Chapter 17
Re-evaluation of diagnosis over time

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Key points

- Long-term follow-up of people with dementia is needed as new symptoms and physical signs may appear and lead to a change in the original diagnosis and prognosis.
- Some causes of dementia may be partially reversible.
- Dementia due to conditions other than Alzheimer's disease may require additional clinical and laboratory assessments.
- As research is progressing on the biological definition of Alzheimer's disease, similar efforts are needed for non-Alzheimer dementias.

This is a chapter of the *World Alzheimer Report 2021, Journey to a Diagnosis of Dementia* which can be accessed in full at: https://www.alzint.org/resource/world-alzheimer-report-2021/

General background

The diagnosis of dementia is primarily clinical and based on the information obtained from the clinical history and physical examination, supplemented by laboratory tests. Over time, new symptoms will emerge, new physical signs will be detectable, and the suspected cause of the dementia may change. This is particularly true with atypical presentations of dementia such as progressive aphasia which may progress into frontotemporal dementia or Alzheimer's disease, dementia with changes in motor tone affecting the neck or one arm may lead to a diagnosis such as Progressive Supra-Nuclear Palsy (PSP) or Cortico Basal Degeneration (CBD), and for a new group of amyloid negative persons who clinically appear like they have Alzheimer's disease. Even more common is dementia with Lewy bodies, with a mix of Alzheimer and Parkinson symptoms. These various diagnostic categories are discussed in the following essays, preceded by an overview on how to manage a change in diagnosis. The need to follow longitudinally, including autopsy studies, people who look like they have Alzheimer`s disease but do not have excessive amyloid in their brain is explained in the final essay of this Chapter.

Reversible dementia or treatable causes of dementia

The clinical diagnosis of dementia may change under certain clinical circumstances. Frequent nutritional deficiencies such as vitamin B1 (thiamine) or B12 can cause dementia symptoms that can be reversed with treatment. Side effects of medications or drug combinations or substance abuse may cause reversible cognitive impairment, evident when the drug is discontinued. In addition, cognitive impairment secondary to autoimmune inflammatory conditions, such as vasculitis, or infectious diseases, such as chronic meningitis, are also treatable with the administration of immunosuppressive or antibiotics, respectively. Finally, neurosurgical interventions can reverse dementia in normal pressure hydrocephalus, subdural haematoma or non-malignant brain tumours (1–3). Therefore, an individual's initial assessment to rule out treatable causes of dementia should be an integral part of the evaluation. A non-exhaustive list of treatable causes of dementia is provided in Table 1.

Table 1. A non-exhaustive list of treatable causes of dementia

- Drug abuse
- Toxic effects of drugs
- Depression
- Metabolic causes
- Thyroid disease
- Vitamin B12 deficiency
- Calcium disturbance
- Liver disease
- Normal pressure hydrocephalus
- Subdural haematoma
- Neoplasm
- Diabetes
- Thyroid disease
- Parathyroid disease
- Cushing's disease
- Addison's disease
- B12, thiamine and nicotinic acid
- Respiratory disease
- Anaemia
- Head injury
- Space-occupying lesions
- Syphilis
- Encephalitis
- HIV

Change in diagnosis

Neurodegenerative dementias do not always follow predictable patterns of progression. While in typical dementia, amnestic individuals frequently exhibit apraxia, aphasia or dysexecutive symptoms as secondary features during the disease course, anterograde amnesia may be the very first manifestation of other conditions. In atypical dementia cases, the diagnosis may also change (4). People meeting the criteria for behavioural frontotemporal dementia may develop motor neuron diseases meeting typical amyotrophic lateral sclerosis phenotype, frequently with bulbar involvement. Psychotic symptoms are particularly observed in carriers of expansions of the C9ORF72 (5).

Cases initially dominated by a cognitive syndrome meeting criteria of behavioural variant of frontotemporal dementia may develop in 24–48 months, with significant aphasia or extrapyramidal symptoms meeting criteria either for the primary aphasia or progressive supranuclear palsy or corticobasal syndrome (6,7). By contrast, behavioural manifestations may arise in those with initial language or motor symptoms. The overlapping between behavioural, language and extrapyramidal syndromes provides insights related to the propagation of brain pathology across cortical regions (6,8,9).

Survey results

The 1,111 multidisciplinary clinicians who replied to the survey indicated that most (69%) have a flexible schedule regarding follow-up visits based on the patient and family needs, 20% followed up every six months, and very few (4%) did so annually (Chart 1). When asked about being at ease with re-evaluating the diagnosis over time as new symptoms emerged, 56% were confident for all types of dementias, 27% for the more common types of dementia, and 17% would refer the person to a specialist.

When asked whether follow-up appointments took place after the initial diagnosis of dementia, most of the 2,327 persons with cognitive complaints or their carers indicated that it took place within two to six months. This was in both high-income countries (HIC) (43%) and low-income countries (LIC) (42%). In the low-income countries, a higher percentage of respondents received a follow-up appointment within one month (30%), compared to high-income countries (14%). In contrast, 13% of those in low-income countries never had a follow-up in comparison to only 3% in high-income countries. In high income countries, 16% had their follow-up appointment 6 months after their initial diagnosis, compared to 8% for those from lower income countries (Chart 2).

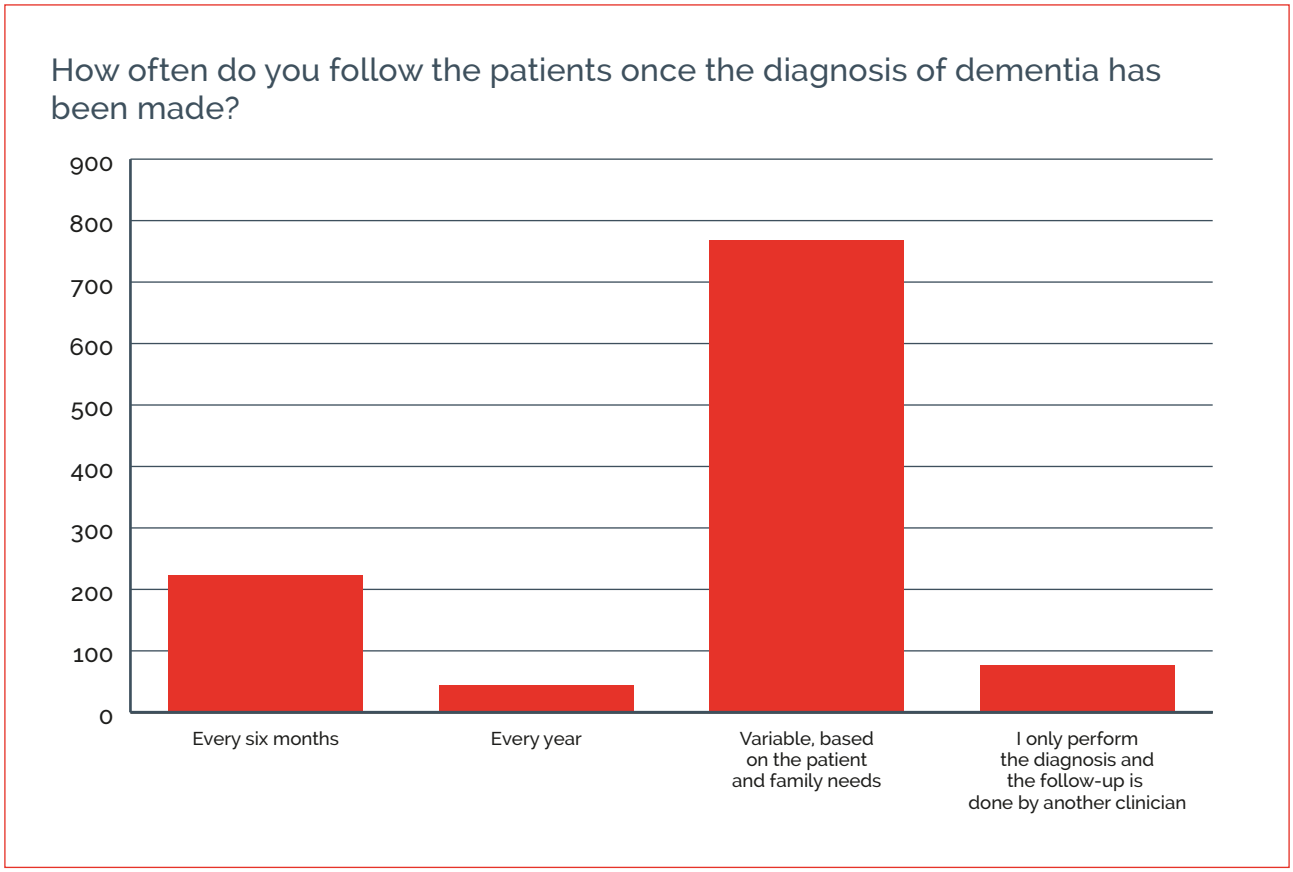

Chart 1. Clinician responses.

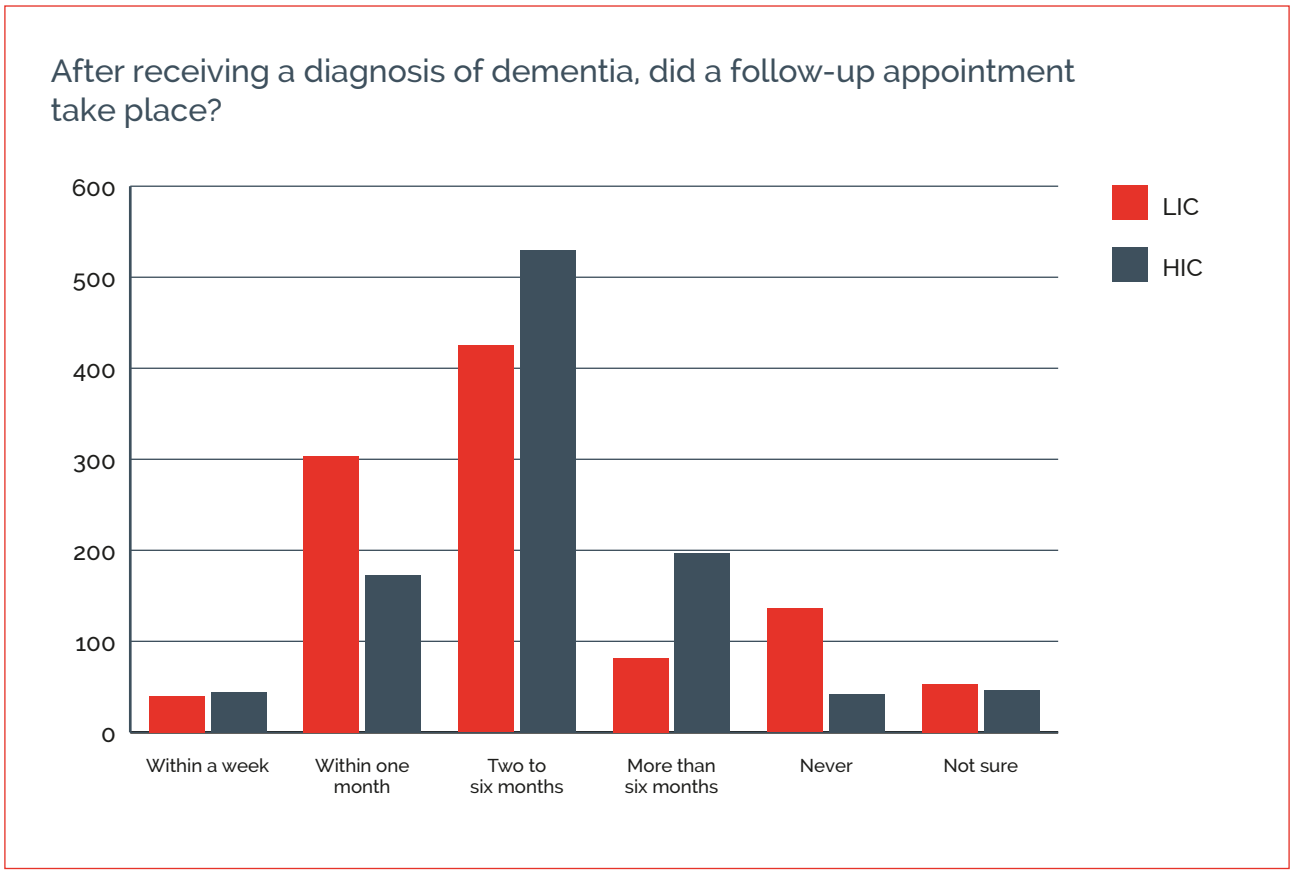

Chart 2. People with dementia and carer responses.

Expert essay

How to tell people with dementia that their diagnosis has changed over time

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The diagnosis of dementia is clinical. It depends on proper identification of the characteristic syndrome, namely cognitive and/or behavioural impairment leading to functional decline, which is not explainable by delirium or by a major psychiatric disorder (1).

Identification of dementia syndrome can be challenging, especially among people with high education levels, where diagnostic sensitivity may be limited at the early stages, as well as among individuals with low educational level, where diagnostic specificity may be initially restricted (2). In this sense, the clinician may consider postponing a dementia diagnosis in situations where there is uncertainty, and this, to avoid any negative effects on the affected individual and their family. It is also important to bear in mind that dementia can be reversible (3) and, in these cases, the initial diagnosis may be revised. Nevertheless, in all these circumstances, follow-up assessments increase diagnostic confidence, allowing adequate care management and support.

Definition of the aetiology of dementia is the second step in the diagnostic workup and is usually more challenging. Blood tests and neuroimaging exams (structural and functional) are the routine ancillary procedures. In recent years, specific diagnostic biomarkers based on biological fluids (for example, plasma and cerebrospinal fluid) and molecular imaging (such as, positron emission tomography with amyloid and tau tracers) have increased diagnostic accuracy of Alzheimer's disease (4), the most common cause of dementia worldwide. Biomarkers for other illnesses related to dementia are also under investigation, with promising results (5). However, diagnosis is not 100% precise and co-pathologies are common, especially among older people, where vascular lesions or brain accumulation of up to four pathological proteins may occur in a significant proportion of people (6,7).

An important additional challenge in the diagnosis and follow-up of individuals with dementia is when the initial aetiological diagnosis proves to be incorrect over the course of the illness. It can happen in scenarios where the clinicians do not have access to specific Alzheimer's disease biomarkers, particularly important for the diagnosis of non-amnestic or atypical cases of Alzheimer's disease, where, for example, a behavioural-dysexecutive phenotype may be misdiagnosed as behavioural variant frontotemporal dementia (FTD) (8).

This situation can also emerge during the longitudinal assessment of non-Alzheimer's disease cases, for which some clinical overlaps are present. A good example applies to the diagnosis of frontotemporal dementia, which encompasses language presentations (primary progressive aphasia variants) and a behavioural variant, besides the associations with motor phenotypes, namely, progressive supranuclear palsy, corticobasal syndrome and motor neuron disease (9). Individuals presenting one of these clinical syndromes may evolve to a second phenotype after months or years. For instance, non-fluent primary progressive aphasia may be the initial clinical manifestation of progressive supranuclear palsy (10). Even genetic cases may modify their cognitive and behavioural profile over time, admitting a different clinical diagnosis. For instance, an individual with genetic frontotemporal dementia (progranulin mutation) initially presented with one of the typical language presentations of the syndrome, yet two years later, manifested prominent changes in behaviour, consistent with the diagnosis of behavioural variant frontotemporal dementia (11). The two examples above illustrate the phenotypical heterogeneity found in frontotemporal dementia and in other degenerative dementias.

How can the clinician respond to such modifications of diagnosis that may emerge with time and adequately communicate it to people with dementia and their families? Interestingly, in a recent Dutch study where the consultations of people with dementia were audio recorded and clinicians were prompted to ask questions from a prepared list of 25 topics, only 10% of people or their partners began a discussion within one of the listed topics and, when this occurred, they usually asked about the least frequently addressed issues (12). These results indicate that clinicians' expectations about what is important to be discussed may not coincide with the opinions of people with dementia and their families. Hence, a key point is to initially ask them what they want to know about their brain health problem. Clinicians need to

understand the individual and familial context, the doubts and worries, and to address all questions openly and in the clearest possible way.

Bear in mind that the ancillary methods (such as blood tests and structural neuroimaging) currently available in most settings allow the clinician to determine with high diagnostic confidence if the dementia is potentially reversible or not, as well as to figure out if the aetiology is most likely degenerative or non-degenerative. This latter aspect is crucial when discussing the prognosis and providing the necessary direction regarding advanced care planning and personal decisions that the person with dementia may need to make (13). Moreover, we must acknowledge that the medical diagnostic process is not necessarily without errors. This applies to most medical specialties (14).

Diagnostic disclosure of dementia and related conversations should be delivered in a clear way, from the explanation about the syndrome to how the specific aetiology has been considered. Wording must be intelligible, taking into consideration the cultural, educational, and social background of the person with dementia and their family. The clinician should remember that is preferable to say 'I'm not sure' or 'the diagnosis is not yet defined' when facing a complex situation, emphasising the importance of follow-up and repetition of complementary tests, if necessary, to increase diagnostic certainty. Clear information that the diagnosis may change with the emergence of more typical signs and symptoms after some time, or that a second clinical syndrome can appear in the context of specific forms of dementia (for example, frontotemporal dementia), should also be provided. It is important to highlight that in many instances, pharmacologic and non-pharmacologic treatments aimed at dementia symptoms shall be recommended regardless of the aetiological diagnosis. In this sense, the clinician must ensure that the person receives the best available care and support.

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Expert essay

Progressive Supranuclear Palsy: clinical diagnosis

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Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative disorder presenting with parkinsonism of insidious onset, other neurological features and progressive course. The incidence of PSP increases with age, and some studies suggest that men are more affected than women (1). Its prevalence varies across studies, ranging from 5 to 18 cases per 100,000 people (2). Despite its low prevalence, PSP is the most frequent cause of atypical parkinsonism.

Pathologically, PSP is a tauopathy classified as a form of frontotemporal lobe degeneration (2). A neuropathological exam usually reveals neurofibrillary tangles and/or neuropil threads in the brainstem and in the basal ganglia, usually associated to gliosis and neuronal loss (2).

PSP was first described by Steele, Richardson and Olszewski in 1964. Since then, it is recognised as a clinical syndrome with marked clinical heterogeneity (3). The original description is now referred as Richardson's syndrome (PSP-RS), which remains the most frequent phenotype (2,3). PSP-RS presents with early postural instability, vertical supranuclear gaze palsy, slow or hypometric saccades, levodopa-resistant bradykinesia, axial rigidity, dysarthria and dysphagia. The other associated phenotypes are PSP with predominant frontal presentation; PSP with corticobasal syndrome; PSP with predominant speech or language disorder; PSP with progressive gait freezing; PSP with predominant parkinsonism, and PSP with predominant cerebellar ataxia (3). This remarkable clinical heterogeneity represents a major diagnostic challenge, as the diagnosis of PSP may be confounded or overlap with other neurodegenerative disorders, such as Parkinson's disease, behavioural variant frontotemporal dementia, corticobasal syndrome and primary progressive aphasia.

In addition to motor features, PSP also presents with cognitive changes. Cognitive dysfunction in PSP has been classically described as a 'subcortical dementia', characterised by bradyphrenia and executive dysfunction due to frontal lobe involvement (4). However, more recently, it has been demonstrated that people with PSP have deficits in more complex cognitive abilities, such as conceptual thinking and social cognition (5,6).

In addition, people with PSP also have prominent behavioural changes. Apathy is the most frequent behavioural disorder, detected in up to 62% of people (7). Some symptoms related to frontal lobe dysfunction, such as eating disorders, impulsivity and stereotypic behaviour may also be observed (7).

The diagnosis is established on clinical grounds, according to the consensual diagnostic criteria proposed by the Movement Disorders Society (8) and requires detailed clinical history and neurological exam. Disease onset usually occurs at the seventh decade (1). People with PSP-RS report a history of recurrent, unprovoked falls and postural instability, which are present early in the disease course. Typically, they tend to fall backwards. They, as well as their carers, may also complain of cognitive and behavioural changes.

Careful neurological examination is the cornerstone of the diagnosis and usually demonstrates an abnormal response of postural reflexes. Other common findings are axial and symmetrical parkinsonism and pseudobulbar syndrome. The most typical feature of PSP-RS is the downward gaze palsy. Of note, it often appears after three or more years of disease onset. There are also other neuro-ophthalmological findings: slowing of saccades; reduced blinking; eyelid apraxia and blepharospasm. The vertical wrinkling of the forehead, known as the 'Procerus sign', is a clinical clue for the diagnosis of PSP, although it is not present in all people. Similarly, the 'applause sign' (the tendency to keep applauding after being instructed to only clap three times) may be observed in PSP people but lacks specificity (9).

Neuroimaging provides supportive evidence for the diagnosis, although these changes often appear late in the course of the disease. Structural brain magnetic resonance imaging (MRI) usually shows mild to moderate prefrontal atrophy, atrophy of the superior cerebellar peduncles, and marked midbrain atrophy. The latter, the most frequent sign on an MRI, is described as 'penguin', 'hummingbird' or a 'morning glory' sign. Notably, although rather specific, these findings lack sensitivity (2). Quantitative analysis of the pons: midbrain ratio increases the sensitivity to predict the diagnosis of PSP-RS (2).

Individuals with PSP usually exhibit impaired binding of pre-synaptic dopamine transporter in the striatum on functional imaging (1). However, this finding is also present in other parkinsonian disorders and is not useful for the differential diagnosis. On the other hand, there are no reliable wet biomarkers for PSP.

More recently, the advent of molecular neuroimaging (for example, positron emission tomography [PET]) with tau markers provide the in vivo pathophysiological diagnosis of tauopathy in people with different types of parkinsonism. However, while PET-tau is expensive and restricted to a few research centres, its clinical usefulness still lacks validation. In the perspective of disease-modifying treatments, it is possible that in vivo demonstration of tauopathy may be required as inclusion criteria for the selection of individuals in clinical trials.

PSP may be mistaken for other neurodegenerative diseases, especially in the initial stages, when the typical oculomotor features are lacking. The differential diagnosis may be a tough conundrum and involves Parkinson's disease and other forms of atypical parkinsonism, such as multiple system atrophy, corticobasal syndrome, dementia with Lewy bodies, and others. People with prominent behavioural symptoms may be misdiagnosed as behavioural variant frontotemporal dementia. Asymmetrical parkinsonism, absence of falls, psychosis and clinically relevant response to levodopa should lead to a reconsideration of the PSP diagnosis.

In summary, the diagnosis of PSP is based on accurate clinical history and neurological exam. Midbrain atrophy on structural brain MRI supports the diagnosis in suspected patients. The absence of reliable biomarkers and the clinical heterogeneity of PSP represent a diagnostic challenge. The next advances on biomarkers and molecular neuroimaging may provide valuable tools for the diagnosis and follow-up of people with PSP.

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Expert essay

The silent minority of persons with Alzheimer-like symptoms but no amyloid build-up in their brain: what is their diagnosis?

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Introduction

Alzheimer's disease is defined by the accumulation of cerebral amyloid-β plaques and intracellular neurofibrillary tangles comprised of 3R+4R hyperphosphorylated tau (1), which are thought to lead to neurodegeneration. Accepted biomarker models of Alzheimer's disease derived from autosomal dominant (2) and sporadic (3) populations provide converging evidence that detectable amyloid-β abnormality precedes detectable tau abnormality by several years. Amyloid-β accumulation often occurs in the absence of symptoms, while the topographical distribution and magnitude tau accumulation and tau-mediated neurodegeneration are more closely related to the clinical presentation that characterises Alzheimer's disease. While details of the process remain poorly understood, multiple studies support the notion that elevated amyloid-β levels are required for the propagation of tau pathology from the medial temporal lobe to regions of the neocortex, associated with severe cognitive symptoms (4).

Multiple recent in vivo Alzheimer's disease biomarker studies support the notion that tau abnormality (T+) occurs almost exclusively in the presence of amyloid abnormality (A+) (5,6). T+ is more closely associated with N+ and with cognitive impairment. While the general pattern from these studies supports A+ as a requirement for T+, a non-negligible portion (generally <5%) of subjects are defined by elevated tau pathology (T+) without abnormal amyloid (A-) (5,6).

An especially interesting finding is the rare pattern of A-T+N+ in individuals who are diagnosed with probable Alzheimer's disease (6). According to 2018 NIA-AA criteria (1) as well as consensus neuropathological criteria for Alzheimer's disease (7), these individuals do not have Alzheimer's disease, which requires the presence of abnormal amyloid. An important question arises:

What is the diagnosis for individuals with the A-T+N+ profile and an Alzheimer phenotype?

The 2018 NIA-AA research framework for biological Alzheimer's disease labels the A-T+N+ biomarker profile in individuals with dementia as 'non-Alzheimer pathologic change with dementia'. This concept is supported by evidence that amyloid-β accumulation occurs years before tau and subsequent tau-mediated neurodegeneration (2,3).

If not Alzheimer's disease, where does the A-T+N+ biomarker profile point us to in cases of amnestic dementia? Several neuropathology studies have described a condition termed Neurofibrillary Tangle Predominant Dementia (NFTPD), characterised by neurofibrillary tangle accumulation (T+) in the absence of significant amyloid-beta plaques (A-), with a clinical phenotype that resembles probable Alzheimer's disease.

Outside of their different biomarker profiles, some differences exist between Alzheimer's disease and NFTPD which may give clues about its aetiology. People with NFTPD are generally older than people with Alzheimer's disease, their cognitive dysfunction is milder, their cognitive decline is typically slower, and they are very rarely APOE4

carriers (8). Autopsy studies suggest another important difference: aside from the absence of amyloid-β plaques, NFTs in NFTPD are more limited in both topography and magnitude than in Alzheimer's disease. NFTPD is characterised by extensive tau accumulation in allocortical regions, but only mild involvement of neocortical regions, typically extending only as far as Braak stages III or IV (8). In contrast, people with advanced Alzheimer's disease typically display tau accumulation in Braak stages V and VI.

Overall, NFTPD highlights important limitations of collapsing continuous biomarker measurements with topographical information into dichotomised categories. While they are T+, the milder spatial extent of their tauopathy suggests that it may not be identical to the T+ that characterises Alzheimer's disease. Furthermore, the lower magnitude of tau aggregation in this condition may indicate that despite surpassing a threshold for T+, the magnitude of tau pathology is not identical to what is observed in Alzheimer's disease.

Conceptual and methodological considerations

Despite differences in clinical and neuropathological data, it is difficult to conclude with certainty whether a biomarker profile of A-T+N+ equates with NFTPD in living individuals with amnestic dementia. One important possibility is that individuals with a A-T+N+ biomarker profile are not truly A-. For example, dichotomisation into positive/negative groups will by definition classify individuals just under the positive/negative threshold as negative. Despite the advantages of binary classification for diagnosis and clinical trial recruitment, binary cut points without biological bases may result in misclassifications. Correspondingly, it may be important to consider A biomarkers as continuous values in cases of suspected A-T+N+.

A related conceptual issue is that an A- status does not signify the absence of cerebral amyloid-β: rather, it signifies that this individual has not crossed a specific predetermined threshold of abnormality. It is conceivable that certain vulnerability factors in some individuals permit the Alzheimer's disease pathogenic process to unfold at lower concentrations of amyloid-β abnormality (9).

Remaining questions

A comprehensive understanding of A-T+N+ cases is limited by their low prevalence: estimates place NFTPD prevalence at between 0.7% and 5.8% of dementia cases (8), and population-based Alzheimer's disease biomarker studies estimate the prevalence of the A-T+N+ profile to be between 5–10% at age 80, with even lower prevalence at younger ages (10).

A number of questions remain unanswered. While A-T+N+ individuals will almost certainly not be eligible for anti-Aβ therapeutic trials, would they be eligible for anti-tau therapies? Special considerations of testing therapies in rare diseases may apply to these individuals.

Despite the limitations described above, Alzheimer's disease biomarkers are critical for separating individuals with the A-T+N+ profile accompanied by amnestic dementia from those with Alzheimer's disease. There is hope that given similar disease processes that anti-tau treatments designed for Alzheimer's disease may be beneficial to individuals with a A-T+N+ biomarker profile.

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Expert essay

Dementia with Lewy Bodies

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Lewy bodies, an intracellular protein aggregate, were first described in the context of Parkinson's disease (1). Further studies revealed widespread cortical Lewy bodies in people presenting with progressive dementia (2). Due to its distinct clinical and pathologic findings, this form of dementia was proposed by Kosaka in 1976 to be a different cause of cognitive impairment (3,4), namely Lewy body disease. Later, this diagnostic category was recognised by the scientific community and came to be known as dementia with Lewy bodies (DLB).

Initially thought to be a rare cause of cognitive impairment, the discovery of α-synuclein (a protein) as the main component of Lewy bodies by Spillantini et al. in 1997 (5) as well as the development of α-synuclein immunohistochemistry staining (a way of visualizing the protein in the microscope) allowed greater sensitivity in the detection of the disease in post-mortem samples and revealed dementia with Lewy bodies to be the second most common cause of dementia (6).

Among people newly diagnosed with dementia, 3.1–7.1% fulfil the diagnostic criteria for dementia with Lewy bodies, with an overall incidence of 0.5–1.6 per 1000 person-years. Nonetheless, widespread cortical Lewy bodies can be found in 20–25% of the brains from people who died with dementia (7), as compared to 13.4% of those that died without cognitive impairment (8). These findings suggest that dementia with Lewy bodies may be underdiagnosed by current clinical criteria.

Diagnosis

Published in 2017, the Fourth consensus report of the dementia with Lewy bodies consortium establishes the current clinical criteria for the diagnosis and management of dementia with Lewy bodies (9), Table 1.

As an essential feature for the diagnosis of dementia with Lewy bodies, the person should be diagnosed with dementia, that is, a progressive cognitive decline that interferes with social and occupational functioning as well as activities of daily living. Other features include cognitive, psychiatric, motor and other symptoms and are classified as either core or supportive clinical features. Biomarkers (either imaging or laboratory exams) may further contribute to the diagnosis.

In summary, distinctive characteristics of dementia with Lewy bodies include but are not limited to fluctuating cognition; visual hallucinations; rapid eye movement (REM) sleep behaviour disorder; and parkinsonism (either bradykinesia, manifesting with slow and decreasing intentional movements, muscle rigidity or rest tremor). These will be further characterised in the following paragraphs.

Cognitive and neuropsychiatric symptoms

In contrast with Alzheimer's disease-related cognitive impairment, memory is relatively preserved in early disease. Cognitive decline is mostly seen regarding attention (such as being unable to follow a film or TV series), executive function (for example, loss of multitasking skills) and visuospatial skills (such as difficulties parking a car, more frequent GPS use, 'missing' the chair when sitting). The presence of fluctuations, waxing-and-waning, variable attention and cognitive activity in early stages is a core feature of dementia with Lewy bodies. These may present as spells of altered attention, incoherent speech, daytime sleepiness or staring into space with variable duration from minutes to hours, occurring rarely at first then increasing up to a daily basis.

Visual hallucinations, like seeing people, children and small animals, is commonly observed in the early stages and is also a hallmark of dementia with Lewy bodies (9). Later in the disease course, delusions (irrational, fixed beliefs) may become more prominent and disabling, often with paranoid content (10).

Changes in sleep should also be noted, as violent movements, agitation and shouting during sleep are the key symptoms of the REM sleep behaviour disorder. This is a very frequent phenomena in people with dementia with Lewy bodies and may predate the cognitive impairment by years (11). Although a bed partner report of violent behaviour and shouting is highly suggestive of this disorder, a polysomnographic study is needed for diagnostic confirmation (9).

Apathy, depression and anxiety are common symptoms in dementia with Lewy bodies and may be present before characteristic symptoms and cognitive decline (11).

Parkinsonism

Bradykinesia (slow body movements), muscle rigidity and resting tremor, as seen in Parkinson's disease, are also core features in dementia with Lewy bodies. However, unlike Parkinson's disease, these present concurrently or after the cognitive symptoms, usually isolated (that is either bradykinesia, rigidity or tremor) and symmetrically, affecting left and right limbs at the same time and with the same intensity (9).

Posture and gait difficulties are present during the disease course and occur earlier than seen in Parkinson's disease. Along with visuospatial disturbances and postural hypotension (as described in the upcoming sections), these features increase the risk of falling for people, potentially causing significant distress and clinical deterioration (12).

Dysautonomia symptoms

The loss of control over bodily functions, medically defined as dysautonomia, is an important phenomenon in dementia with Lewy bodies. Some of these symptoms may occur early in the disease course, such as constipation, and others are usually a concern in advanced stages, such as orthostatic hypotension (an abrupt decrease in blood pressure after one stands) and urinary incontinence (10).

Treatment

Currently, no treatment is available to cure dementia with Lewy bodies or to control the underlying process causing the disease. Nonetheless, pharmacological and non-pharmacological therapies may offer relief to the most distressing symptoms (13).

Pharmacological treatment

The use of acetylcholinesterase inhibitors, a group of medications for the treatment of Alzheimer's disease, has been shown to ameliorate cognitive performance and slow its decline. Among those, rivastigmine and donepezil have been studied in double-blind randomised trials with positive results (14).

Neuropsychiatric symptoms such as hallucinations and delusions are best treated by optimising the use of the drugs mentioned above. However, residual symptoms may persist and, in these cases, some antipsychotic drugs, namely quetiapine and clozapine, may be used with caution. Other antipsychotics, especially typical ones such as haloperidol, severely exacerbate parkinsonian symptoms and are contraindicated. Pimavanserin, a novel drug for the treatment of neuropsychiatric symptoms in Parkinson's disease, has been proposed as an alternative in people with dementia with Lewy bodies (15).

Other symptoms are treated similarly as with other diseases, such as with the use of blood-pressure raising medications in orthostatic hypotension, anti-depressants for anxiety and depressive symptoms (14).

Non-pharmacological treatment

Most studies have shown benefits with non-pharmacological approaches to dementia with Lewy bodies. Low cost and low likelihood of side effects make the use of some of these approaches very reasonable (15),

Carer education is fundamental in dementia. Plain language orientation regarding possible symptoms, disease progression and potential complications should always be available to carers. Special aspects of the disease, such as visuospatial impairment, posture instability and orthostatic hypotension, should be emphasised as they predispose the person to preventable burden.

Table 1. dementia with Lewy bodies clinical criteria (adapted from (9))

Essential: Dementia

Core clinical features:

- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations
- REM sleep behaviour disorder
- Parkinsonism

Supportive clinical features:

- Severe sensitivity to antipsychotics
- Postural instability
- Repeated falls
- Syncope
- Severe autonomic dysfunction
- Increase somnolence
- Loss of the sense of smell
- Other hallucinations
- Delusions
- Apathy, depression, anxiety

Task-oriented occupational therapy, through motor practice and task adaptation, may enhance and slow the loss of fundamental abilities, such as activities of daily living. Supervised exercises and physical therapy reduce motor function decline, including gait and postural instability (15).

Prognosis

Cognitive decline seems to be faster in dementia with Lewy bodies than in Alzheimer's disease (16). As a consequence, quality of life in people with dementia with Lewy bodies is substantially decreased (17) and carer burden increased (18) when compared to their Alzheimer's disease counterparts.

Hospital admissions are also more frequent in dementia with Lewy bodies, mainly due to falls, pneumonia and cognitive fluctuations, frequently misinterpreted as delirium (19). Mortality is increased compared to the general population, with almost 4 times greater risk of death and an average survival of 4.7 years after diagnosis (20).

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Expert essay

Alzheimer's disease: separating the clinical from the biological

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Introduction

The field of Alzheimer's disease research has undergone important conceptual changes in recent years, guided by the evolving understanding of Alzheimer's disease biology. This article will briefly review previous definitions of Alzheimer's disease before describing the current conceptualisation as a biological entity characterised by the accumulation of amyloid-β plaques and tau neurofibrillary tangles.

The first diagnostic criteria for Alzheimer's disease were introduced in 1984 (1). In the 1984 framework, individuals who had progressive memory impairment that led to dementia (without other attributable causes) were labelled as 'probable Alzheimer's disease'. Definitive diagnosis could only be given at autopsy in the presence of amyloid-β plaques and tau neurofibrillary tangles. While the 'probable Alzheimer's disease' diagnosis was associated with higher sensitivity and specificity for amyloid-β plaques and tau neurofibrillary tangles at autopsy, imperfect agreement between the two assured the need for the 'probable' term to be applied to living individuals, though it was often omitted (2).

Revisions in 2011, commissioned by the National Institute of Aging (NIA) and the Alzheimer's Association (AA), retained the core clinical features of probable Alzheimer's disease from 1984 and the notion of Alzheimer's disease as a clinico-pathological entity (3). Importantly, following the progress in research of other neurodegenerative diseases that resulted in dementia, Alzheimer's disease dementia was separated from all-cause dementia. The 2011 framework also integrated advances in in vivo biomarkers of amyloid-β and neurodegeneration, which could be used to support the clinico-pathological relationships.

In 2014, the International Working Group (IWG), an independent group of researchers, described Alzheimer's disease as a combination of clinical symptoms (amnestic dementia or a non-amnestic 'atypical' phenotype) in combination with biomarker evidence of Alzheimer's disease pathology (4). Thus, Alzheimer's disease remained an entity defined by symptoms, with biomarkers used to support the diagnosis.

In 2018, following rapid advances in tau biomarkers (specifically tau-PET), the NIA-AA revised its research framework to diagnose Alzheimer's disease based on the concurrent presence of both abnormal amyloid-β and tau biomarkers, regardless of cognitive symptoms (5). Therefore, the 2018 framework extends the neuropathological definition of Alzheimer's disease in place since the 1990s (6) by applying in vivo biomarkers of amyloid-β and tau to living individuals. In the recent biological research framework, individuals can be grouped according to their Amyloid-β/Tau/Neurodegeneration [A/T/(N)] biomarker status. A and T are biomarkers considered specific to Alzheimer's disease, while the (N) is stylised in parentheses to denote the fact that it is also a feature of other neurodegenerative diseases. In the 2018 framework, the 'probable Alzheimer's disease' clinical presentation of progressive amnestic multidomain cognitive impairment resulting in dementia is now termed 'Alzheimer Clinical Syndrome' (5).

Advantages of a biological framework

The immediately obvious advantage of the transition to a biological research framework is that Alzheimer's disease is now specific to a biological process, and not a set of clinical symptoms.

Multiple neurodegenerative processes can result in a clinical presentation that resembles the Alzheimer's disease phenotype; this is part of what makes an accurate Alzheimer's disease diagnosis based on clinical symptoms so challenging. Adopting a consistent biological definition of the disease helps ensure that different research groups are indeed discussing the same thing. The alternative clinical definition of progressive amnestic multidomain cognitive impairment collapses many different disease processes into one term. In fact, the 'probable Alzheimer's disease' clinical syndrome can be caused by other diseases. Differentiating

Alzheimer's disease from these other conditions will also allow for the recognition and treatment of other causes of cognitive decline.

A second important advantage of the biological research framework is that Alzheimer's disease can now be studied in asymptomatic persons. The abnormal protein accumulation that characterises biological Alzheimer's disease takes place over a longer time frame (estimated 10–20 years) than the time frame of Alzheimer's disease symptoms (4–8 years). There is hope that targeting biological Alzheimer's disease during the preclinical phase will result in better outcomes than the multiple trials conducted in individuals with symptomatic Alzheimer's disease.

Criticisms of the biological Alzheimer's disease framework

A common criticism levied against the biological definition of Alzheimer's disease is that biomarkers are either expensive, unavailable, or both. This is a fair criticism that reflects deeply rooted inequities in the access to medical care and systematic inequalities in healthcare technology. While this criticism is legitimate, the hope is that developments in blood-based biomarkers of Alzheimer's disease (7) will allow for Alzheimer's disease biomarker studies to be conducted at lower costs and without the need for highly specialised equipment.

Another criticism raised against the biological definition of Alzheimer's disease is that amyloid-β plaques and tau neurofibrillary tangles often occur in individuals without cognitive impairment, and therefore should not be used to define a disease. While it is correct that biological Alzheimer's disease can be detected in individuals without overt cognitive symptoms, this observation helps identify individuals at risk for the development of cognitive symptoms, with the hope of treating Alzheimer's disease before symptoms develop. Preclinical Alzheimer's disease (abnormal levels of amyloid-beta and tau in the absence of clinical symptoms) can be considered analogous to preclinical disease in other areas of medicine.

A third important criticism of the Alzheimer's disease biological framework is that it does not include other common pathologies. Again, while this is correct, it is important to emphasise that other pathologies such as vascular pathology, alpha synuclein, TDP-43 pathology, or processes such as neuroinflammation, do not define Alzheimer's disease among other neurodegenerative diseases. Moreover, biomarkers for these other processes await further validation.

Current applications

Informed by a biological framework for studying Alzheimer's disease, some clinical trials are recruiting individuals not based on the presence of amnestic dementia, but rather on abnormal levels of amyloid-β as determined by amyloid-PET (8). These studies, designed to lower concentrations of cerebral amyloid-β, are thought to have increased chances of meeting primary endpoints because the trials include individuals who stand to benefit from anti-Aβ therapies. Moreover, the biological Alzheimer's disease framework allows for the disambiguation of Alzheimer's clinical syndrome into different diseases which have the same symptoms but different biomarker profiles. Finally, it is crucial to emphasise that the current conceptualisation of Alzheimer's disease as a biological entity is to guide research and is not intended to have clinical applications at this time.

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Expert essay

Spectrum of Alzheimer's disease and the need for post-mortem examination

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Early diagnosis of Alzheimer's disease is a key issue in the global fight against dementia. Numerous efforts are being made to search for reliable biomarkers for the accurate diagnosis of clinically defined Alzheimer's disease. Despite variability in clinical presentations of Alzheimer's disease and confounding atypical symptoms, biomarkers are necessary to improve the overall diagnosis as well as accelerate the development of effective disease-modifying treatments. To improve the definition and understand the progression of Alzheimer's disease at the forefront, body fluids including plasma and cerebrospinal fluid (CSF) are being extensively screened to monitor hallmark protein components of biologically defined Alzheimer's disease pathology, namely amyloid β (Aβ) and τau. Current developments suggest four fluid-based biomarkers are essential to indicate brain changes in the Alzheimer's disease process (1). These are the ratio of Aβ 42 to 40 amino acid peptides, a marker of plaque pathology, total-tau and phosphorylated tau (T-τau and P-τau, respectively), markers of Alzheimer's disease-related changes in τau metabolism, phosphorylation and secretion; and neurofilament light (NfL), a marker of neurodegeneration. Recent technological advances have enabled these to be measured in blood samples besides the cerebrospinal fluid. Remarkably, there is reasonable agreement between Alzheimer's disease proteins, or fragments thereof measured in cerebrospinal fluid and plasma, and the degree of pathology found at post-mortem. cerebrospinal fluid Aβ42, when used together with Aβ40 or P-τau, to predict the subsequent development of Alzheimer's disease dementia in people with mild cognitive impairment (MCI) with high accuracy (2,3). Even more remarkably, plasma P-τau 181 can predict specific Alzheimer's disease neuropathology years before post-mortem confirmation, thus supporting the use of this marker for prognosis in primary care and recruitment for clinical trials (4). Nevertheless, the widespread application as well as the sensitivity of these assays remain a challenge. Easily accessible and cost-effective blood-based biomarkers detecting the same Alzheimer's disease pathologies may revolutionise the diagnostic workup of Alzheimer's disease globally. Could it be as easy as testing fasting blood for sugar levels to confirm diabetes? Time will tell.

Neuroimaging has been earnestly used to demonstrate structural and functional changes associated with Alzheimer's disease. Different imaging modalities in the brain as well as retina have been used to scrutinise clinical criteria. The radiolabelled Pittsburgh compound B (PiB) is now widely used as a tracer for positron emission tomography (PET) imaging to demonstrate the presence of cerebral Aβ in the living brain as an indicator of the presence of Alzheimer's disease pathology. Similarly, ligands for the microtubule associated protein τau to demonstrate neurofibrillary pathology are also being used, but these latter advancements are still largely being properly evaluated. The specificity and sensitivity for Aβ or PiB PET are probably at their best, but several nagging concerns remain. For example, up to 20% of cognitively normal older individuals may retain substantial levels of PiB although current analysis shows on the whole baseline PiB positive status is associated with increased risk of cognitive impairment in healthy elderly and people with mild cognitive impairment(4). Conversely, up to 20% of clinically diagnosed dementia or Alzheimer's disease cases can be Aβ negative. These may also comprise various other types of dementias, including those primarily with vascular dementia. Post-stroke dementia was thought to uncover Alzheimer's disease-type of syndromes but just 20% of stroke survivors retain high enough levels of PiB to diagnose Alzheimer's disease in stroke people who developed dementia but in reality have mixed dementia (5).

Studies comparing clinical diagnoses with autopsy diagnoses indicate that, even at specialised memory or dementia clinics, up to 30% of people fitting into currently used clinical criteria for the diagnosis of Alzheimer's disease may be misdiagnosed. Similarly, the accuracy of clinical diagnosis seems even lower for other dementias, including dementia with Lewy bodies, frontotemporal dementia and vascular dementia. Frequencies of misdiagnosis are even greater in

general practice clinics handling primary care. Diagnosis of Alzheimer's disease in people with self-reported memory problems or with reported mild cognitive impairment can be highly heterogeneous although as many as 50% of people with mild cognitive impairment could have incipient Alzheimer's disease. However, the underlying aetiology is difficult to determine in these without screening for other biomarkers. This is further complicated by the fact that recent neuroimaging and pathological studies have suggested the existence of at least three distinct variants of Alzheimer's disease (6,7). These include the typical, limbic predominant and hippocampal sparing Alzheimer's disease types and there is likely a posterior cortical variant.

Despite refinements in criteria and use of more biomarkers, there is a cause for concern for the low accuracy of clinical diagnosis of Alzheimer's disease in predicting underlying characteristic brain pathology. For example, from 2005–2010, clinicopathological studies of the NACC database showed that in some 919 clinically diagnosed Alzheimer's disease cases, 25% did not match Alzheimer's disease pathological diagnosis. The sensitivity ranged 71–87% and the specificity 44–71%. Sensitivity was generally increased with more liberal clinical criteria and specificity was increased with more stringent criteria, but interestingly the opposite was true when neuropathological criteria were applied (8). When a clinical diagnosis was not confirmed by the minimum degree of Alzheimer's disease pathology, the most frequent primary neuropathological diagnoses were tangle-only dementia or argyrophilic grain disease, frontotemporal lobar degeneration, cerebrovascular disease, Lewy body disease and hippocampal sclerosis. When dementia was not clinically diagnosed as Alzheimer's disease, ~40% of the cases met or exceeded the minimum threshold levels of Alzheimer's disease pathology. In a recent analysis by Kalaria, Penantian and Hase (unpublished observations) of the NACC database, from a total of 14,131 cases of clinically diagnosed Alzheimer's disease, only 72% were confirmed pathologically with Braak staging (neurofibrillary pathology) V and VI. The remaining cases met various pathological diagnoses including vascular dementia. This shows that there is a 30% risk of including people living with Alzheimer's disease without the pathology of interest in clinical trials and estimates for epidemiological studies.

While misdiagnosis and overdiagnosis is a concern that may be resolved in the future with possible precision medicine or management, there is an urgent need for investigation of dementias which are Aβ negative or those that bear features of Alzheimer's disease syndrome. Such investigation could prove important to fill knowledge gaps in the entire spectrum of dementia. Thus, clinicians and ancillary medical discipline colleagues can encourage collection of such cases for biorepositories. There is an absolute need for brain tissues from individuals suffering from various types of disorders. However, we also need to know the norm. Thus, there is an urgent need for brain donations from healthy ageing individuals who might have lived a physically balanced life but may still have been afflicted by age-related problems.

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Without doubt, the current knowledge of the spectrum of dementia has come from post-mortem examination and brain banking. For example, we would not be at this juncture if amyloid material or fibrils were not first extracted from cerebral vessels retained at post-mortem from individuals with Alzheimer's disease. Without the sequenced Aβ peptide(s) or A4 peptide, we could not have advanced in the neurobiology of Alzheimer's disease evident today. Brain banks have been important biorepositories of central nervous system tissue. They store research samples of whole brains, biopsies and spinal cord, and body fluids including cerebrospinal fluid and blood. Brain banking is a rapidly developing field of science with a promising future of enabling research to bring creative solutions on board for central nervous system disorders through collection, characterisation, management, and accessibility of human brain tissue for analysis (9). The majority of these are established in high income countries with well-connected networks in North America, Europe, Australasia and SE Asia/Pacific with recent efforts also emerging in developing regions including Africa (10). However, international collaboration among brain banks can foster networking, interactions among researchers, standardisation of criteria and protocols as well as access to diverse tissue samples for robust research. This has the potential to engage in cutting-edge translational research which can lead to personalised (or precision) medicine globally.

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Conclusions

There is a need for longitudinal follow-up of people with a dementia diagnosis not only for the comprehensive management of their condition, but also to reassess the diagnosis which may change over time. Clinicians are advised to be on the lookout for new symptoms and physical signs that may indicate a co-morbid event such as a stroke, but also a change of perspective on the cause of the dementia.

There may be rare circumstances where the initial diagnosis of dementia is no longer appropriate, since the person's symptoms have resolved. The term 'pseudo-dementia' can be found in the older medical literature. This should not be considered a misdiagnosis but rather a natural evolution of symptoms explained by reversible causes such as depression, substance abuse, or a systemic disorder.

As more and more biological characterisations of the probable cause of dementia takes place using biomarkers, people who appear to have Alzheimer's disease but are amyloid negative will need closer follow-up to clarify the underlying cause of their condition, which may alter prediction for progression and treatments.

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