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Down syndrome-associated Alzheimer's disease: a genetic form of dementia

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Abstract

Persons with Down syndrome have a form of genetically determined Alzheimer's disease due to the amyloid precursor protein gene dose effect. Consequently, amyloid plaques and tau neurofibrillary tangles are virtually universal by age 40 years, and the lifetime risk to develop dementia is over 90%. Alzheimeŕs disease is now the main medical problem and leading cause of death in this population. However, diagnosis of dementia remains a clinical challenge due to a lack of awareness and validated diagnostic criteria. Most importantly, there are no treatments to prevent the disease. Unprecedented research activity is rapidly changing the scenario. Biomarkers, including those in plasma, have proven good diagnostic performances. The natural history is strikingly similar to that described in sporadic and autosomal dominant Alzheimeŕs disease suggesting that Down syndrome is an optimal population in which to conduct Alzheimer's disease

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Contributors section

JF and MCI devised the paper and invited the other authors to provide parts of the text according to their expertise.

JF and MCI collated and edited the contributions and did additional literature searches. All authors contributed to parts of the paper, reviewed the full paper, and gave final approval.

Search strategy and selection criteria

We searched PubMed for research studies published since database inception until May 2021. All relevant articles relating to Alzheimer disease (AD) in individuals with Down syndrome (DS) were identified for consideration. Search terms include: ("Down syndrome" OR "Down's syndrome" OR Downs) AND (Alzheimer OR Alzheimer's OR dementia). Additional search terms for specific sections were considered. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this Review.

prevention trials. Those disease modifying treatments would not only benefit persons with Down syndrome but also the general population.

1. Introduction

Adults with Down syndrome develop the neuropathological hallmarks of Alzheimer's disease and are at ultra-high risk of developing early onset dementia,[1,2] which is now the leading cause of death in this population.[3] However, diagnosis of dementia remains a clinical challenge due to a lack of awareness from families, caregivers, and clinicians and validated diagnostic criteria, and despite the excellent diagnostic performance of several biomarkers, including those in plasma.[4–6] The most important clinical need is the development of therapies to prevent or delay Alzheimer's disease. Unfortunately, few trials have been performed so far in this population. This situation is rapidly changing as research groups from around the world are creating new consortia and trial-ready cohorts. Down syndrome presents a unique opportunity in which to perform prevention trials due to the higher prevalence of Down syndrome compared to autosomal dominant Alzheimeŕs disease, and its more homogeneous pathophysiology relative to the sporadic late onset form of Alzheimer's disease.

In this Review, we summarise data indicating that Alzheimeŕs disease is the main medical problem and cause of death in people with Down syndrome. We discuss how the natural history and clinical presentation of Down syndrome associated Alzheimer's disease is similar to that of autosomal dominant Alzheimer's disease. Finally, we explain how people with Down syndrome could possibly be the best population in which to conduct Alzheimer's disease prevention trials.

2. Epidemiology

Down syndrome is the most frequent cause of intellectual disability of genetic origin, affecting 5.8 million people worldwide.[7] Improvements in healthcare and management of co-occurring illnesses have greatly increased life expectancy of people with Down syndrome over the last five decades, and individuals older than 40 years represent a rapidly growing population.[8] Consequently, there is an important and urgent need to focus on aging challenges in Down syndrome, with Alzheimer's disease at the forefront.

Clinical research and longitudinal studies consistently estimate the lifetime risk of dementia in people with Down syndrome to be over 90%.[2,4] Dementia is rare before the age of 40 years, but its incidence and prevalence exponentially increase thereafter, reaching 88–100% in persons with Down syndrome older than 65 years (Figure 1).[2]

Importantly, Alzheimer's disease dementia is recorded on 30% [9] of death certificates of people with Down syndrome and is the leading cause of death.[9,10] However, this proportion might be an underestimate because dementia is often not recorded as the cause of death.[9] In a longitudinal study of adults with Down syndrome, dementia was the proximate cause of death in 70% of cases.[3] Future studies should investigate the exact contribution of Alzheimeŕs disease on mortality in Down syndrome.

3. Genetics, pathology, and pathophysiology

Complete trisomy of chromosome 21 is found in 95% of people with Down syndrome; translocations (4%) and mosaicism (1%) occur less frequently. The triplication of amyloid precursor protein gene is both sufficient and necessary to produce early onset dementia in Down syndrome.[11] However, other chromosome 21 genes and consequent imbalance in other chromosomes may also affect the age of onset.[7,12] For example, the *APOE4* haplotype accelerates amyloid deposition and has an earlier symptomatic disease onset by 2 years.[1313,14]

Alzheimer's disease neuropathology is almost universal in adults with Down syndrome by the age of 40 years.[15] The characteristic lesions, including β-amyloid plaques and neurofibrillary tangles are similar in appearance and distribution to those of the sporadic and autosomal dominant forms (Figure 1 appendix), although some presenilin-1 mutations (especially those mutations in exons 8 and 9) display more frequent cotton-wool plaques.[16] The development of the pathology is a decades-long process (Figure 1). The earliest signs of amyloid overexpression are noted as an accumulation within enlarged endosomes and lysosomes, which may start as early as 28 weeks of gestation.[17,18] These enlarged endosomes are more numerous normal-sized and clustered in ultrastructural studies (Figure 2 appendix).[19] Intracellular Aβ within endosomes can promote mitochondrial dysfunction and oxidative damage.[20] Between ages 20 and 30 years β-amyloid systematically deposits as diffuse plaques (although plaques at younger ages have been noted), followed by neuritic plaques in the fourth decade of life.[21,22] Neurofibrillary tangles appear after the initial deposition of β-amyloid in a pattern consistent with Braak staging (Figure 1).[15] This abnormal tau aggregation plays a critical role in the development of dementia in Down syndrome.[23]

β-amyloid also accumulates in the blood vessels of the brain, as cerebral amyloid angiopathy (Figure 3 appendix). In Down syndrome, the extent of cerebral amyloid angiopathy is higher than in sporadic Alzheimeŕs disease.[24] However, it might be lesser than in rare euploid cases with amyloid precursor protein gene duplications,[25,26] which more often present with clinical intracerebral haemorrhages, suggesting possible protective factors in Down syndrome brain.[26–28]

Other pathological substrates have been less studied in Down syndrome. α-synuclein pathology might be found in up to 50% of brains with Down syndrome-associated Alzheimer's disease.[29] In this sense, α-synuclein also appears in very young individuals with autosomal dominant Alzheimer's disease.[30] Phosphorylated TAR-DNA binding protein of 43 kDa (pTDP-43) is significantly reduced in Down syndrome (or autosomal dominant Alzheimer's disease).[31,32] pTDP-43 co-pathology is, thus, relatively rare in younger persons with Alzheimer's disease irrespective of the genetic aetiology.

All these processes can initiate and exacerbate neuroinflammation (Figure 4 appendix), noted as higher levels of expression various cytokines and chemokines,[33,34] and as microglial activation and dysfunction.[34,35] In part, a consequence of neuroinflammation, is significant oxidative damage in the brains of persons with Down syndrome.[36,37] Plasma

inflammatory proteins may be important as a biomarker for Alzheimer's disease in Down syndrome. Two recent studies using a proteomic profile approach found that some of the markers that best discriminate mild cognitive impairment in adults with Down syndrome and distinguished Alzheimer's disease from cognitive stable people with Down syndrome were markers of inflammation.[38,39]

In addition, immune dysregulation is inherent to Down syndrome, which is associated with defects in T-cell maturation, B-cell function, and pro-oxidative state. Four (out of the six) interferon receptors are coded in chromosome 21, leading to a chronic inflammatory state.[40] Finally, several comorbidities associated with Down syndrome, such as periodontitis, [41] might produce a low-grade peripheral chronic inflammation and may influence Alzheimeŕs disease pathophysiology. However, there is still limited data. Further investigation is warranted, as they might offer new avenues for intervention.

4. Clinical presentation and diagnosis

4.1 Diagnosis

There is a long lag (up to 20 years) between the development of pathology and the onset of the prodromal stage of Alzheimer's disease in Down syndrome (Figure 1).[4,15] The diagnosis of prodromal Alzheimer's disease requires a change in cognition from previous level of functioning. Dementia is diagnosed when cognitive decline affects activities of daily living. However, in persons with Down syndrome, the variable degree of premorbid intellectual disability makes these definitions difficult, as well as the validation of population norms.

Figure 2 presents a typical case study and neuroimaging changes across 7 years in a 48-year-old man with Down syndrome. The initial presentation was depressive symptoms but no behavioural changes. Pittsburgh Compound-B PET showed amyloid deposition in the striatum and precuneus and no major atrophy. A follow-up visit 3 years later (age 51 years) showed amyloid accumulation on imaging. Two years later (age 53 years), a diagnosis of prodromal Alzheimer's disease was made; signs and symptoms included lack of motivation, slower thinking, poorer memory, stubbornness, repetitive language, word-finding problems, and an inability to keep up with conversation. Brain atrophy was evident. At a clinical visit 2 years later (aged 55 years), a diagnosis of Alzheimer's disease dementia was made. Both brain atrophy and cognitive decline (as measured by CAMCOG-DS) further progressed. At this visit, [18-F]-AV-1451 PET was done, which showed widespread cortical tau uptake with a typical AD regional distribution.

In the general population, due to dementia mimics and lack of awareness, dementia can frequently be misdiagnosed and underdiagnosed.[42] These problems are exacerbated in Down syndrome due to an even larger lack of awareness from families, caregivers and clinicians. Consultations for cognitive decline are often only done when activities of daily living are substantially affected or when behavioural problems emerge. Given these challenges, population-based health plans in Europe to screen for Alzheimeŕs disease have shown a substantial increase in detection.[43]

The diagnosis of symptomatic Alzheimeŕs disease in Down syndrome is a challenge. Early symptoms can be mistaken as part of lifelong intellectual disability[44] or obscured by coexisting medical comorbidities that might impact cognition, such as obstructive sleep apnoea, hypothyroidism and depression.[45–47] In contrast, due to the younger age of onset of dementia, differential diagnosis rarely includes other neurodegenerative dementias. There are no validated or widely accepted clinical diagnostic criteria. In most specialized clinics and research settings, a physician and neuropsychologist make the diagnosis of prodromal or Alzheimer's disease dementia independently or use a case consensus process.[4,48,49]

4.2. Assessment and neuropsychology

Most neuropsychological test batteries used in the general population are of limited use in adults with Down syndrome, as most individuals score at floor levels. Adapted tests are required, such as the Down Syndrome Mental Status Examination, the Test for Severe Impairment, the Cambridge Cognitive Examination for Older Adults with Down's Syndrome, the Arizona Cognitive Test Battery or the modified Cued Recall Test.[7,15,50–54] Given differences in premorbid intellectual levels, studies have emphasized tracking within-person change over time[4,55] and focused on adjusted clinical cut-offs for screening for Alzheimeŕs disease.[44,50,56] Assessment of decline should be patient-specific, taking into consideration the personal best level of achievement. A caveat is that adults with profound or severe intellectual disability have often been excluded from research, highlighting the critical need for valid and reliable measures of cognitive functioning and dementia symptoms in low functioning adults.[50]

Research advancements over the past 5–10 years provide new insights into the clinical presentation. Much of the early research suggested an initial frontal-type clinical presentation.[57] However, the clinical picture has evolved over the past 5–10 years as a consequence of the creation of large Down syndrome research international consortia,[50,58] which have assembled larger sample sizes and more advanced analytic methods (e.g., meta-analyses and machine-learning approaches) to determine the sequence of cognitive and behavioural changes. Moreover, identification of imaging and fluid biomarkers in the past 5 years has created new opportunities to investigate cognitive indicators of the transition from preclinical to prodromal Alzheimeŕs disease in Down syndrome.

This research now recognizes a similar clinical presentation to that of sporadic and autosomal dominant Alzheimeŕs disease. Declines in episodic memory are consistently reported early in the disease course,[44,55,59–62] particularly in individuals who are amyloid positive at presentation or in those who become amyloid positive in the follow-up.[55] Declines in attention as well as in executive functions are also found early. These initial declines are closely followed by declines in visuospatial ability, verbal fluency, motor coordination and planning.[55,59–62] Direct tests of cognition capture decline earlier than informant reports.[50,59] Also, while mild cognitive impairment in the general population is considered to have minimal impact on functional skills, decline in everyday living skills is seen in people with early prodromal Alzheimer's disease and Down syndrome,[50,63] perhaps because everyday living skills are more cognitively demanding in this population.

4.3. Late onset myoclonic epilepsy in Down syndrome

Epilepsy is one of the most frequent neurological comorbidities in Down syndrome with prevalence estimates of up to 13%.[64] Epilepsy prevalence has a bimodal distribution with onset in early childhood and after the 5th decade of life, the later presentation being in close relation to symptomatic Alzheimer's disease. Up to 75% of adults with Down syndrome and dementia develop epilepsy,[65] a higher proportion than in sporadic (1.5%- 12.7%) and autosomal dominant Alzheimer's disease (2.8%−41.7%).[66] In fact, the occurrence of a first episode of an untriggered seizure after the age 40–45 years is highly suggestive of symptomatic Alzheimer's disease.

The most frequent epileptic seizures in this context are generalized tonic-clonic or myoclonic seizures, which usually coexist and have a morning predominance.[67] Sleep abnormalities might contribute to worse seizure control. The interictal electroencephalograph is variable but might yield a low diagnostic performance. The characteristic epileptiform activity consists in polyspike waves and slow background activity.[68] Due to these specific clinical characteristics the term, "Late-Onset Myoclonic Epilepsy in Down syndrome" has been coined. Given the high risk of recurrence, chronic treatment with an antiepileptic (oftentimes levetiracetam) should be recommended. These epileptic seizures are probably underdiagnosed and inadequately treated.[69]

5. Biomarkers and Alzheimeŕs disease natural history

5.1. Biofluid biomarkers

Cerebrospinal fluid biomarkers are incorporated into the diagnostic criteria for sporadic Alzheimeŕs disease, and commonly used in clinical trials.[57,70] There are fewer studies in Down syndrome, but all have consistently shown a similar biochemical signature of symptomatic Alzheimer's disease, with a 50% reduction in the β-amyloid 42/40 ratio and a two-fold increase in total tau and 181-phosphorylated tau concentrations in symptomatic patients.[4,5,71,72] These cerebrospinal fluid biomarkers have excellent diagnostic performance.[4–6] Some studies suggest synaptic biomarkers such as neurogranin[6] or neuronal pentraxin-2, a protein implicated in inhibitory circuit function,[73] or nerve growth factor pathway biomarkers may also be useful.[74]

Blood-based biomarkers have obvious advantages. The development of ultrasensitive technology, such as Single Molecule Array, has enabled the development of new blood-based biomarkers.[75] Plasma neurofilament light chain concentrations, a biomarker of neurodegeneration, also have excellent diagnostic and prognostic performance.[4,76,77] Although neurofilament light chain concentrations are not specific to Alzheimer's disease, but rather a biomarker of axonal damage, they are highly indicative of symptomatic Alzheimer's disease in Down syndrome, as other neurodegenerative disorders are exceedingly rare.[77]

Novel plasma phosphorylated-tau assays have been recently developed and tested in Down syndrome. A recent study has shown that 181phospho-tau concentrations start to increase in the mid-30s, and are highly accurate for the diagnosis of symptomatic Alzheimer's disease.[78] Plasma concentrations correlate with cerebrospinal 181phospho-tau

concentrations, as well as with neurodegeneration biomarkers such as neurofilament light chain levels, cortical thinning and brain hypometabolism in Alzheimer's disease-related brain regions.[78]

Adults with Down syndrome have higher plasma β-amyloid 1–42 and 1–40 concentrations compared to euploid controls, but these biomarkers have not yet proven to be useful for diagnosing symptomatic Alzheimer's disease.[79,80] Of note, there are no reports in Down syndrome with the novel mass spectrometry techniques that accurately detect brain amyloidosis in sporadic Alzheimer's disease.[81]

Plasma neurofilament light chain and phospho-tau concentrations will most likely change clinical practice and clinical trials in Down syndrome. Admittedly, there are still challenges, shared with the overall Alzheimeŕs disease field, to standardize and develop universal cut-offs for clinical practice. However, impressive advances are being made as a result of enormous efforts and funding. In short, plasma biomarkers can now stage the whole AT(N) framework[82] and have the potential to become useful, easy, and cost-effective screening tools to detect symptomatic Alzheimeŕs disease in Down syndrome.

5.2 Neuroimaging biomarkers

Several studies in the last five years have been performed using multimodal MRI and / or PET with amyloid and tau tracers in adults with Down syndrome.[83]

MRI structural features reflect both neurodevelopmental and Alzheimer's disease related changes in Down syndrome. Neurodevelopmental brain anatomy abnormalities include smaller whole brain volumes and brachycephalia with smaller frontal lobes, hippocampi, cerebellum and brain stem.[84] The atrophy pattern associated with Alzheimer's disease involves posterior dominant cortical thinning with atrophy of hippocampus, thalamus, and striatum in a similar pattern to what is seen in sporadic Alzheimer's disease.[83,85]

Amyloid-PET radioligands indicate the presence of neuritic plaques in accordance with the Thal staging system described in sporadic Alzheimeŕs disease[86] in the parieto-temporal, precuneus, posterior cingulate, and frontal regions. Some adults with Down syndrome might present with initial increased uptake in the striatum, a finding that is described in some cases of autosomal dominant Alzheimer's disease.[87] The significance of this early striatal uptake remains uncertain. It might reflect less efficient clearance mechanisms in the striatum in the context of amyloid overproduction, but this remains speculative.

Studies using ^{18}fluorodeoxyglucose (^{18}FDG)-PET, a measure of regional brain metabolism, also show the same regional pattern of hypometabolism in Down syndrome described in sporadic Alzheimeŕs disease involving the parietal, precuneus and posterior cingulate.[88,89] Of note, some reports show regional hypermetabolism in young individuals with Down syndrome as a consequence of potential compensatory activity and/or less efficient glycolysis.[90–92]

There are a very small number of studies using tau-PET tracers in Down syndrome, but the available data also shows the expected pattern in accordance with the tau Braak staging system.[93,94] As in sporadic Alzheimeŕs disease, tau uptake only occurs in amyloid

positive individuals, and correlates with brain atrophy, hypometabolism as well as cognitive decline.[94,95]

The more frequent cerebral amyloid angiopathy found in pathological studies has a correlate in imaging studies (Figure 3 appendix). Findings on the modified Boston criteria for CAA (i.e. lobar intracerebral haemorrhage, lobar microbleeds, cortical superficial siderosis) are more frequent in Down syndrome than in sporadic Alzheimer's disease, but similar to autosomal dominant cases.[28] Other cerebrovascular disease biomarkers, such as white matter hyperintensities, enlarged perivascular spaces and infarcts, are also frequently found in adults with Down syndrome despite the lower prevalence of traditional vascular risks factors (namely hypertension) compared to the general population.[96] This recent study found a monotonic increase in these markers along the Alzheimeŕs disease continuum suggesting cerebrovascular disease is a core feature of the disease (and not simply a comorbidity). Similar findings are reported in autosomal dominant Alzheimeŕs disease.[97]

More advanced MRI techniques have also been studied in adults with Down syndrome. Using diffusion weighted sequences; the integrity of white matter tracts has been mapped. A pattern of white matter abnormalities is proposed, in which the late myelinating commissural and limbic fibres are affected by disease before the early myelinating ones.[98] Of note, developmental abnormalities in myelination are likely to overlap with those due to Alzheimeŕs disease pathology. Functional MRI also shows pre-symptomatic changes in Down syndrome in the default mode network,[99] the large scale network primarily affected in Alzheimer's disease.

5.3. Natural history

Over the past decade, significant progress has been made in understanding the natural history of Alzheimer's disease in Down syndrome. A predictable sequence of events in biomarker changes begins more than two decades before the onset of dementia, in a strikingly similar order and timing to that described in autosomal dominant Alzheimer's disease.[4,100] Figure 3 compares the sequence of clinical and biomarkers changes in Down syndrome and autosomal dominant Alzheimer's disease.

Cerebrospinal β-amyloid levels decrease after there are widespread diffuse plaques in the brain, beginning in the early 30s, at least 20 years before prodromal Alzheimeŕs disease diagnosis. Of note, there might be a period of pseudo-normality in these levels, as changes might start at younger ages. Thus, higher cerebrospinal fluid β-amyloid 42 concentrations are found in children with Down syndrome than in age-matched euploid controls.[101] Amyloid tracers in positron emission tomography detect plaques a decade later, most likely due to preferential binding of fibrillar deposits. These changes are in agreement with those reported in Dominantly Inherited Alzheimer's disease Network or in the Colombian kindred.[100,102]

Tau biomarkers show a similar dissociation, cerebrospinal fluid and plasma tau are elevated at age 35 years, but increased tau positron emission tomography uptake occurs more than a decade later in amyloid positive individuals.[4,78] A similar gap and time-lag is described in autosomal dominant Alzheimer's disease.[103] Of note, recent work with plasma exosomes

of neuronal origin shows elevated amyloid and tau levels in children and adolescents with Down syndrome opening a new window to study Alzheimeŕs disease pathophysiology.[104]

Different neurodegeneration biomarkers abnormalities begin at different ages. Plasma neurofilament light levels start to increase in the early 30s, but is further increased in the 40s and symptomatic stages. Brain metabolism shows a linear decrease, with significant differences in the late 30s, nearly 13 years before prodromal Alzheimer's disease diagnosis. Hippocampal volumes reflect Down syndrome-associated neurodevelopmental differences, but also show Alzheimeŕs disease-related atrophy in the early 40s. A decline in cognitive scores is observed shortly thereafter. The median age of prodromal Alzheimer's disease diagnosis is around 51 years, and that of Alzheimer's disease dementia between 53 and 55 years.[4,105] Death typically occurs between 57 and 60 years of age.[81,105,106]

In short, clinical and biomarker changes in Down syndrome associated Alzheimer's disease are similar in their direction, magnitude, and temporality to those in sporadic and autosomal dominant forms. Furthermore, the patterns of cerebral amyloid and tau uptake, atrophy, and hypometabolism show that Alzheimer's disease in persons with Down syndrome targets the same cortical regions affected in the other forms.[4]

6. Existing treatments and clinical trials

Currently, there are no approved drugs for the treatment of Alzheimer's disease dementia in persons with Down syndrome. A Cochrane review in 2015 concluded that there is insufficient evidence to determine whether drugs approved for the treatment of sporadic Alzheimer's dementia (cholinesterase inhibitors and the glutamate receptor antagonist memantine) are effective in treating cognitive decline in persons with Down syndrome.[107] Only small clinical trials using drugs approved for treatment of Alzheimeŕs disease in persons with Down syndrome have been performed (e.g. four clinical trials evaluated the efficacy of donepezil in a total of 192 participants and a relatively larger trial in 173 tested memantine).[107,108] However, given the clear evidence of cholinergic deficits in adults with Down's syndrome [109] and the anecdotal evidence that cholinesterase inhibitors might increase survival,[105] a common clinical practice is to use cholinesterase inhibitors, but not memantine.[108] As with many psychotropic medications, there may be increased adverse events in adults with Down syndrome with cholinesterase inhibitors, which are, nonetheless generally well tolerated.[107]

There is a clear ethical imperative to perform clinical trials to reduce disease burden in persons with Down syndrome. Anti-amyloid therapies are obvious candidates and should be tested in adults with Down syndrome with a close monitoring of vasculogenic oedema and haemorrhages given the more prominent cerebral amyloid angiopathy. However, Alzheimeŕs disease has a complex pathophysiology that most likely will require a multidimensional approach including, but not limited to anti-tau and anti-inflammatory therapies. However, despite the clinical need (and advantages), only a handful of such trials have been conducted in adults with Down syndrome in the last 5 years.[110] We highlight several clinical trials in Table 1. In this sense, the ongoing trials and infrastructure built for autosomal dominant Alzheimeŕs disease[111] should inspire progress in Down syndrome.

Down syndrome is arguably the best population in which to conduct Alzheimeŕs disease prevention trials: First, similar to autosomal dominant Alzheimer's disease, adults with Down syndrome have a high risk for developing symptomatic Alzheimer's disease, and a predictable sequence of pathogenic events. Second, Alzheimeŕs disease in Down syndrome is more homogeneous than sporadic Alzheimer's disease, in which many co-pathologies frequently coexist. However, due to the triplication of other genes in chromosome 21, there might be differences in some processes (such as neuroinflammation) that might impact the generalizability of some of the findings.

Figure 4 summarizes the age-spans in which primary and secondary prevention trials as well as trials in symptomatic individuals could be performed in adults with Down syndrome, as well as following the new Food and Drug Administration guidance.[112] The relatively high numbers of people with Down syndrome ensure recruitment for any stage of the disease. Admittedly, there are additional challenges regarding informed consent and feasibility. Nonetheless, the aforementioned studies support that a substantial proportion of adults with Down syndrome are capable and willing perform such trials.

7. Future directions

Randomized clinical trials are the most urgent unmet clinical need for people with Down syndrome. Such trials will require reliable, valid, and sensitive clinical measures for inclusion and monitoring disease progression. A collective effort is underway by the research community, regulators and pharmacological industry to agree on the outcome measures for the different stages of the disease. We are now on the cusp of being able to launch clinical trials utilizing data from a number of longitudinal biomarker studies in this population.[4,48,113]

Another major unmet clinical need is the development of validated and widely accepted diagnostic criteria for the preclinical, prodromal, and dementia stages of Down syndrome associated Alzheimeŕs disease, similar to those developed for sporadic Alzheimeŕs disease by the National Institute of Aging-Alzheimer's Association (NIA-AA criteria),[114] and incorporating standard Alzheimer's disease biomarker data.[138]

There are few studies assessing the relationship of inflammatory and Alzheimeŕs disease biomarkers, and a relative paucity of data longitudinal tau-PET, plasma or cerebrospinal fluid data. Also, more studies assessing the relationships (and interactions) between biomarkers and cognitive decline are needed. Biomarker studies will also elucidate if the AT(N) biomarker classification system can be applied to adults with Down syndrome.[113] Finally, future studies should assess the effects of potential risk and protective factors. These should include cognitive reserve and resilience, genetic studies (both genome wide association studies and the influence of mosaicism, which might temper the phenotype), co-occurring illnesses, as well as socio-demographic and environmental factors.

There are reasons for optimism. Research in Down syndrome-associated Alzheimeŕs disease is benefiting from unprecedented research activity and funding (Table 2). These initiatives

will undoubtedly accelerate the discovery of disease modifying treatments that would not only benefit persons with Down syndrome but also the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests / Conflict of interest statement

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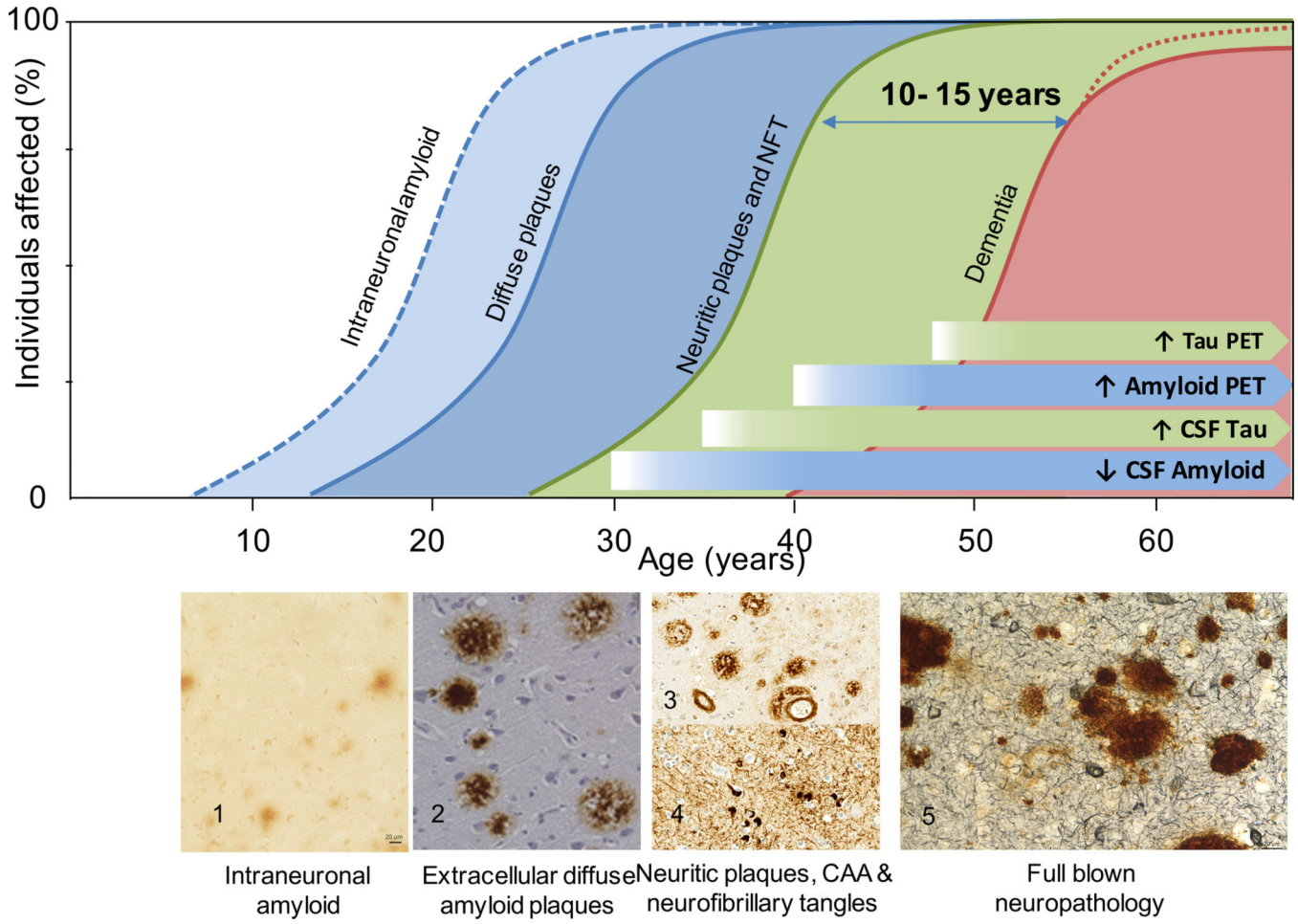

Figure 1: Lifelong accumulation of Alzheimer's disease neuropathology.

Intraneuronal amyloid accumulation starts in the first decade of life (blue dotted line, 1- frontal cortex). Extracellular diffuse plaques (blue line) start in teenagers and are systematically observed after 30 years of age (2- cingulate gyrus). Amyloid deposition progresses with the accumulation of compact neuritic plaques (3- superior temporal gyrus) in the fourth decade. Tau pathological changes are observed starting in the third decade, with subsequent appearance of neurofibrillary tangles in the fourth decade (NFT) (4- superior temporal gyrus). After 40 years pathological diagnostic criteria for Alzheimer's disease are fulfilled (green line,3, 4) and pathological changes continue to increase in severity in old age (5- frontal cortex). Amyloid and tau deposition can be detected through in vivo biomarkers. Cerebrospinal fluid changes occur almost 10 years before they are detectable in PET. After age 40, the prevalence of dementia increases exponentially affecting more than 90% of the adults in those older than 60 years of age (red line).

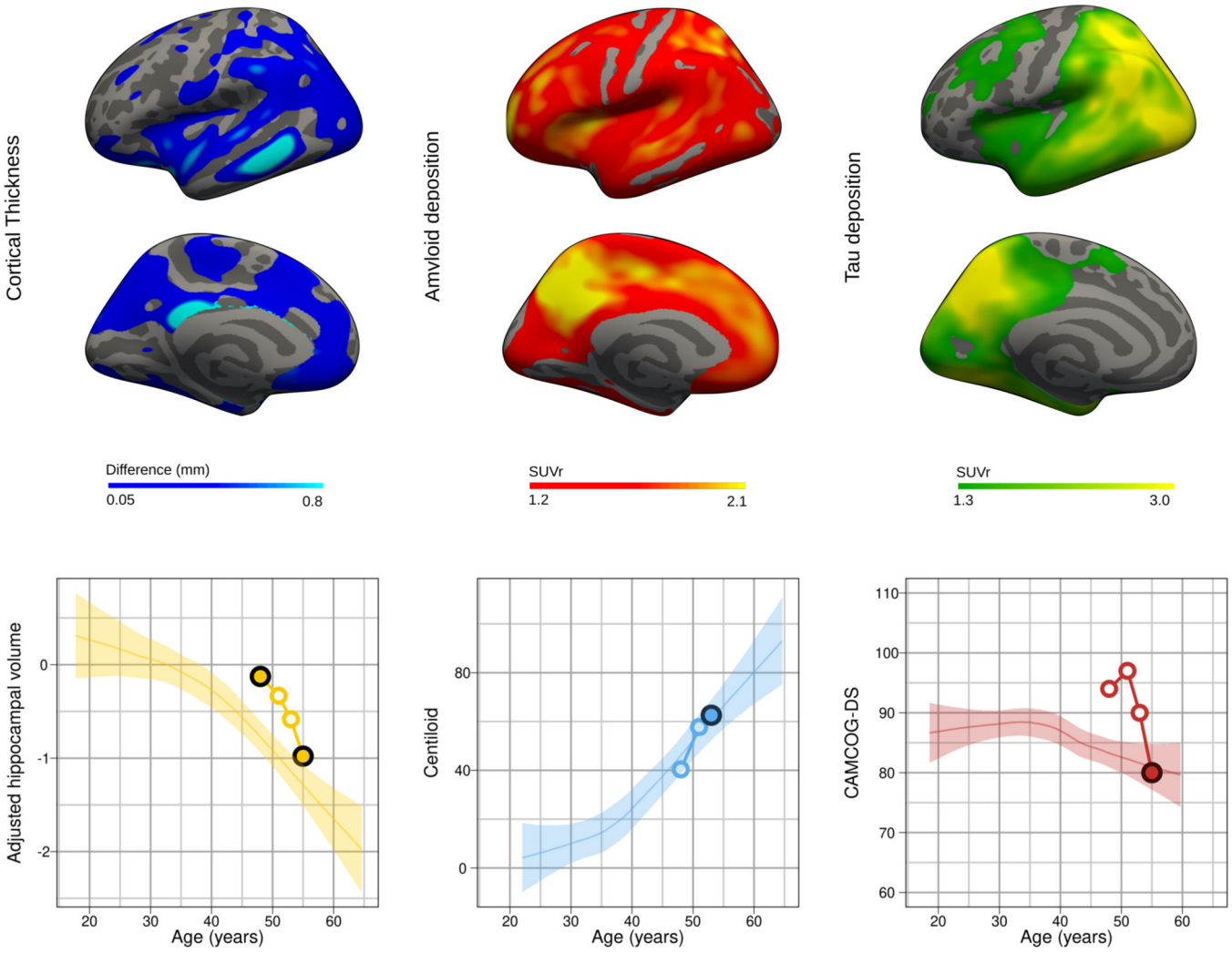

Figure 2. Case study.

The upper row shows the cortical atrophy (difference map between the first and las MRI scan) and both the amyloid and tau PET SUVRs using the Pittsburgh compound B and flortaucipir ligands respectively. The lower row shows the longitudinal intra-individual trajectory of the biomarker changes with respect the described changes with age in Down syndrome as described by Fortea & colleagues.[4] The plotted changes with age for the CAMCOG-DS were those described in individuals with mild intellectual disability.[44] Coloured dots indicate the different timepoints for assessment and black dots indicate the timepoint in which the displayed neuroimage was performed.

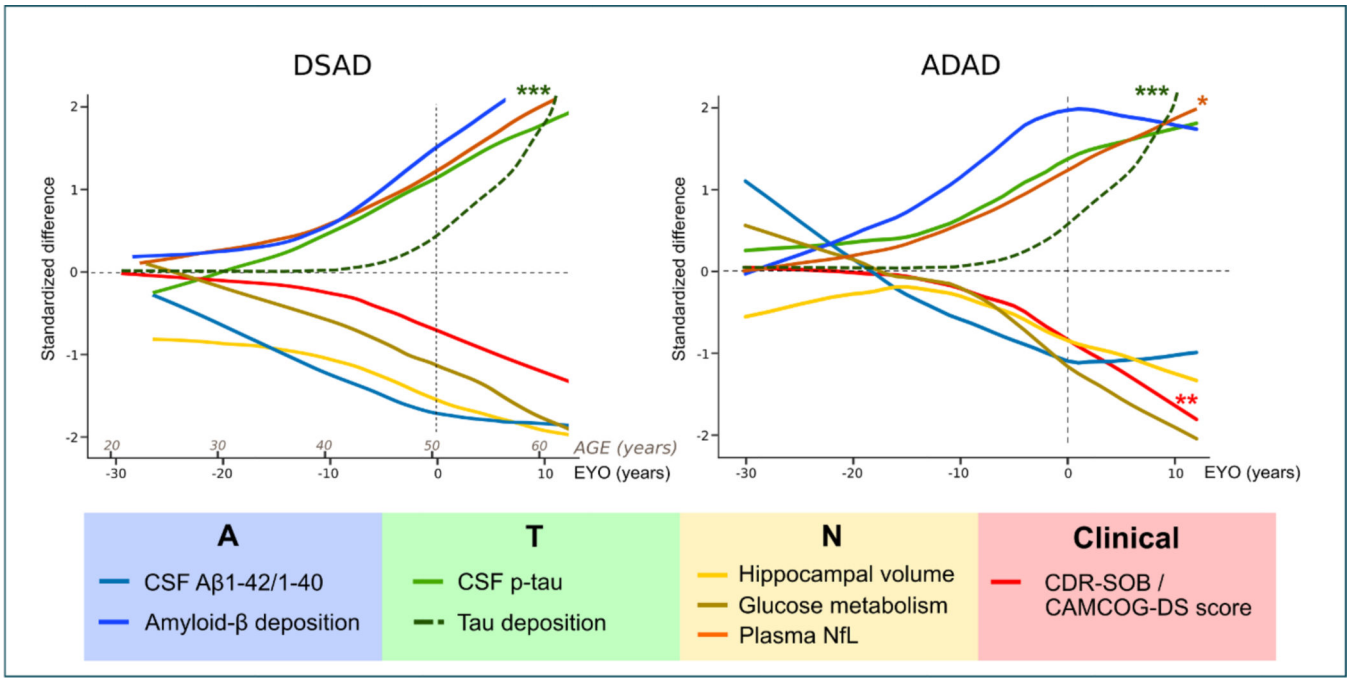

Figure 3: Integrated models of the natural history of Down syndrome-associated Alzheimer's disease (DSAD) and autosomal dominant Alzheimer's disease (ADAD).

Comparison of the clinical and biomarker changes (standardised differences) as a function of age in Down syndrome (left) and autosomal dominant Alzheimer's disease (right).

The DSAD model is based on the study published by Fortea & colleagues[4] and includes a hypothetical for tau uptake in PET (***green dotted line) based on the scarce data in Down syndrome.[93] The ADAD model is based on that published by Bateman & colleagues.[100] We have added the trajectory of plasma neurofilament light based on a large recent study (*orange line),[115] and the hypothetical trajectory of Tau deposition measured by Tau-PET (***green dotted line). We have inverted the trajectory of the clinical dementia rating scale sum of boxes (CDR-SOB) to more easily compare the cognitive changes in ADAD and DSAD.

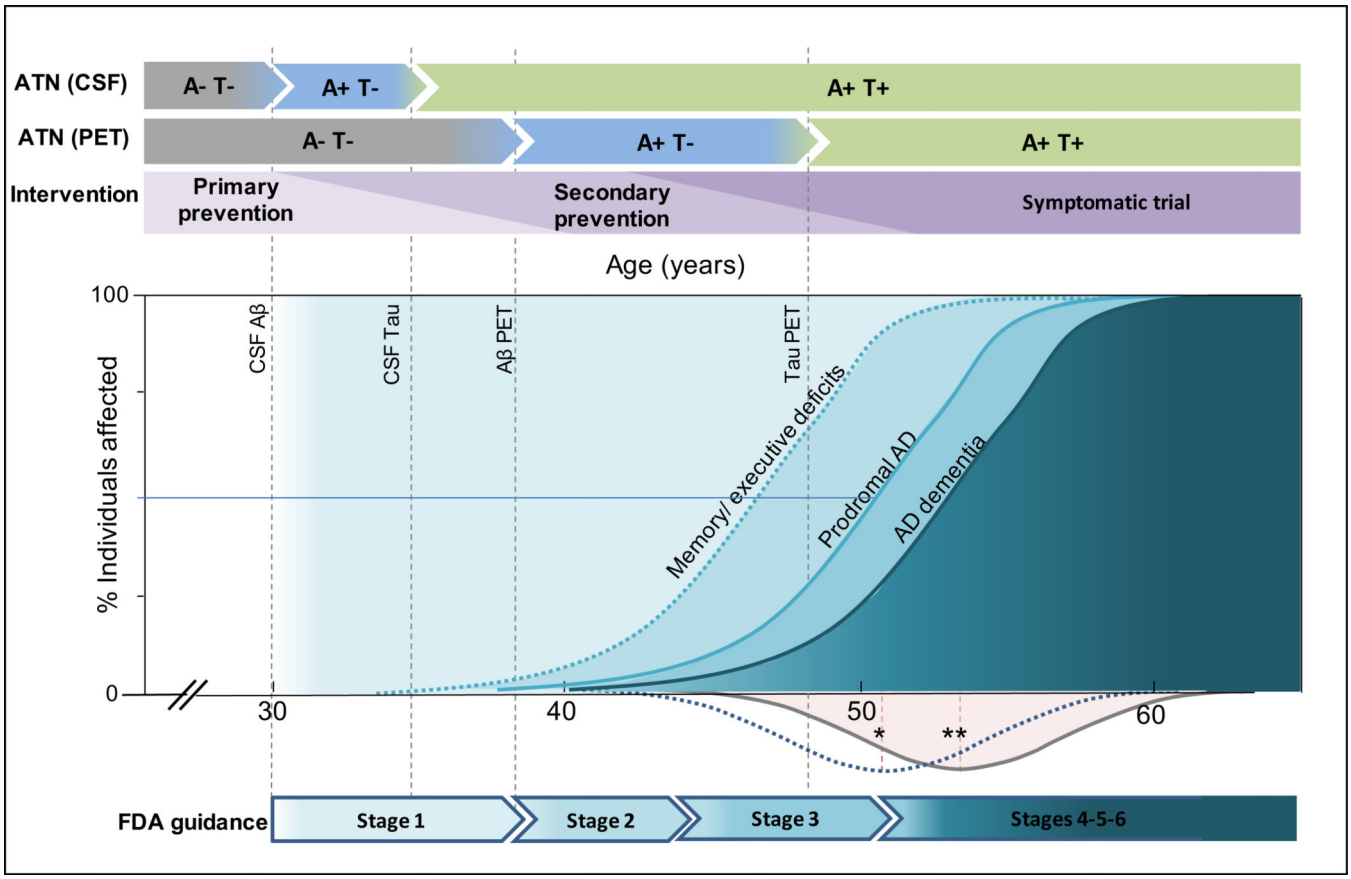

Figure 4. Framework for clinical trials in Down syndrome.

The two upper arrows for the AT(N) reflect the different timings for the earliest changes in CSF and PET, which in turn would affect the definition of primary or secondary prevention trials (third arrow). The model includes the different clinical outcomes reflecting the clinical progression of Alzheimer disease in Down syndrome. Subtle memory/executive deficits can appear from 35 years of age, prodromal Alzheimer's disease appears with a mean age of presentation of 50·8 years (*) while dementia presents with a mean age of onset of 53·8 (**) years of age. The Gaussians below the X-axis reflect de density of prodromal and AD dementia diagnosis in Fortea et al paper.[4] The vertical dotted lines reflect the earliest biomarker changes for the amyloid and tau biomarkers. The lower arrow summarizes the age spans in which different types of intervention trials could be performed in adults with Down syndrome, following the new Food and Drug Administration guidance[o].[112]

Table 1:

Clinical trials of pharmacological interventions for people with Down síndrome

	Study type	Setting	Eligibility criteria	Investigational agent	Dosage	Primary endpoint	Result
NCT01594346	36-month randomised, double-blind, placebo-controlled phase 3 trial	Recruitment occurred at 21 sites with research experience in adults with Down syndrome in five countries (Australia, Canada, Ireland, UK, and USA)	Adults with Down syndrome aged 50 years or older (n=337)	Alpha-tocopherol (vitamin E) versus placebo	1000 international units twice per day orally	Rate of change on the Brief Praxis Test	One or more non-serious adverse event: 96% treatment group *vs* 93% placebo group (p=0·90). Serious adverse events (ie, medical conditions requiring hospitalisation or substantial care): 31·5% treatment group *vs* 32·0% placebo group (p=1·00). No between-group difference in Brief Praxis Test (generalised estimating equation: b=0·159; CI 20·732–1·049; p=0·729).
NCT01791725 (DS201)	4-week randomised, double-blind, placebo-controlled phase 2 trial	Three centres in the USA	Adults with Down syndrome without dementia (n=26)	ELND005 (scyllo-Inositol; cyclohexane-1,2,3,4,5,6-hexol) versus placebo	250 mg once or twice per day orally	Safety and tolerability	Treatment-emergent adverse events: five (41·7%) participants in the 250 mg twice daily group, two (40·0%) in the 250 mg once daily group, and none in the placebo group. All events were mild in intensity.
NCT02738450 (3 Star)	12-month, placebo-controlled, phase 1b multicentre study plus 12-month follow-up	Four centres in the USA	Adults with Down syndrome aged 25–45 years (n=16)	ACI-24 (liposomal vaccine against aggregated β-amyloid peptides) versus placebo	Seven subcutaneous injections of 300 or 1000 μg	Safety and tolerability, antibody titre	Not yet available; a phase 2a trial is planned (NCT04373616

Table 2:

Observational studies of cognition and biomarkers in people with Down syndrome

	Sites	Objectives	Variables
Down Alzheimer Barcelona Neuroimaging Initiative cohort	Population-based cohort of Catalonia (Spain) centralised in a university tertiary hospital	To study the natural history of Alzheimer's disease in Down syndrome through biomarkers; to recruit a trial-ready cohort	Longitudinal clinical and cognitive data; biofluid biomarkers; genetics; neuroimaging biomarkers; sleep studies; EEG; brain banking
The LonDowns Consortium	Four university, clinical, and research centres in the UK	To explore the cognitive, genetic and cellular factors underlying individual differences in susceptibility to Alzheimer's disease; to study individual differences in cognitive abilities and brain activity	Longitudinal clinical and cognitive data; biofluid biomarkers; genetics; neuroimaging biomarkers
Horizon 21 consortium	Ten university, clinical, and research centres from eight European countries (France, Germany, Ireland, Netherlands, Norway, Spain, Sweden, and UK)	To identify factors that influence Alzheimer's disease development in people with Down syndrome; to develop clinical trials to prevent or slow the disease in this population	Longitudinal clinical and cognitive data; biofluid biomarkers; genetics; neuroimaging biomarkers; sleep studies
Alzheimer's Biomarkers Consortium—Down Syndrome	Nine academic centres in the USA and UK	To identify biomarkers of cognitive impairment and dementia; to identify crucial factors that link cerebral amyloid deposition to neurodegeneration and dementia; to understand the relationships between biomarkers; to provide rapid public access to all data	Longitudinal clinical and cognitive data; biofluid biomarkers; neuroimaging biomarkers; genetics
TRC-DS	14 academic, clinical, and research sites in three countries (USA, UK, and Spain)	To analyse the relationships between cognitive measures and biomarkers of Alzheimer's disease; to identify endpoints for Alzheimer's disease clinical trials in people with Down syndrome that best reflect disease progression	Longitudinal cognitive and clinical assessment; biofluid biomarkers; genetics; neuroimaging biomarkers
Lumind IDSC LIFE-DSR	Ten academic centres in the USA	To better understand the cognitive and behavioural changes along with the health issues found in adults with Down syndrome as they progress towards Alzheimer's disease	Longitudinal health examination; blood biomarkers, cognitive measures, MRI, PET scan, CSF biomarkers, plasma biomarkers