scans [39]. Amyloid and tau imaging [40] are also important, as is functional MRI [41,42]. In particular, functional imaging coupled with electrophysiology can provide information about the brain connectome [43]. The Alzheimer's Disease Neuroimaging Initiative (https://adni.loni.usc.edu/, accessed on 24 September 2022) has made great progress in this direction, but this pioneering work is just a beginning, and must be extended.

2.1.5. Electrophysiology

Much information on the function of brain networks is available in neurophysiologic studies, such as EEG and evoked potentials in dementia [44–47] and should be included in the patient database when available

2.1.6. Serum/CSF Biomarkers

Various biomarkers [48] provide valuable information on diagnosing and understanding the mechanisms underlying dementia [49,50]. Some of these are neurofilaments [51], Aβ42 [52,53], tau [54,55], GAP-43 [56], neurogranin [57], trem2 [58], neuron-specific enolase [59], YKL-40 [60], and neuroregulin [61] among others. These also include exosomes and microRNA, which contain important information about the state and function of cells in the central nervous system [62–64].

2.1.7. Neuropathology/Histology/Electronmicroscopy

When available, understanding the microstructure of the brain and the individual neurons can provide vital information about the mechanisms of cognitive decline in dementia [65–67]. This includes standard histology and immunopathology [68,69]. However, electron microscopy provides crucial information regarding the state of subcellular organelles and structures [70,71].

2.1.8. Omics

Geneomic, proteomics, metabolomics and other similar approaches have been proposed as valuable markers in the study of dementia [72].

Genomics

Knowledge of the individual genome [73,74], as well as epigenetic markers of expression [75], are also critical in understanding dementia.

Proteomics

In-depth proteomic profiling to identify diagnostic and prognostic markers and gain understanding of complex pathophysiologic mechanisms [76].

Denomics

This is the study of the demographic factors that may influence health outcomes including diet [77], education, income, age, exercise and other activities. It also includes exposures to various environmental factors included in the exposome [78].

Metabolomics

These studies [79,80] can find patterns of metabolites in the blood that could correlate with dementia, and may thus provide insight into mechanisms.

2.1.9. Managing the Data

What is proposed above is an enormous amount of information, but starting with a database that is too limited is problematic:

1. As more is learned about the different dementias, it may be that factors initially thought of low importance could become increasingly significant.
2. More data will help find the most effective tools for diagnosing and distinguishing among the different dementias.
3. More detailed knowledge will help build model systems that better reflect each type of dementia.
4. Increases the chance of unique new discoveries.
5. Data must be collected longitudinally over time.

2.1.10. Making It Practical

It is easy to conceive of such a large database, but the key to this challenge is to bring together the elements to make it practical:

1. Funding.
2. Government and regulatory agency buy in.
3. "Assuring beneficence, justice and respect for all persons involved" [81].
4. Allowing individuals control over the use of private information.
5. Data storage, access and availability. It is important that elements of the database be available at multiple levels, allowing maximal researcher access at various levels without compromising private information. Allowing general access to elements of the database can allow crowd-sourcing [82] that can lead to new insights.
6. Data analysis. New statistical methods and computing methods will need to be developed to analyze the data, including machine learning [83–85], as well as other techniques [86,87].
7. Large patient number. Using a large data set with many dependent variables requires a sizeable number of patients in order to find patterns in the data.

2.2. Challenge 2: Quantifying Normal Aging

There are many biologic processes that result in a dementia phenotype. Some of these processes arise from causes outside of the neuronal/glial networks responsible for cognition, such as stroke, infections, trauma and metabolic disorders. Some processes causing progressive cognitive impairment are pathologic, but some may be inherent to the normal brain. Although it is easy to recognize pathologic brain function when it is severe, in order to identify the initial steps in the progression of dementia, it is critical to have very precise definitions of normal function at each age. A database such as the one described under Challenge 1 provides the basis for comparing changes during normal ageing and dementiaa, and allows us to ask more specific questions.

2.2.1. Changes over Time

In the absence of any pathology, what is the fate of the neuronal/glial networks over time? This needs to be determined from many viewpoints including: behavioral [88–91], imaging [92–95], exosomes [96], metabolomics [97] and molecular biologic [98].

1. What is the time course of this change? There may in fact be multiple time dependent changes in different variables. Which variables demonstrate the first changes?
2. What mechanisms underlie the changes in normal elderly patients?
3. Are any of these "normal aging" changes seen in humans, also seen in animals and isolated neurons? Are the time courses of the changes the same in each system?
4. Are there natural processes, exposures or genetic factors in humans or animals that ameliorate or accelerate these time dependent changes?
5. Beware overzealous extrapolation from animals to humans [3].

2.2.2. Model Systems

Eventually, progress toward understanding normal brain ageing and dementia will be facilitated by robust model systems. Model systems that explain only a very few of the changes will not be as valuable as systems that explain many different changes. Models can be based in animals (with caution) [99], in vitro systems [100], mathematical or computational [101,102]. These models will be critical to exploring and creating new ideas.

2.3. Challenge 3: Quantifying Pathologic Aging

The same techniques used to study and quantify normal aging can be applied to patients who have diagnoses of different types of dementia:

1. Use the existing data to refine the definitions of the various dementia types [103–108].

2. Follow-up longitudinal data over time to find the first difference noted between normal brain aging and pathological aging in patients eventually diagnosed with dementia [109–112]. This will form a more effective focus for disease modifying treatment than changes that occur late in the illness.
3. What are the characteristics of the nervous system that are different (see Challenge 2) at the onset [113] of pathological aging?
4. What is the detailed temporal relationship between amyloid and tau pathology, and the various biomarkers and behavioral changes in the database [114–116]?

2.4. Challenge 4: Building New Model Systems for Dementia

There has been much work on animal models [117–120], cellular models, [121–125] and computational/mathematical models [126–129] of dementia. However, none of these has captured all of the critical elements involved in the pathogenesis of the dementias and so cannot generate the sought-after answers. With the additional information obtained as part of these challenges, more effective models capturing more of the critical elements of dementia can be created, that will better serve the goal of understanding and treating dementia.

The complexity of the human brain is such that it may not be possible to immediately find a single model. Thus, it is necessary to have multiple overlapping models beginning at the smallest scale. There has been much work on the dynamics of protein folding and molecular dynamics [130–132] that has been stretched to the organelle level [133]. Beginning with this, models of the relevant aspects of single cell behavior [134,135] can be created and matched to cellular models. The interplay between predictions and observations at this level can help optimize modelling at this low level. Subsequently, modelling using organoids and tissue slices can be used and compared to mouse rat and primate models, all of which will be compared to humans in various ways.

This requires large scale collaborations between scientists with different backgrounds using different techniques.

2.5. Challenge 5: Search for Factors That Modify the Trajectory of Dementia Related Changes

The data generated by the previous challenges forms the substrate to generate hypotheses and test potential treatments for dementia. The model systems can be used to help choose the most appropriate molecules and doses, while predicting side effects of treatment before applying them to humans. Once potential therapies reach the level of human trials, the comprehensive data sets will be the key to understanding outcomes and refining future therapies. In addition, analysis of the demographic and exposure data in the context of multivariable outcomes will be key to using the natural experiments resulting from different genetic and environmental variables to look for potential therapies that can be tested. This requires large numbers of patients and modern computational techniques. Maximal data access that does not compromise individual privacy must be allowed to maximize finding important trends in such a large database.

3. Discussion

The costs of dementia at the personal and family level are incalculable, but the global financial costs are estimated to be on the order of USD 3 trillion [136] yearly. By comparison, the total yearly NIH budget at USD 45 billion dollars is only 1.5% of this number, and the operating expenses of a huge corporation such as Amazon are on the order of USD 100 billion each year, or 3% of the costs of dementia. Although the cost of solving the challenges proposed in this paper (Table 1) is huge, they can likely be met with resources of that magnitude, if they are well organized. Despite the cost, the reward is so large that such an investment is warranted.

Table 1. Summary of Challenges in Dementia.

Challenge	Details	Cost	Difficulty	Comment
Optimizing and Quantifying the Evaluation	Develop and maintain huge clinical databases with clinical, imaging, molecular and biochemical data for large numbers of patients.	++++	++++	Although difficult, this is the necessary pathway to progress in diagnosing, understanding the mechanisms of and treating dementia.
Quantifying Normal Aging	Without a comprehensive understanding of normal brain, aging it is impossible to identify the events that initiate the downward decline we see in dementia.	+++	+++	Once the first challenge has been met, this is much simpler but still requires substantial resources due to the need for long term studies.
Quantifying Pathologic Aging		+++	+++	
Building New Model Systems		++	++	The key is collaboration between teams of scientists with different backgrounds ranging from quantum and statistical physics, chemistry, biochemistry and systems biology to clinical care.
Search for factors that modify the trajectory of dementia related changes		++	++	Once the database is established appropriate computational resources need to be available to allow for analysis.

4. Conclusions

Finding a cure for dementia has so far proven intractable using current scientific models. It is now time to pursue a new model driven by large scale collaborations, not only between researchers and clinicians, but also including large corporations and world governments as partners. In addition, involving the general population in decisions about data use and crowd-sourcing analyses on big data will be critical elements of this new approach.

References

1. Alzheimer, A.; Stelzmann, R.A.; Schnitzlein, H.N.; Murtagh, F.R. An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde". *Clin. Anat.* **1995**, *8*, 429–431. [CrossRef]
2. Reiss, A.B.; Glass, A.D.; Wisniewski, T.; Wolozin, B.; Gomolin, I.H.; Pinkhasov, A.; De Leon, J.; Stecker, M.M. Alzheimer's disease: Many failed trials, so where do we go from here? *J. Investig. Med.* **2020**, *68*, 1135–1140. [CrossRef]
3. Reiss, A.B.; Montufar, N.; DeLeon, J.; Pinkhasov, A.; Gomolin, I.H.; Glass, A.D.; Arain, H.A.; Stecker, M.M. Alzheimer Disease Clinical Trials Targeting Amyloid: Lessons Learned From Success in Mice and Failure in Humans. *Neurologist* **2021**, *26*, 52–61. [CrossRef]
4. Chandler, D.L. Discovering Cancer Earlier: A New US$100 Million X Prize Aims to Shift the Odds in Cancer Survival. *IEEE Pulse* **2018**, *9*, 8–10. [CrossRef]
5. Hilbert, D. Mathematical Problems. *Bull. Amer. Math. Soc.* **1902**, *8*, 437–479. [CrossRef]
6. Watson, J.D. *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*; Atheneum: New York, NY, USA, 1968.
7. Planck, M. On the law of distribution of energeny in the normal spectrum. *Ann. Phys.* **1901**, *4*, 553. [CrossRef]

8. Rogan, S.; Lippa, C.F. Alzheimer's disease and other dementias: A review. *Am. J. Alzheimers Dis. Other Demen.* **2002**, *17*, 11–17. [CrossRef]

9. Arvanitakis, Z.; Shah, R.C.; Bennett, D.A. Diagnosis and Management of Dementia: Review. *JAMA* **2019**, *322*, 1589–1599. [CrossRef]

10. Jobst, K.A.; Barnetson, L.P.; Shepstone, B.J. Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: The use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and APO E4 medial temporal lobe dementias. The Oxford Project to Investigate Memory and Aging. *Int. Psychogeriatr.* **1997**, *9* (Suppl. 1), 191–222, discussion 247–252.

11. Jutten, R.J.; Thompson, L.; Sikkes, S.A.M.; Maruff, P.; Molinuevo, J.L.; Zetterberg, H.; Alber, J.; Faust, D.; Gauthier, S.; Gold, M.; et al. A Neuropsychological Perspective on Defining Cognitive Impairment in the Clinical Study of Alzheimer's Disease: Towards a More Continuous Approach. *J. Alzheimers Dis.* **2022**, *86*, 511–524. [CrossRef]

12. Fällman, K.; Lundgren, L.; Wressle, E.; Marcusson, J.; Classon, E. Normative data for the oldest old: Trail Making Test A, Symbol Digit Modalities Test, Victoria Stroop Test and Parallel Serial Mental Operations. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* **2020**, *27*, 567–580. [CrossRef]

13. Vicente, S.G.; Rivera, D.; Barbosa, F.; Gaspar, N.; Dores, A.R.; Mascialino, G.; Arango-Lasprilla, J.C. Normative data for tests of attention and executive functions in a sample of European Portuguese adult population. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* **2021**, *28*, 418–437. [CrossRef]

14. Enobi, Y.; Kemmotsu, N.; Robinson, E.; Murphy, C. Effects of language and acculturation on neurocognitive performance of Japanese Americans. *Neuropsychology* **2022**, *36*, 651–663. [CrossRef]

15. Boone, K.B.; Victor, T.L.; Wen, J.; Razani, J.; Pontón, M. The association between neuropsychological scores and ethnicity, language, and acculturation variables in a large patient population. *Arch. Clin. Neuropsychol.* **2007**, *22*, 355–365. [CrossRef]

16. Curtis, A.F.; Williams, J.M.; McCoy, K.J.M.; McCrae, C.S. Chronic Pain, Sleep, and Cognition in Older Adults with Insomnia: A Daily Multilevel Analysis. *J. Clin. Sleep Med.* **2018**, *14*, 1765–1772. [CrossRef]

17. McCrae, C.S.; Curtis, A.F.; Williams, J.M.; Dautovich, N.D.; McNamara, J.P.H.; Stripling, A.; Dzierzewski, J.M.; Berry, R.B.; McCoy, K.M.; Marsiske, M. Effects of Brief Behavioral Treatment for Insomnia on Daily Associations between Self-Reported Sleep and Objective Cognitive Performance in Older Adults. *Behav. Sleep Med.* **2020**, *18*, 577–588. [CrossRef]

18. Chandler, M.J.; Lacritz, L.H.; Hynan, L.S.; Barnard, H.D.; Allen, G.; Deschner, M.; Weiner, M.F.; Cullum, C.M. A total score for the CERAD neuropsychological battery. *Neurology* **2005**, *65*, 102–106. [CrossRef]

19. Longhurst, J.K.; Rider, J.V.; Cummings, J.L.; John, S.E.; Poston, B.; Held Bradford, E.C.; Landers, M.R. A Novel Way of Measuring Dual-Task Interference: The Reliability and Construct Validity of the Dual-Task Effect Battery in Neurodegenerative Disease. *Neurorehabil. Neural Repair* **2022**, *36*, 346–359. [CrossRef]

20. Hartle, L.; Martorelli, M.; Balboni, G.; Souza, R.; Charchat-Fichman, H. Diagnostic accuracy of CompCog: Reaction time as a screening measure for mild cognitive impairment. *Arq. Neuropsiquiatr.* **2022**, *80*, 570–579. [CrossRef]

21. Ashraf, A.; Taati, B. Automated Video Analysis of Handwashing Behavior as a Potential Marker of Cognitive Health in Older Adults. *IEEE J. Biomed. Health. Inform.* **2016**, *20*, 682–690. [CrossRef]

22. Liu, Z.; Paek, E.J.; Yoon, S.O.; Casenhiser, D.; Zhou, W.; Zhao, X. Detecting Alzheimer's Disease Using Natural Language Processing of Referential Communication Task Transcripts. *J. Alzheimers Dis.* **2022**, *86*, 1385–1398. [CrossRef]

23. Tahami Monfared, A.A.; Stern, Y.; Doogan, S.; Irizarry, M.; Zhang, Q. Stakeholder Insights in Alzheimer's Disease: Natural Language Processing of Social Media Conversations. *J. Alzheimers Dis.* **2022**, *89*, 695–708. [CrossRef]

24. Bueno, A.P.A.; Sato, J.R.; Hornberger, M. Eye tracking-The overlooked method to measure cognition in neurodegeneration? *Neuropsychologia* **2019**, *133*, 107191. [CrossRef]

25. Russell, L.L.; Greaves, C.V.; Convery, R.S.; Bocchetta, M.; Warren, J.D.; Kaski, D.; Rohrer, J.D. Eye movements in frontotemporal dementia: Abnormalities of fixation, saccades and anti-saccades. *Alzheimers Dement.* **2021**, *7*, e12218. [CrossRef]

26. Mahajan, D.; Votruba, M. Can the retina be used to diagnose and plot the progression of Alzheimer's disease? *Acta Ophthalmol.* **2017**, *95*, 768–777. [CrossRef]

27. Lin, Y.C.; Hsu, W.C.; Wu, C.K.; Chang, W.H.; Wu, K.P.; Wong, A.M. Comparison of motor performance of upper and lower extremities in dual-task tests in patients with mild Alzheimer's dementia. *Aging Clin. Exp. Res.* **2016**, *28*, 491–496. [CrossRef]

28. Payne, M.; Manera, V.; Robert, P.; Vandersteen, C.; Beauchet, O.; Galery, K.; Sacco, G.; Fabre, R.; Gros, A. Olfactory identification disorders due to Alzheimer's disease: A new test from France to Quebec. *PLoS ONE* **2022**, *17*, e0265764. [CrossRef]

29. Thompson, M.D.; Knee, K.; Golden, C.J. Olfaction in persons with Alzheimer's disease. *Neuropsychol. Rev.* **1998**, *8*, 11–23. [CrossRef]

30. Kouzuki, M.; Ichikawa, J.; Shirasagi, D.; Katsube, F.; Kobashi, Y.; Matsumoto, H.; Chao, H.; Yoshida, S.; Urakami, K. Detection and recognition thresholds for five basic tastes in patients with mild cognitive impairment and Alzheimer's disease dementia. *BMC Neurol.* **2020**, *20*, 110. [CrossRef]

31. Ilardi, C.R.; Iavarone, A.; La Marra, M.; Iachini, T.; Chieffi, S. Hand movements in Mild Cognitive Impairment: Clinical implications and insights for future research. *J. Integr. Neurosci.* **2022**, *21*, 67. [CrossRef]

32. Besser, L.; Kukull, W.; Knopman, D.S.; Chui, H.; Galasko, D.; Weintraub, S.; Jicha, G.; Carlsson, C.; Burns, J.; Quinn, J.; et al. Version 3 of the National Alzheimer's Coordinating Center's Uniform Data Set. *Alzheimer Dis. Assoc. Disord.* **2018**, *32*, 351–358. [CrossRef] [PubMed]

33. Potvin, A.R.; Tourtellotte, W.W. The neurological examination: Advancements in its quantification. *Arch. Phys. Med. Rehabil.* **1975**, *56*, 425–437. [PubMed]

34. Steenland, K.; Dick, R.; Fine, L. Agreement between clinical examination and quantitative tests of neurologic function among 384 subjects. *Am. J. Ind. Med.* **2001**, *39*, 361–368. [CrossRef] [PubMed]

35. Battineni, G.; Chintalapudi, N.; Hossain, M.A.; Losco, G.; Ruocco, C.; Sagaro, G.G.; Traini, E.; Nittari, G.; Amenta, F. Artificial Intelligence Models in the Diagnosis of Adult-Onset Dementia Disorders: A Review. *Bioengineering* **2022**, *9*, 370. [CrossRef] [PubMed]

36. Uchida, Y.; Kan, H.; Sakurai, K.; Oishi, K.; Matsukawa, N. Quantitative susceptibility mapping as an imaging biomarker for Alzheimer's disease: The expectations and limitations. *Front. Neurosci.* **2022**, *16*, 938092. [CrossRef]

37. Krishnan, S.; Talley, B.D.; Slavin, M.J.; Doraiswamy, P.M.; Petrella, J.R. Current status of functional MR imaging, perfusion-weighted imaging, and diffusion-tensor imaging in Alzheimer's disease diagnosis and research. *Neuroimaging Clin. N. Am.* **2005**, *15*, 853–868. [CrossRef]

38. Aichner, F.; Wagner, M.; Kremser, C.; Felber, S. MR-imaging of non-Alzheimer's dementia. *J. Neural Transm. Suppl.* **1996**, *47*, 143–153. [CrossRef]

39. Burkett, B.J.; Babcock, J.C.; Lowe, V.J.; Graff-Radford, J.; Subramaniam, R.M.; Johnson, D.R. PET Imaging of Dementia: Update 2022. *Clin. Nucl. Med.* **2022**, *47*, 763–773. [CrossRef]

40. Villemagne, V.L.; Doré, V.; Bourgeat, P.; Burnham, S.C.; Laws, S.; Salvado, O.; Masters, C.L.; Rowe, C.C. Aβ-amyloid and Tau Imaging in Dementia. *Semin. Nucl. Med.* **2017**, *47*, 75–88. [CrossRef]

41. Qiu, Q. Neural Networks in Autosomal Dominant Alzheimer's Disease: Insights From Functional Magnetic Resonance Imaging Studies. *Front. Aging Neurosci.* **2022**, *14*, 903269. [CrossRef]

42. Franzmeier, N.; Düzel, E.; Jessen, F.; Buerger, K.; Levin, J.; Duering, M.; Dichgans, M.; Haass, C.; Suárez-Calvet, M.; Fagan, A.M.; et al. Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease. *Brain* **2018**, *141*, 1186–1200. [CrossRef]

43. Yu, M.; Sporns, O.; Saykin, A.J. The human connectome in Alzheimer disease-relationship to biomarkers and genetics. *Nat. Rev. Neurol.* **2021**, *17*, 545–563. [CrossRef] [PubMed]

44. Torres-Simón, L.; Doval, S.; Nebreda, A.; Llinas, S.J.; Marsh, E.B.; Maestú, F. Understanding brain function in vascular cognitive impairment and dementia with EEG and MEG: A systematic review. *Neuroimage Clin.* **2022**, *35*, 103040. [CrossRef] [PubMed]

45. Babiloni, C.; Blinowska, K.; Bonanni, L.; Cichocki, A.; De Haan, W.; Del Percio, C.; Dubois, B.; Escudero, J.; Fernández, A.; Frisoni, G.; et al. What electrophysiology tells us about Alzheimer's disease: A window into the synchronization and connectivity of brain neurons. *Neurobiol. Aging* **2020**, *85*, 58–73. [CrossRef] [PubMed]

46. Núñez, P.; Poza, J.; Gómez, C.; Rodríguez-González, V.; Hillebrand, A.; Tola-Arribas, M.A.; Cano, M.; Hornero, R. Characterizing the fluctuations of dynamic resting-state electrophysiological functional connectivity: Reduced neuronal coupling variability in mild cognitive impairment and dementia due to Alzheimer's disease. *J. Neural Eng.* **2019**, *16*, 056030. [CrossRef] [PubMed]

47. Morrison, C.; Rabipour, S.; Knoefel, F.; Sheppard, C.; Taler, V. Auditory Event-related Potentials in Mild Cognitive Impairment and Alzheimer's Disease. *Curr. Alzheimer Res.* **2018**, *15*, 702–715. [CrossRef]

48. Cummings, J.; Kinney, J. Biomarkers for Alzheimer's Disease: Context of Use, Qualification, and Roadmap for Clinical Implementation. *Medicina* **2022**, *58*, 952. [CrossRef]

49. Dulewicz, M.; Kulczyńska-Przybik, A.; Mroczko, P.; Kornhuber, J.; Lewczuk, P.; Mroczko, B. Biomarkers for the Diagnosis of Alzheimer's Disease in Clinical Practice: The Role of CSF Biomarkers during the Evolution of Diagnostic Criteria. *Int. J. Mol. Sci.* **2022**, *23*, 8598. [CrossRef]

50. Hawksworth, J.; Fernández, E.; Gevaert, K. A new generation of AD biomarkers: 2019 to 2021. *Ageing Res. Rev.* **2022**, *79*, 101654. [CrossRef]

51. Das, S.; Dewit, N.; Jacobs, D.; Pijnenburg, Y.A.L.; In't Veld, S.G.J.G.; Coppens, S.; Quaglia, M.; Hirtz, C.; Teunissen, C.E.; Vanmechelen, E. A Novel Neurofilament Light Chain ELISA Validated in Patients with Alzheimer's Disease, Frontotemporal Dementia, and Subjective Cognitive Decline, and the Evaluation of Candidate Proteins for Immunoassay Calibration. *Int. J. Mol. Sci.* **2022**, *23*, 7221. [CrossRef]

52. Botella Lucena, P.; Vanherle, S.; Lodder, C.; Gutiérrez de Ravé, M.; Stancu, I.C.; Lambrichts, I.; Vangheluwe, R.; Bruffaerts, R.; Dewachter, I. Blood-based Aβ42 increases in the earliest pre-pathological stage before decreasing with progressive amyloid pathology in preclinical models and human subjects: Opening new avenues for prevention. *Acta Neuropathol.* **2022**, *144*, 489–508. [CrossRef] [PubMed]

53. Kokkinou, M.; Beishon, L.C.; Smailagic, N.; Noel-Storr, A.H.; Hyde, C.; Ukoumunne, O.; Worrall, R.E.; Hayen, A.; Desai, M.; Ashok, A.H.; et al. Plasma and cerebrospinal fluid ABeta42 for the differential diagnosis of Alzheimer's disease dementia in participants diagnosed with any dementia subtype in a specialist care setting. *Cochrane Database Syst. Rev.* **2021**, *2*, CD010945. [CrossRef] [PubMed]

54. Wilczyńska, K.; Waszkiewicz, N. Diagnostic Utility of Selected Serum Dementia Biomarkers: Amyloid β-40, Amyloid β-42, Tau Protein, and YKL-40: A Review. *J. Clin. Med.* **2020**, *9*, 3452. [CrossRef] [PubMed]

55. Varesi, A.; Carrara, A.; Pires, V.G.; Floris, V.; Pierella, E.; Savioli, G.; Prasad, S.; Esposito, C.; Ricevuti, G.; Chirumbolo, S.; et al. Blood-Based Biomarkers for Alzheimer's Disease Diagnosis and Progression: An Overview. *Cells* **2022**, *11*, 1367. [CrossRef]

56. Zhang, H.; Lyu, D.; Jia, J.; Alzheimer's Disease Neuroimaging Initiative. The Trajectory of Cerebrospinal Fluid Growth-Associated Protein 43 in the Alzheimer's Disease Continuum: A Longitudinal Study. *J. Alzheimers Dis.* **2022**, *85*, 1441–1452. [CrossRef] [PubMed]

57. Yoong, S.Q.; Lu, J.; Xing, H.; Gyanwali, B.; Tan, Y.Q.; Wu, X.V. The prognostic utility of CSF neurogranin in predicting future cognitive decline in the Alzheimer's disease continuum: A systematic review and meta-analysis with narrative synthesis. *Ageing Res. Rev.* **2021**, *72*, 101491. [CrossRef]

58. Winfree, R.L.; Dumitrescu, L.; Blennow, K.; Zetterberg, H.; Gifford, K.A.; Pechman, K.R.; Jefferson, A.L.; Hohman, T.J.; Alzheimer's Disease Neuroimaging Initiative. Biological correlates of elevated soluble TREM2 in cerebrospinal fluid. *Neurobiol. Aging* **2022**, *118*, 88–98. [CrossRef]

59. Katayama, T.; Sawada, J.; Takahashi, K.; Yahara, O.; Hasebe, N. Meta-analysis of cerebrospinal fluid neuron-specific enolase levels in Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. *Alzheimers Res. Ther.* **2021**, *13*, 163. [CrossRef]

60. Mavroudis, I.; Chowdhury, R.; Petridis, F.; Karantali, E.; Chatzikonstantinou, S.; Balmus, I.M.; Luca, I.S.; Ciobica, A.; Kazis, D. YKL-40 as a Potential Biomarker for the Differential Diagnosis of Alzheimer's Disease. *Medicina* **2021**, *58*, 60. [CrossRef]

61. Vrillon, A.; Mouton-Liger, F.; Martinet, M.; Cognat, E.; Hourregue, C.; Dumurgier, J.; Bouaziz-Amar, E.; Brinkmalm, A.; Blennow, K.; Zetterberg, H.; et al. Plasma neuregulin 1 as a synaptic biomarker in Alzheimer's disease: A discovery cohort study. *Alzheimers Res. Ther.* **2022**, *14*, 71. [CrossRef]

62. Iranifar, E.; Seresht, B.M.; Momeni, F.; Fadaei, E.; Mehr, M.H.; Ebrahimi, Z.; Rahmati, M.; Kharazinejad, E.; Mirzaei, H. Exosomes and microRNAs: New potential therapeutic candidates in Alzheimer disease therapy. *J. Cell. Physiol.* **2019**, *234*, 2296–2305. [CrossRef] [PubMed]

63. Blount, G.S.; Coursey, L.; Kocerha, J. MicroRNA Networks in Cognition and Dementia. *Cells* **2022**, *11*, 1882. [CrossRef] [PubMed]

64. Kim, K.Y.; Shin, K.Y.; Chang, K.A. Brain-Derived Exosomal Proteins as Effective Biomarkers for Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Biomolecules* **2021**, *11*, 980. [CrossRef] [PubMed]

65. Hadley, G.; Zhang, J.; Harris-Skillman, E.; Alexopoulou, Z.; DeLuca, G.C.; Pendlebury, S.T. Cognitive decline and diabetes: A systematic review of the neuropathological correlates accounting for cognition at death. *J. Neurol. Neurosurg. Psychiatry* **2022**, *93*, 246–253. [CrossRef]

66. Viejo, L.; Noori, A.; Merrill, E.; Das, S.; Hyman, B.T.; Serrano-Pozo, A. Systematic review of human post-mortem immunohisto-chemical studies and bioinformatics analyses unveil the complexity of astrocyte reaction in Alzheimer's disease. *Neuropathol. Appl. Neurobiol.* **2022**, *48*, e12753. [CrossRef] [PubMed]

67. Jester, H.M.; Gosrani, S.P.; Ding, H.; Zhou, X.; Ko, M.C.; Ma, T. Characterization of Early Alzheimer's Disease-Like Pathological Alterations in Non-Human Primates with Aging: A Pilot Study. *J. Alzheimers Dis.* **2022**, *88*, 957–970. [CrossRef]

68. Maxwell, S.P.; Cash, M.K.; Darvesh, S. Neuropathology and cholinesterase expression in the brains of octogenarians and older. *Chem. Biol. Interact.* **2022**, *364*, 110065. [CrossRef]

69. Nelson, P.T.; Brayne, C.; Flanagan, M.E.; Abner, E.L.; Agrawal, S.; Attems, J.; Castellani, R.J.; Corrada, M.M.; Cykowski, M.D.; Di, J.; et al. Frequency of LATE neuropathologic change across the spectrum of Alzheimer's disease neuropathology: Combined data from 13 community-based or population-based autopsy cohorts. *Acta Neuropathol.* **2022**, *144*, 27–44. [CrossRef]

70. Ingham, D.J.; Hillyer, K.M.; McGuire, M.J.; Gamblin, T.C. In vitro Tau Aggregation Inducer Molecules Influence the Effects of MAPT Mutations on Aggregation Dynamics. *Biochemistry* **2022**, *61*, 1243–1259. [CrossRef]

71. Aso, E.; Lomoio, S.; López-González, I.; Joda, L.; Carmona, M.; Fernández-Yagüe, N.; Moreno, J.; Juvés, S.; Pujol, A.; Pamplona, R.; et al. Amyloid generation and dysfunctional immunoproteasome activation with disease progression in animal model of familial Alzheimer's disease. *Brain Pathol.* **2012**, *22*, 636–653. [CrossRef]

72. Tan, M.S.; Cheah, P.L.; Chin, A.V.; Looi, L.M.; Chang, S.W. A review on omics-based biomarkers discovery for Alzheimer's disease from the bioinformatics perspectives: Statistical approach vs machine learning approach. *Comput. Biol. Med.* **2021**, *139*, 104947. [CrossRef] [PubMed]

73. Cruchaga, C.; Del-Aguila, J.L.; Saef, B.; Black, K.; Fernandez, M.V.; Budde, J.; Ibanez, L.; Deming, Y.; Kapoor, M.; Tosto, G.; et al. Polygenic risk score of sporadic late-onset Alzheimer's disease reveals a shared architecture with the familial and early-onset forms. *Alzheimers Dement.* **2018**, *14*, 205–214. [CrossRef] [PubMed]

74. Schwartzentruber, J.; Cooper, S.; Liu, J.Z.; Barrio-Hernandez, I.; Bello, E.; Kumasaka, N.; Young, A.M.H.; Franklin, R.J.M.; Johnson, T.; Estrada, K.; et al. Genome-wide meta-analysis, fine-mapping and integrative prioritization implicate new Alzheimer's disease risk genes. *Nat. Genet.* **2021**, *53*, 392–402. [CrossRef] [PubMed]

75. Villa, C.; Stoccoro, A. Epigenetic Peripheral Biomarkers for Early Diagnosis of Alzheimer's Disease. *Genes* **2022**, *13*, 1308. [CrossRef]

76. Kononikhin, A.S.; Zakharova, N.V.; Semenov, S.D.; Bugrova, A.E.; Brzhozovskiy, A.G.; Indeykina, M.I.; Fedorova, Y.B.; Kolykhalov, I.V.; Strelnikova, P.A.; Ikonnikova, A.Y.; et al. Prognosis of Alzheimer's Disease Using Quantitative Mass Spectrometry of Human Blood Plasma Proteins and Machine Learning. *Int. J. Mol. Sci.* **2022**, *23*, 7907. [CrossRef]

77. Stecker, M.; Stecker, M.; Reiss, A.B.; Kasselman, L. Dementia and Diet, Methodological and Statistical Issues: A Pilot Study. *Front. Aging Neurosci.* **2022**, *14*, 606424. [CrossRef]

78. Stecker, M.M.; Peltier, M.R.; Reiss, A.B. The role of massive demographic databases in intractable illnesses: Denomics for dementia. *AIMS Public Health* **2022**, *9*, 618–629. [CrossRef]

79. Zhang, X.; Hu, W.; Wang, Y.; Wang, W.; Liao, H.; Zhang, X.; Kiburg, K.V.; Shang, X.; Bulloch, G.; Huang, Y.; et al. Plasma metabolomic profiles of dementia: A prospective study of 110,655 participants in the UK Biobank. *BMC Med.* **2022**, *20*, 252. [CrossRef]

80. Kalecký, K.; German, D.C.; Montillo, A.A.; Bottiglieri, T. Targeted Metabolomic Analysis in Alzheimer's Disease Plasma and Brain Tissue in Non-Hispanic Whites. *J. Alzheimers Dis.* **2022**, *86*, 1875–1895. [CrossRef]

81. Anonymous. Protection of human subjects; Belmont Report: Notice of report for public comment. *Fed. Regist.* **1979**, *44*, 23191–23197.

82. Marshall, P.J.; Verma, A.; More, A.; Davis, C.P.; More, S.; Kapadia, A.; Parrish, M.; Snyder, C.; Wilcox, J.; Baeten, E.; et al. Space Warps—I. Crowdsourcing the discovery of gravitational lenses. *Mon. Not. R. Astron. Soc.* **2015**, *455*, 1171–1190. [CrossRef]

83. Li, Z.; Jiang, X.; Wang, Y.; Kim, Y. Applied machine learning in Alzheimer's disease research: Omics, imaging, and clinical data. *Emerg. Top. Life. Sci.* **2021**, *5*, 765–777. [CrossRef] [PubMed]

84. Luckett, P.H.; McCullough, A.; Gordon, B.A.; Strain, J.; Flores, S.; Dincer, A.; McCarthy, J.; Kuffner, T.; Stern, A.; Meeker, K.L.; et al. Modeling autosomal dominant Alzheimer's disease with machine learning. *Alzheimers Dement.* **2021**, *17*, 1005–1016. [CrossRef] [PubMed]

85. Cao, H.; Meyer-Lindenberg, A.; Schwarz, E. Comparative Evaluation of Machine Learning Strategies for Analyzing Big Data in Psychiatry. *Int. J. Mol. Sci.* **2018**, *19*, 3387. [CrossRef]

86. Mor, U.; Cohen, Y.; Valdés-Mas, R.; Kviatcovsky, D.; Elinav, E.; Avron, H. Dimensionality reduction of longitudinal 'omics data using modern tensor factorizations. *PLoS Comput. Biol.* **2022**, *18*, e1010212. [CrossRef]

87. Olivier, M.; Asmis, R.; Hawkins, G.A.; Howard, T.D.; Cox, L.A. The Need for Multi-Omics Biomarker Signatures in Precision Medicine. *Int. J. Mol. Sci.* **2019**, *20*, 4781. [CrossRef]

88. Malek-Ahmadi, M.; O'Connor, K.; Schofield, S.; Coon, D.W.; Zamrini, E. Trajectory and variability characterization of the Montreal cognitive assessment in older adults. *Aging Clin. Exp. Res.* **2018**, *30*, 993–998. [CrossRef]

89. Flicker, C.; Ferris, S.H.; Reisberg, B. A two-year longitudinal study of cognitive function in normal aging and Alzheimer's disease. *J. Geriatr. Psychiatry Neurol.* **1993**, *6*, 84–96. [CrossRef]

90. Farias, S.T.; Mungas, D.; Reed, B.; Haan, M.N.; Jagust, W.J. Everyday functioning in relation to cognitive functioning and neuroimaging in community-dwelling Hispanic and non-Hispanic older adults. *J. Int. Neuropsychol. Soc.* **2004**, *10*, 342–354. [CrossRef]

91. Korten, A.E.; Henderson, A.S.; Christensen, H.; Jorm, A.F.; Rodgers, B.; Jacomb, P.; Mackinnon, A.J. A prospective study of cognitive function in the elderly. *Psychol. Med.* **1997**, *27*, 919–930. [CrossRef]

92. Janahi, M.; Aksman, L.; Schott, J.M.; Mokrab, Y.; Altmann, A.; Alzheimer's Disease Neuroimaging Initiative. Nomograms of human hippocampal volume shifted by polygenic scores. *eLife* **2022**, *11*, e78232. [CrossRef] [PubMed]

93. Lu, J.; Testa, N.; Jordan, R.; Elyan, R.; Kanekar, S.; Wang, J.; Eslinger, P.; Yang, Q.X.; Zhang, B.; Karunanayaka, P.R. Functional Connectivity between the Resting-State Olfactory Network and the Hippocampus in Alzheimer's Disease. *Brain Sci.* **2019**, *9*, 338. [CrossRef] [PubMed]

94. Cheung, E.Y.W.; Shea, Y.F.; Chiu, P.K.C.; Kwan, J.S.K.; Mak, H.K.F. Diagnostic Efficacy of Voxel-Mirrored Homotopic Connectivity in Vascular Dementia as Compared to Alzheimer's Related Neurodegenerative Diseases-A Resting State fMRI Study. *Life* **2021**, *11*, 1108. [CrossRef]

95. Shu, J.; Qiang, Q.; Yan, Y.; Wen, Y.; Ren, Y.; Wei, W.; Zhang, L. Distinct Patterns of Brain Atrophy associated with Mild Behavioral Impairment in Cognitively Normal Elderly Adults. *Int. J. Med. Sci.* **2021**, *18*, 2950–2956. [CrossRef]

96. Lark, D.S.; LaRocca, T.J. Expression of Exosome Biogenesis Genes Is Differentially Altered by Aging in the Mouse and in the Human Brain During Alzheimer's Disease. *J. Gerontol. A Biol. Sci. Med. Sci.* **2022**, *77*, 659–663. [CrossRef]

97. Borkowski, K.; Taha, A.Y.; Pedersen, T.L.; De Jager, P.L.; Bennett, D.A.; Arnold, M.; Kaddurah-Daouk, R.; Newman, J.W. Serum metabolomic biomarkers of perceptual speed in cognitively normal and mildly impaired subjects with fasting state stratification. *Sci. Rep.* **2021**, *11*, 18964. [CrossRef] [PubMed]

98. Sheinerman, K.; Tsivinsky, V.; Mathur, A.; Kessler, D.; Shaz, B.; Umansky, S. Age- and sex-dependent changes in levels of circulating brain-enriched microRNAs during normal aging. *Aging* **2018**, *10*, 3017–3041. [CrossRef]

99. Struys-Ponsar, C.; Florence, A.; Gauthier, A.; Crichton, R.R.; van den Bosch de Aguilar, P. Ultrastructural changes in brain parenchyma during normal aging and in animal models of aging. *J. Neural Transm. Suppl.* **1994**, *44*, 111–132. [CrossRef] [PubMed]

100. Shaker, M.R.; Hunter, Z.L.; Wolvetang, E.J. Robust and Highly Reproducible Generation of Cortical Brain Organoids for Modelling Brain Neuronal Senescence In Vitro. *J. Vis. Exp.* **2022**, *183*, e63714. [CrossRef]

101. Jones, D.; Lowe, V.; Graff-Radford, J.; Botha, H.; Barnard, L.; Wiepert, D.; Murphy, M.C.; Murray, M.; Senjem, M.; Gunter, J.; et al. A computational model of neurodegeneration in Alzheimer's disease. *Nat. Commun.* **2022**, *13*, 1643. [CrossRef]

102. Toescu, E.C. Normal brain ageing: Models and mechanisms. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2005**, *360*, 2347–2354. [CrossRef] [PubMed]

103. Creavin, S.T.; Noel-Storr, A.H.; Langdon, R.J.; Richard, E.; Creavin, A.L.; Cullum, S.; Purdy, S.; Ben-Shlomo, Y. Clinical judgement by primary care physicians for the diagnosis of all-cause dementia or cognitive impairment in symptomatic people. *Cochrane Database Syst. Rev.* **2022**, *6*, CD012558. [CrossRef] [PubMed]

104. Previtali, F.; Bertolazzi, P.; Felici, G.; Weitschek, E. A novel method and software for automatically classifying Alzheimer's disease patients by magnetic resonance imaging analysis. *Comput. Methods Programs Biomed.* **2017**, *143*, 89–95. [CrossRef] [PubMed]

105. Halliday, G.; Ng, T.; Rodriguez, M.; Harding, A.; Blumbergs, P.; Evans, W.; Fabian, V.; Fryer, J.; Gonzales, M.; Harper, C.; et al. Consensus neuropathological diagnosis of common dementia syndromes: Testing and standardising the use of multiple diagnostic criteria. *Acta Neuropathol.* **2002**, *104*, 72–78. [CrossRef] [PubMed]

106. Lin, W.; Gao, Q.; Yuan, J.; Chen, Z.; Feng, C.; Chen, W.; Du, M.; Tong, T. Predicting Alzheimer's Disease Conversion From Mild Cognitive Impairment Using an Extreme Learning Machine-Based Grading Method with Multimodal Data. *Front. Aging Neurosci.* **2020**, *12*, 77. [CrossRef] [PubMed]

107. Nagy, Z.; Esiri, M.M.; Joachim, C.; Jobst, K.A.; Morris, J.H.; King, E.M.; Hindley, N.J.; McDonald, B.; Litchfield, S.; Barnetson, L.; et al. Comparison of pathological diagnostic criteria for Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* **1998**, *12*, 182–189. [CrossRef] [PubMed]

108. Silver, M.H.; Newell, K.; Brady, C.; Hedley-White, E.T.; Perls, T.T. Distinguishing between neurodegenerative disease and disease-free aging: Correlating neuropsychological evaluations and neuropathological studies in centenarians. *Psychosom. Med.* **2002**, *64*, 493–501. [CrossRef]

109. Hendriks, S.; Peetoom, K.; Tange, H.; van Bokhoven, M.A.; van der Flier, W.M.; Bakker, C.; Papma, J.M.; Koopmans, R.; Verhey, F.; Köhler, S.; et al. Pre-Diagnostic Symptoms of Young-Onset Dementia in the General Practice up to Five Years Before Diagnosis. *J. Alzheimers Dis.* **2022**, *88*, 229–239. [CrossRef]

110. Frank, B.; Ally, M.; Tripodis, Y.; Puzo, C.; Labriolo, C.; Hurley, L.; Martin, B.; Palmisano, J.; Chan, L.; Steinberg, E.; et al. Trajectories of Cognitive Decline in Brain Donors with Autopsy-Confirmed Alzheimer Disease and Cerebrovascular Disease. *Neurology* **2022**, *98*, e2454–e2464. [CrossRef]

111. Karanth, S.D.; Schmitt, F.A.; Nelson, P.T.; Katsumata, Y.; Kryscio, R.J.; Fardo, D.W.; Harp, J.P.; Abner, E.L. Four Common Late-Life Cognitive Trajectories Patterns Associate with Replicable Underlying Neuropathologies. *J. Alzheimers Dis.* **2021**, *82*, 647–659. [CrossRef]

112. Tanprasertsuk, J.; Johnson, E.J.; Johnson, M.A.; Poon, L.W.; Nelson, P.T.; Davey, A.; Martin, P.; Barbey, A.K.; Barger, K.; Wang, X.D.; et al. Clinico-Neuropathological Findings in the Oldest Old from the Georgia Centenarian Study. *J. Alzheimers Dis.* **2019**, *70*, 35–49. [CrossRef] [PubMed]

113. Braak, H.; Braak, E.; Bohl, J. Staging of Alzheimer-related cortical destruction. *Eur. Neurol.* **1993**, *33*, 403–408. [CrossRef] [PubMed]

114. Westwood, S.; Baird, A.L.; Anand, S.N.; Nevado-Holgado, A.J.; Kormilitzin, A.; Shi, L.; Hye, A.; Ashton, N.J.; Morgan, A.R.; Bos, I.; et al. Validation of Plasma Proteomic Biomarkers Relating to Brain Amyloid Burden in the EMIF-Alzheimer's Disease Multimodal Biomarker Discovery Cohort. *J. Alzheimers Dis.* **2020**, *74*, 213–225. [CrossRef] [PubMed]

115. Yamashita, K.; Miura, M.; Watanabe, S.; Ishiki, K.; Arimatsu, Y.; Kawahira, J.; Kubo, T.; Sasaki, K.; Arai, T.; Hagino, K.; et al. Fully automated and highly specific plasma β-amyloid immunoassays predict β-amyloid status defined by amyloid positron emission tomography with high accuracy. *Alzheimers Res. Ther.* **2022**, *14*, 86. [CrossRef]

116. Janelidze, S.; Christian, B.T.; Price, J.; Laymon, C.; Schupf, N.; Klunk, W.E.; Lott, I.; Silverman, W.; Rosas, H.D.; Zaman, S.; et al. Detection of Brain Tau Pathology in Down Syndrome Using Plasma Biomarkers. *JAMA Neurol.* **2022**, *79*, 797–807. [CrossRef]

117. Guénette, S.Y.; Tanzi, R.E. Progress toward valid transgenic mouse models for Alzheimer's disease. *Neurobiol. Aging* **1999**, *20*, 201–211. [CrossRef]

118. Dewachter, I.; van Dorpe, J.; Spittaels, K.; Tesseur, I.; Van Den Haute, C.; Moechars, D.; Van Leuven, F. Modeling Alzheimer's disease in transgenic mice: Effect of age and of presenilin1 on amyloid biochemistry and pathology in APP/London mice. *Exp. Gerontol.* **2000**, *35*, 831–841. [CrossRef]

119. Sanchez-Varo, R.; Mejias-Ortega, M.; Fernandez-Valenzuela, J.J.; Nuñez-Diaz, C.; Caceres-Palomo, L.; Vegas-Gomez, L.; Sanchez-Mejias, E.; Trujillo-Estrada, L.; Garcia-Leon, J.A.; Moreno-Gonzalez, I.; et al. Transgenic Mouse Models of Alzheimer's Disease: An Integrative Analysis. *Int. J. Mol. Sci.* **2022**, *23*, 5404. [CrossRef]

120. Van Dam, D.; De Deyn, P.P. Non human primate models for Alzheimer's disease-related research and drug discovery. *Expert Opin. Drug Discov.* **2017**, *12*, 187–200. [CrossRef]

121. Wu, Y.; West, N.R.; Bhattacharyya, A.; Wiseman, F.K. Cell models for Down syndrome-Alzheimer's disease research. *Neuronal Signal.* **2022**, *6*, NS20210054. [CrossRef]

122. Hargus, G.; Ehrlich, M.; Hallmann, A.L.; Kuhlmann, T. Human stem cell models of neurodegeneration: A novel approach to study mechanisms of disease development. *Acta Neuropathol.* **2014**, *127*, 151–173. [CrossRef] [PubMed]

123. Bubnys, A.; Tsai, L.H. Harnessing cerebral organoids for Alzheimer's disease research. *Curr. Opin. Neurobiol.* **2022**, *72*, 120–130. [CrossRef] [PubMed]

124. Tan, H.Y.; Cho, H.; Lee, L.P. Human mini-brain models. *Nat. Biomed. Eng.* **2021**, *5*, 11–25. [CrossRef] [PubMed]

125. Dubey, S.K.; Ram, M.S.; Krishna, K.V.; Saha, R.N.; Singhvi, G.; Agrawal, M.; Ajazuddin; Saraf, S.; Saraf, S.; Alexander, A. Recent Expansions on Cellular Models to Uncover the Scientific Barriers Towards Drug Development for Alzheimer's Disease. *Cell. Mol. Neurobiol.* **2019**, *39*, 181–209. [CrossRef] [PubMed]

126. Hunanyan, L.; Ghamaryan, V.; Makichyan, A.; Popugaeva, E. Computer-Based Drug Design of Positive Modulators of Store-Operated Calcium Channels to Prevent Synaptic Dysfunction in Alzheimer's Disease. *Int. J. Mol. Sci.* **2021**, *22*, 13618. [CrossRef]

127. Ugbaja, S.C.; Lawal, I.A.; Kumalo, H.M.; Lawal, M.M. Alzheimer's Disease and β-secretase Inhibition: An Update with a Focus on Computer-aided Inhibitor Design. *Curr. Drug Targets* **2022**, *23*, 266–285. [CrossRef]

128. Gandolfi, D.; Boiani, G.M.; Bigiani, A.; Mapelli, J. Modeling Neurotransmission: Computational Tools to Investigate Neurological Disorders. *Int. J. Mol. Sci.* **2021**, *22*, 4565. [CrossRef]

129. Vosoughi, A.; Sadigh-Eteghad, S.; Ghorbani, M.; Shahmorad, S.; Farhoudi, M.; Rafi, M.A.; Omidi, Y. Mathematical Models to Shed Light on Amyloid-Beta and Tau Protein Dependent Pathologies in Alzheimer's Disease. *Neuroscience* **2020**, *424*, 45–57. [CrossRef]

130. Paiva, V.A.; Gomes, I.S.; Monteiro, C.R.; Mendonça, M.V.; Martins, P.M.; Santana, C.A.; Gonçalves-Almeida, V.; Izidoro, S.C.; Melo-Minardi, R.C.; Silveira, S.A. Protein structural bioinformatics: An overview. *Comput. Biol. Med.* **2022**, *147*, 105695. [CrossRef]

131. Okumura, H.; Itoh, S.G. Molecular Dynamics Simulation Studies on the Aggregation of Amyloid-β Peptides and Their Disaggregation by Ultrasonic Wave and Infrared Laser Irradiation. *Molecules* **2022**, *27*, 2483. [CrossRef]

132. Itoh, S.G.; Okumura, H. All-Atom Molecular Dynamics Simulation Methods for the Aggregation of Protein and Peptides: Replica Exchange/Permutation and Nonequilibrium Simulations. *Methods Mol. Biol.* **2022**, *2340*, 197–220. [CrossRef] [PubMed]

133. Jones, M.D.; Naylor, K. Simple to Complex: The Role of Actin and Microtubules in Mitochondrial Dynamics in Amoeba, Yeast, and Mammalian Cells. *Int. J. Mol. Sci.* **2022**, *23*, 9402. [CrossRef] [PubMed]

134. Qi, T.; McGrath, K.; Ranganathan, R.; Dotti, G.; Cao, Y. Cellular kinetics: A clinical and computational review of CAR-T cell pharmacology. *Adv. Drug Deliv. Rev.* **2022**, *188*, 114421. [CrossRef] [PubMed]

135. Salahub, D.R. Multiscale molecular modelling: From electronic structure to dynamics of nanosystems and beyond. *Phys. Chem. Chem. Phys.* **2022**, *24*, 9051–9081. [CrossRef]

136. Nandi, A.; Counts, N.; Chen, S.; Seligman, B.; Tortorice, D.; Vigo, D.; Bloom, D.E. Global and regional projections of the economic burden of Alzheimer's disease and related dementias from 2019 to 2050: A value of statistical life approach. *EClinicalMedicine* **2022**, *51*, 101580. [CrossRef]