

Chapter 14

Differential diagnosis

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Key points

- The diagnosis is generally finalised at the second visit, usually within six months after the initial assessment.
- Over 80% of people over the age of 65 with a typical amnestic presentation of dementia will receive a diagnosis of Alzheimer's disease.
- If the structural MRI indicates the presence of significant vascular pathology, the diagnosis might be mixed Alzheimer and vascular dementia.
- Atypical dementias (non-amnestic presentations) usually require specialised assessments that may include neuropsychology, biomarkers and genetics testing since they may be caused by several possible conditions.
- As disease-specific blood biomarkers become available and machine learning is being developed to support clinical diagnosis, early identification of Alzheimer's disease will facilitate access to secondary prevention and disease-modifying therapies.



General background

Usually, within six months of the initial clinical assessment, a second visit is scheduled, and some clarification may be required regarding an individual's medical history. This process is greatly helped by having a family member or friend present at the appointment. Some of the cognitive/memory tests may be repeated, and the first laboratory test results are reviewed with the individual. The clinician should have enough information to formulate a diagnosis. If some uncertainty exists because of unusual symptoms (such as looking for words or having visual complaints), changes in the physical examination (such as one-sided muscle stiffness/rigidity), or unexpected results on brain imaging (such as large ventricles), a referral to a specialist may be required. Additional information about how clinicians differentiate the various causes of dementia is below.

Amnesic dementia is the most common clinical presentation in people over the age of 65, with a clinical history of difficulty retaining new information and subsequent decline of other cognitive domains, which ultimately compromise a person's independence and autonomy. People who present with amnesic symptoms, apart from abnormal cognition, have a normal neurological examination at the very early stage. The routine laboratory test results are normal. Their neuroimaging tests show some degree of ventricular enlargement and brain volume reduction (atrophy), particularly in the hippocampus. These individuals

can be treated and followed in the primary care setting; at later stages, they will require significant functional support. Over 80% of these individuals will have a pathological diagnosis of Alzheimer's disease characterised by amyloid plaques and tau aggregates in the brain. If assessed with biomarkers, they will present high retention of amyloid and tau PET imaging agents and hypometabolism. In the CSF, A β 42 will be reduced, and tau and p-tau will have increased (1).

In an alternative scenario called atypical dementias, rather than obvious memory decline, the first and dominant clinical manifestation might include loss of language function, behavioural abnormalities, executive dysfunction, hallucinations, attention deficit, loss of perceptual-motor functions and social cognition abnormalities. The dementia symptoms frequently emerge before 65 years of age. The neurological examination is often abnormal. The structural MRI frequently reveals focal abnormalities. Yet, the atypical presentation of Alzheimer's disease may be the source of these cases. In addition, dementia with Lewy bodies, frontotemporal dementia and Parkinson's disease dementia also cause atypical dementias phenotypes.

Cognitive decline may also be the principal manifestation in rare neurodegenerative disorders such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multisystem atrophy and other uncommon diseases.

Background for clinicians

The diagnosis of dementia is predominantly clinical, so the physician's preliminary assessment is likely bolstered during this second visit by viewing the progression of symptoms as well as a slight decline indicated on the cognitive test results. The main cause of the dementia is

also mostly based on the profile of symptoms (amnesic versus non-amnesic), the person's age and co-morbidities (predominantly vascular). Table 1 lists the causes of dementia in adulthood. The common types are examined in detail in the next section.

Table 1. Non-exhaustive list of causes of dementia

Neurodegenerative dementias	Toxic environmental	Neurometabolic disorders
<ul style="list-style-type: none"> Alzheimer's disease PART LATE-NC Argyrophilic grain disease Autosomal Dominant Alzheimer's disease Corticobasal degeneration Down syndrome related dementia Frontotemporal dementias Dementia with Lewy bodies Parkinson's disease dementia Progressive supranuclear palsy 	<ul style="list-style-type: none"> Chronic traumatic encephalopathy Alcohol-related dementia 	<ul style="list-style-type: none"> Adult-onset leukodystrophies Adult polyglucosan body disease Adult neuronal ceroid lipofuscinosis Diffuse hereditary leukoencephalopathy with axonal spheroids Late-onset lysosomal storage diseases Mitochondrial disease
Vascular diseases	Infectious diseases	Others
<ul style="list-style-type: none"> Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy Cerebral amyloid angiopathy Primary angiitis of the central nervous system Secondary central nervous system vasculitis Vascular dementia 	<ul style="list-style-type: none"> HIV-associated neurocognitive disorder Herpes encephalitis Neurosyphilis Prion disease Progressive multifocal leukoencephalopathy Whipple disease Subacute sclerosing panencephalitis 	<ul style="list-style-type: none"> Dentatorubral pallidoluysian atrophy Familial idiopathic basal ganglia calcification (Fahr disease) Familial encephalopathy with neuroserpin inclusion bodies Huntington's disease Normal pressure hydrocephalus Pantothenate kinase associated neurodegeneration Spinocerebellar atrophy Superficial siderosis Wilson disease
	Inflammatory and autoimmune diseases	
	<ul style="list-style-type: none"> Encephalopathy due to systemic autoimmune disease Multiple sclerosis Neurosarcoidosis Non-paraneoplastic autoimmune encephalopathy Paraneoplastic encephalopathy 	

Dementia syndromes

Dementia is a syndrome characterised by a decline in at least two cognitive functions such as learning and memory, language, executive function, complex attention, perceptual-motor or social cognition. These symptoms must represent a decline from a previous level of function and be severe enough to interfere with daily function and independence.

Abnormalities in the blood supply flow to the brain as well as cerebrovascular diseases cause dementia. It is widely accepted that dementia symptoms reflect neuronal depletion resultant from the progressive accumulation of dysfunctional brain proteins, a process called proteinopathies. Specifically, the accumulation of beta amyloid and hyperphosphorylated tau (3/4 R tau) are the signature markers of Alzheimer's disease. Frontotemporal lobar degeneration and amyotrophic lateral sclerosis result from

the brain accumulation of either tau protein isoforms (3R-tau; Pick's disease), the transactive response DNA binding protein (TDP43), or the Fused-in-Sarcoma (FUS) protein. Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy result from the abnormal accumulation of dysfunctional alpha synuclein protein. This framework allows us to appreciate some features from the clinical syndromes described below. Firstly, distinct proteinopathies can cause similar symptoms if they affect similar brain circuits. Secondly, as the accumulation of these dysfunctional proteins started many years before the onset of their symptoms, dementia reflects an advanced stage of various brain proteinopathies. Progress in biomarkers allow an in vivo diagnosis of these conditions. Biomarkers for non-Alzheimer's disease neurodegenerative conditions constitute an unmet need as most of these disorders require an autopsy to confirm the final diagnosis (2).

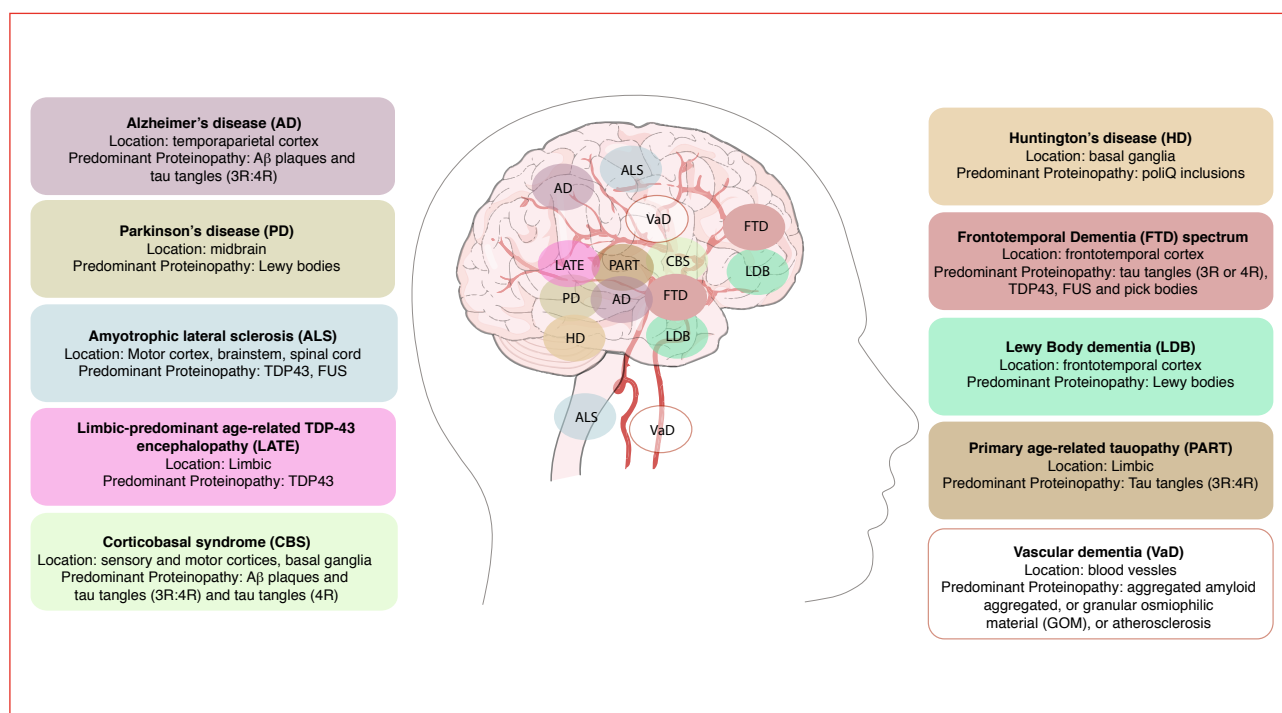


Figure 1. Schematic diagram summarising vascular abnormalities and proteinopathies involved in cognitive decline and dementia.

Diagnostic approach

The diagnostic approach is summarised in Figure 2. Based on clinical history, cognitive screening, neurological examination, neuropsychiatric and functional assessments, dementia is classified as typical, atypical, or non-degenerative. People with a typical amnesic syndrome present with normal laboratory test results, as well as the presence of degenerative features on the structural neuroimaging, receive a probable Alzheimer's disease diagnosis. If the structural MRI indicates the presence of vascular pathology, the diagnosis may shift to mixed dementia. As biomarkers for amyloid and tau are unavailable for large-scale use, their role is limited in this population.

Cases of atypical dementias should be further assessed with specialised tests that include a customised investigation with neuropsychology, biomarkers and genetics testing. A comprehensive diagnostic assessment takes into consideration a wide range of diagnoses (Figure 1). A summary description of relevant syndromes follows.

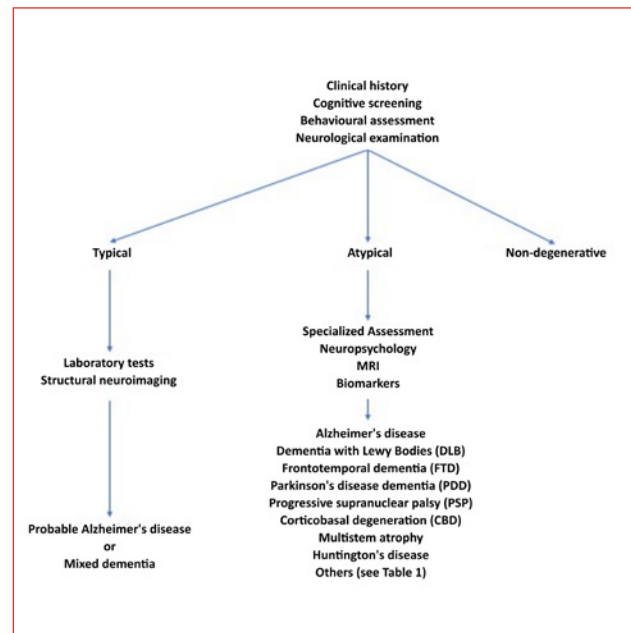


Figure 2. Diagnostic approach for people with dementia with typical and atypical presentations.

Dementias with dominance of amnesic symptoms

Amnesic Alzheimer disease is the most common form of dementia where forgetfulness is the central cognitive symptom. Amnesic individuals may also search for words during a conversation (language) and have difficulty handling complex tasks (executive functions). As the disease progresses, they may also struggle to adapt to new circumstances (reasoning), get lost in familiar places (orientation) and develop problems dressing themselves and/or handling objects (praxis). As expected, individuals who present with these amnesic symptoms, apart from abnormal cognition, receive normal range results on the neurological examination, and this, when in its initial stages. Biomarkers display positivity for Alzheimer's disease pathophysiology in the predicted 80% range of all cases (3, 4). Their structural neuroimaging shows some degree of brain volume reduction (atrophy), particularly in the hippocampus. They may show signs of small vessel or more extensive cerebrovascular disease. PET typically shows hypometabolism in the hippocampus, posterior cingulate, precuneus and inferior parietal cortices. Amnesic dementia cases without biomarker evidence of amyloid are designated as suspected non-Alzheimer's disease pathophysiology (SNAP). These individuals can be followed and treated in primary care (Figure 2). Autopsy series show amyloid plaques, neurofibrillary tangles as well as neuronal depletion in 70–80 % of the cases. Possible non-Alzheimer's pathological entities observed in

amnesic cases are hippocampal sclerosis, argyrophilic grain disease, and primary age-related tauopathy and limbic-predominant age-related TDP-43 encephalopathy (5).

Argyrophilic grain disease is a finding frequently described in pathological series. Clinicopathological studies reveal a heterogeneous clinical presentation characterised by slowly progressive amnesic Alzheimer's type dementia. Neuropsychiatric symptoms such as anxiety, mood and personality changes are frequently described. Few studies describe asymmetric amygdala and hippocampus atrophy, sometimes extending to the lateral temporal neocortex as the major MRI findings. PET reveals important mesial temporal lobe hypometabolism. The pathology is characterised by grain like deposits in neuronal dendrites labelled with antibodies specific for 4R, accompanied by oligodendroglial inclusions, ramified astrocytes and ballooned neurons in the amygdala, hippocampus and medial temporal lobe (6).

Limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) affects the mesial temporal and limbic frontal cortex. In these memory circuits, TDP-43 proteinopathy has been associated with cognitive and functional impairment nearly indistinguishable from amnesic Alzheimer's dementia. LATE-NC explains typical amnesic dementia negative for amyloid and tau biomarkers. MRI reveals atrophy predominantly

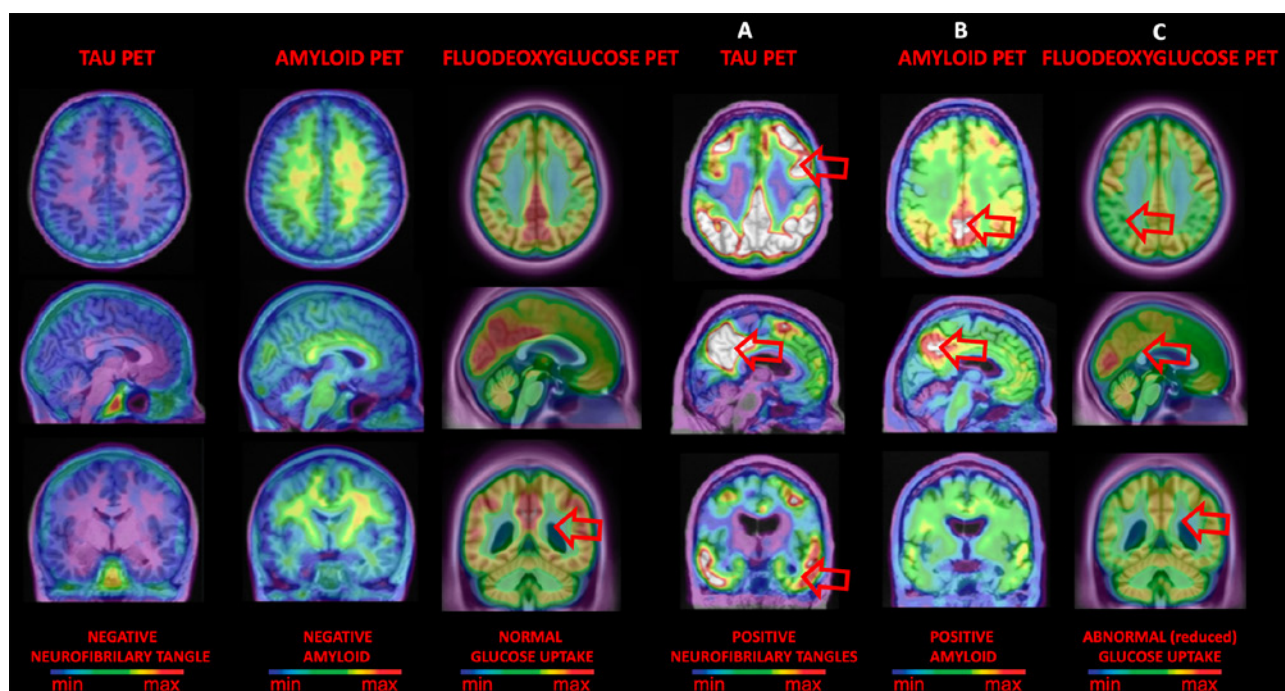


Figure 3. Typical dementia case with PET scans showing abnormal load of neurofibrillary tangles (a), amyloid (b) and presence of neuronal injury (c).

in medial temporal regions. In LATE-NC, PET reveals important mesial temporal lobe hypometabolism with increased ratio of inferior to medial temporal metabolism as compared to Alzheimer's dementia cases. TDP-43 accumulation is commonly observed after the seventh decade and frequently is associated with hippocampal sclerosis and Alzheimer's disease pathophysiology. The absence of biomarkers for TDP-43 aggregates requires an autopsy to diagnose LATE-NC (7).

Primary age-related tauopathy (PART) is a neurodegenerative condition characterised by neurofibrillary tangles (NFT) in the presence of infrequent or no amyloid plaques. In PART, the neurofibrillary pathology is mostly restricted to structures in the medial temporal lobe, basal forebrain, brainstem, and olfactory areas (8). In the autopsy studies, PART is frequently described in cognitively unimpaired individuals, occasionally found in people with mild cognitive impairment, and infrequently observed in dementia cases. Biomarkers can diagnose PART in living individuals (negative biomarker evidence for amyloid and positive for neurofibrillary tangles; Figure 3). PART biomarker profile also meets criteria for non-Alzheimer's disease pathologic change. PART hypometabolism observed in PET is indistinguishable from amnesic Alzheimer's dementia (9).

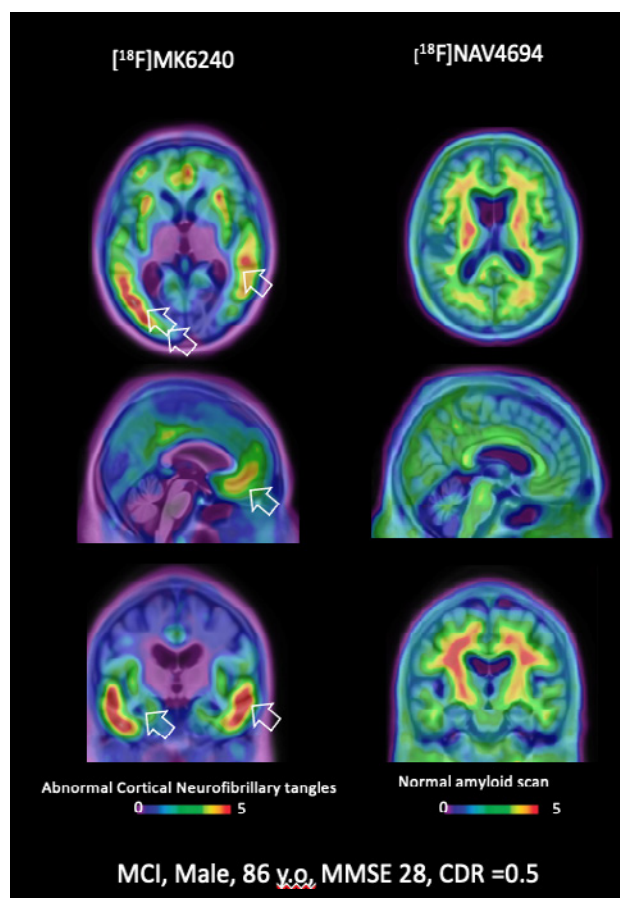


Figure 4. Typical presentations of imaging in patients with PART. Typical dementia case with PET scans showing normal load of amyloid and abnormal load of tau and presence of neuronal injury.

Dementias with dominance of non-amnestic cognitive symptoms

Posterior cortical atrophy (PCA) is an atypical dementia variant characterised by neurodegeneration in the interface between temporal parietal and occipital cortices. As visual abnormalities constitute the first and dominant symptom (difficulty reading or driving), affected individuals are often initially evaluated by optometrists for visual complaints. The neuropsychology assessment reveals minimal memory impairment. The neurological examination shows a wide range of visual spatial deficits. Neuroimaging shows predominant occipitoparietal or occipitotemporal atrophy. The same regions appear hypometabolic in PET. Biomarkers reveal the presence of Alzheimer's disease pathophysiology (positive for amyloid and tau) in most cases. In PCA autopsied cases, apart from Alzheimer's disease, the neuropathology might also reveal 4R tau, dementia with Lewy bodies, gliosis and prion disease (10).

Primary progressive aphasia (PPA) designates a clinically and pathologically heterogeneous group of dementias in which language difficulties are the first and dominant symptoms, with relative sparing of memory deficits (11). Based on the language deficits patterns, these cases are subcategorised as non-fluent, semantic, or logopenic (12). The logopenic variant is characterised by effortful speech due to word-finding pauses and paraphasic speech errors. They show difficulties in repeating sentences. Grammar or comprehension remain intact in mild stages of the disease. Biomarkers for Alzheimer's disease are typically positive logopenic PPA. MRI normally indicates atrophy while PET indicates hypometabolism in posterior temporal language areas. On the semantic PPA, individuals are fluent, but comprehension is impaired mainly for single words. People with PPA also lose their ability to read words with irregular spelling (surface dyslexia). While biomarkers for Alzheimer's disease are typically negative in these cases, MRI reveals atrophy and PET exposes hypometabolism predominantly in the left anterior temporal lobes. Semantic PPA is frequently due to TDP43 pathology. For people with nonfluent PPA speech is effortful as a consequence of agrammatism, and articulatory difficulties. Comprehension and memory are relatively spared in mild disease stages. Non-fluent PPA symptoms might remain restricted to expressive language function

for years before dementia emerges. While biomarkers for Alzheimer's disease are typically negative in these cases, MRI reveals atrophy and PET shows hypometabolism predominantly in the left anterior insula, premotor and inferior frontal cortices (Broca region). Regarding the pathology, the vast non-fluent cases are associated with non-Alzheimer's disease pathology including TDP43 or 4R tau aggregates (11).

Individuals with dominance of behavioural and dysexecutive symptoms display difficulties with planning and organising daily activities or completing routine tasks. They also struggle with listening to others, paying attention or following instructions. Family members and friends report a change in previous personality traits. Behavioural changes may include irritability and difficulties controlling their emotions or impulses. They may also have no interest in previously enjoyed hobbies or social events. Family and friends also describe an uncharacteristic indifference and lack of empathy towards them. In social interactions, they frequently make inappropriate comments and may engage in inappropriate activity, sometimes touching or kissing strangers or even urinating in public spaces without any sense of embarrassment. Repetitive or ritualistic behaviours such as hoarding, compulsive inspections (such as the need to continuously check the dials on the stove to ensure it is turned off), or obsessive cleaning are commonly reported in these cases. Changes in food preferences, such as developing a sweet tooth and increased consumption of alcohol or tobacco, may also occur. Biomarker evidence of amyloid and tau help identify people with frontal/dysexecutive variant of Alzheimer's disease from frontotemporal dementia. MRI reveals atrophy and PET reveals hypometabolism in frontal and temporal areas. In the subset of people with amyloid and tau, behavioural symptoms overshadow memory deficits. A small percentage of individuals with behavioural or dysexecutive symptoms without evidence of Alzheimer's disease pathophysiology may also develop amyotrophic lateral sclerosis symptoms in the course of the disease (13). The pathology of behavioural variant of frontotemporal dementia includes 3R tau inclusions, also known as Pick's bodies of Pick's disease, TDP, 4R tau and FUS inclusions.

Dementia with motor or extrapyramidal manifestations

Dementia with Lewy bodies is an atypical dementia characterised by early impairments in attention as well as executive and visuospatial functions, with memory impairments emerging later in the course of the disease. Cognition and levels of alertness fluctuates in patients. From the motor perspective, individuals characteristically show parkinsonian symptoms, such as bradykinesia, limb rigidity and gait disorder, which increases the risk of falls. Anxiety and depression are frequently present. Systematised paranoid delusions and visual hallucinations occur in approximately two-thirds of people. Vocalisation during sleep, somniloquy or complex motor behaviours (acting out) are common in dementia with Lewy bodies as REM sleep disorder manifestations. Nearly half of people with dementia with Lewy bodies show severe sensitivity to antipsychotic drugs. As the comorbidity between Alzheimer's disease and dementia with Lewy bodies is high, biomarkers provide evidence of amyloid and tau. While MRI reveals global or hippocampal atrophy, PET shows hypometabolism, particularly in visual associative areas. The sparing of the posterior cingulate metabolism (cingulate islands sign) has been proposed as a biomarker of dementia with Lewy bodies. Imaging dopamine transporters with SPECT shows dopaminergic depletion in the striatum in dementia with Lewy bodies. However, this finding is also observed in Parkinson's dementia, multiple system atrophy, and progressive supranuclear palsy. Autopsy studies shows frequent comorbidity between Alzheimer's disease and vascular pathology with limbic, cortical and striatal Lewy body inclusions.

Parkinson's dementia Cognitive decline and dementia are common in Parkinson's disease. As with dementia with Lewy bodies, the cognitive impairment in Parkinson's disease has an early and heterogeneous profile featuring fatigue, difficulties planning, accomplishing tasks or multitasking (executive dysfunction) as well as difficulties reading, drawing and copying (impaired visuospatial function), though with less prominent language and memory deficits. As in dementia with Lewy bodies, neuropsychiatric symptoms include apathy, mood changes, paranoid delusions, complex visual hallucinations (such as seeing animals or people who are not there). Autonomic deficits, excessive daytime sleepiness and REM sleep behaviour disorder are frequently present. The diagnosis of Parkinson's dementia is made when parkinsonism symptoms start approximately one year before the onset of dementia, and cognitive deficits impair daily life, independent of Parkinson's disease's motor or autonomic symptoms.

Progressive supranuclear palsy is characterised by vertical supranuclear gaze palsy, axial rigidity, and prominent postural instability with falls. Frequently motor manifestations can be preceded by fatigue and apathy. The cognitive changes are characterised by executive dysfunction,

including impaired abstract thought, decreased verbal fluency and motor perseveration. Behavioural changes, including indifference, disinhibition, or non-fluent aphasia, can be early manifestations of progressive supranuclear palsy. Biomarkers for Alzheimer's disease are typically negative. Neuroimaging with MRI reveal midbrain brainstem atrophy (hummingbird sign or penguin silhouette), and superior cerebellar peduncle atrophy. Positron emission tomography (PET) scanning reveals decreased glucose metabolism in the midbrain, striatum and prefrontal cortex. Definite PSP diagnosis is obtained post-mortem by the presence of 4R tau aggregates in the neuropathological examination (14).

Corticobasal syndrome is a movement disorder characterised by progressive asymmetric akinesia, rigidity and dystonia, apraxia, alien-limb phenomena and focal myoclonus. However, cognitive symptoms such as apathy and difficulties multitasking may constitute an early syndrome manifestation. In addition, motor language abnormalities ranging from mild phonologic impairments to nonfluent aphasia may also constitute another early manifestation. Neuropsychiatric manifestations include indifference, social withdrawal, compulsive behaviour, unmotivated laughter and irritability. Unilateral ideomotor apraxia is an important corticobasal syndrome feature. Biomarkers for Alzheimer's disease pathophysiology are positive for amyloid and tau in nearly 50% of the cases. MRI shows asymmetric cortical atrophy encompassing the frontal and parietal regions with ventricle enlargement and corpus callosum atrophy. The atrophic cortex and its underlying white matter might show hyperintensity in T2 weighted images. PET reveals asymmetric hypometabolism in the posterior frontal, inferior parietal, and superior temporal regions and the ipsilateral thalamus and striatum. Definite diagnosis is obtained post-mortem typically by the presence of amyloid and tau or 4R tau aggregates in the neuropathological examination (15, 16).

Prion diseases are a group of neurodegenerative conditions associated with the misfolding and aggregation of a membrane protein called prion protein. In abnormal conditions, the prion protein forms fibrils inside the neurons, causing neuronal death. Sporadic Creutzfeldt-Jakob disease (sCJD), sporadic fatal insomnia and protease-sensitive prionopathy, Gerstmann-Sträussler-Scheinker syndrome are non-transmissible prion diseases. Kuru, iatrogenic Creutzfeldt-Jakob disease, and variant Creutzfeldt-Jakob disease are transmissible forms of prion diseases.

Rapidly progressive dementia and myoclonus are hallmarks of Creutzfeldt-Jakob disease. Cognitive impairment in affected individuals initially impairs memory and concentration. Subsequently, they rapidly develop aphasia, apraxia, visuospatial, and frontal lobe syndromes.

Behavioural abnormalities include apathy, alterations in the sleep-wake cycle and visual hallucinations. Myoclonus is present in nearly all individuals (17). Apart from its typical presentation, Creutzfeldt-Jakob disease has visual (Heidenhain), cerebellar (Oppenheimer-Brownell), thalamic, and striatal variants (18). PET and CSF A β 42 fail to suggest amyloid deposits in Creutzfeldt-Jakob disease. Diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) MRI show hyperintensity in the striatum and cortex. On the electroencephalogram, these individuals show periodic sharp wave complexes.

Non-specific cerebrospinal fluid biomarkers for neuronal injury such as 14-3-3 protein and total tau protein are elevated. Real-time quaking-induced conversion assay supports the presence of disease-associated prion protein in the cerebrospinal fluid. The investigation of Creutzfeldt-Jakob disease should exclude treatable aetiologies as treatable diseases such as paraneoplastic syndromes, and autoimmune encephalitis might mimic Creutzfeldt-Jakob disease. Neuropathology provides the definitive diagnosis (19). Although neuropathology provides a definitive diagnosis of CJD, a brain biopsy is seldom required (20).

Presence of cerebrovascular disease

Vascular dementia along with the risk factors for cerebrovascular disease, is extensively examined in Chapter 22. Vascular dementia refers to dementia caused by or associated with either cerebrovascular disease or abnormal cerebral blood flow. Poststroke dementia has a step-wise cognitive decline after a clinically diagnosed stroke. Vascular dementia follows the same progressive cognitive decline without a concurrent history of symptomatic stroke. The extension and severity of cerebrovascular disease, brain reserve, comorbidities with neurodegeneration, age, education, race, and diabetes are risk factors for these conditions. The cognitive profile of poststroke dementia

is clinically heterogeneous, often marked by prominent impairment of executive functions, sometimes with variable involvements of episodic memory and other cortical signs of including aphasia or apraxia. Strategic anterior thalamic stroke could mimic Alzheimer's dementia in some cases (21, 22). The diagnosis of poststroke or vascular dementia is based on imaging evidence of cerebrovascular disease sufficient to justify cognitive symptoms. MRI-T2, FLAIR and susceptibility sequences better detect cerebral vascular disease than a head CT. Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria provide radiologic definitions of cerebrovascular disease (22).

Coexistence of pathophysiological processes

Multiple-aetiology dementia is diagnosed when a person with vascular dementia also meets the diagnostic criteria for another neurodegenerative disorder. It is common for Alzheimer pathology to coexist with other processes, including vascular lesions, cortical Lewy bodies, TAR DNA binding protein 43 (TDP-43) deposits, argyrophilic grain disease, and Parkinson's disease. The combination of two

pathologies can potentially influence the clinical presentation and course of the disease and present diagnostic challenges (23). In general, these additional pathologies result in a greater likelihood of dementia and rate of decline (24, 25)

Survey results

The replies obtained from the 2,327 people with dementia and carers indicated that basic assessments such as a history, neurological examination, basic laboratory screening tests and cognitive assessment are widely used as dementia tests. Currently, biomarkers are not available

worldwide and therefore not part of the clinical practice in many countries. However, 70% of the 1,111 multidisciplinary clinicians who replied are willing to use blood biomarkers, if available; this is an unmet need in dementia that could make clinical practice more efficient worldwide.

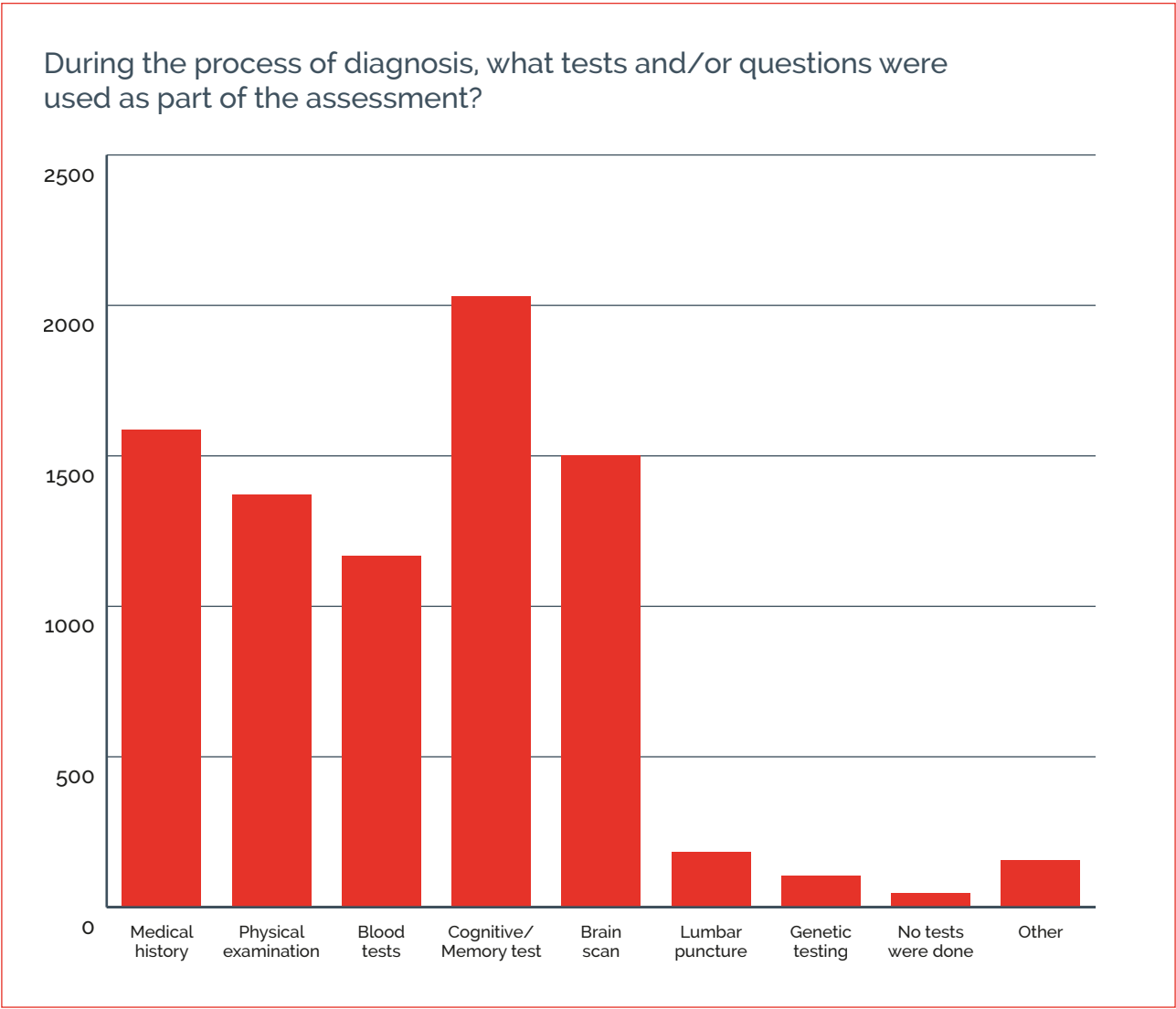


Chart 1. People with dementia and carer responses (multiple answers selected).

What would make your clinical practice more efficient in the diagnosis of people with cognitive decline?

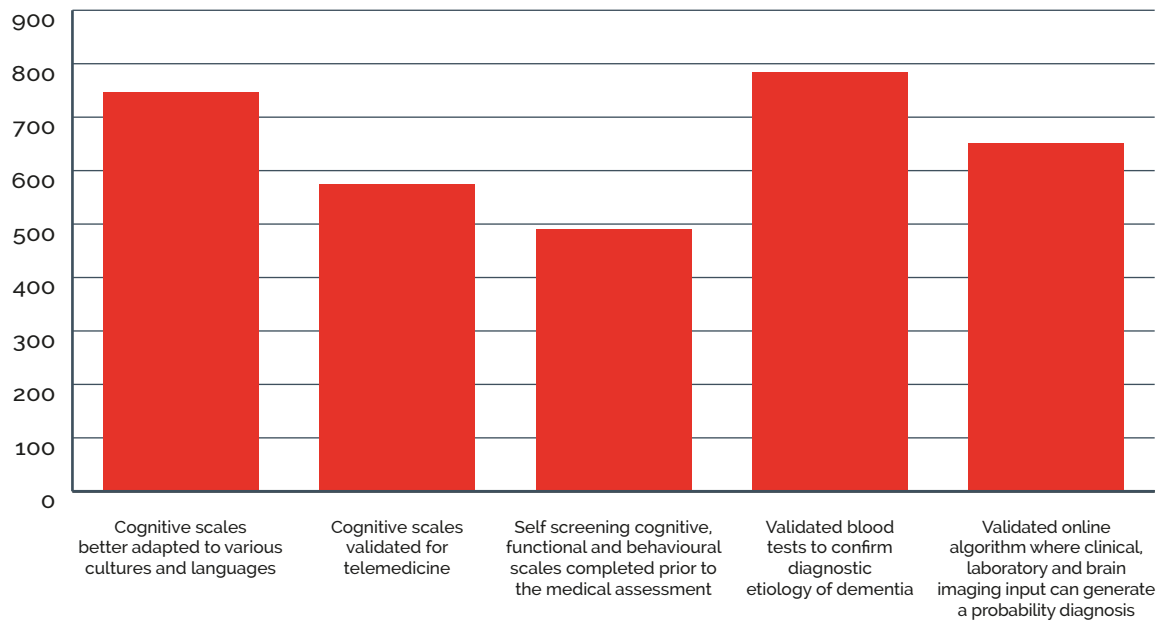


Chart 2. Clinician responses (multiple answers selected).

If there was an adequately validated algorithm available online to help get a probability score on the etiology of cognitive decline based on simple clinical and biological tests, would you likely use it in your clinical practice?

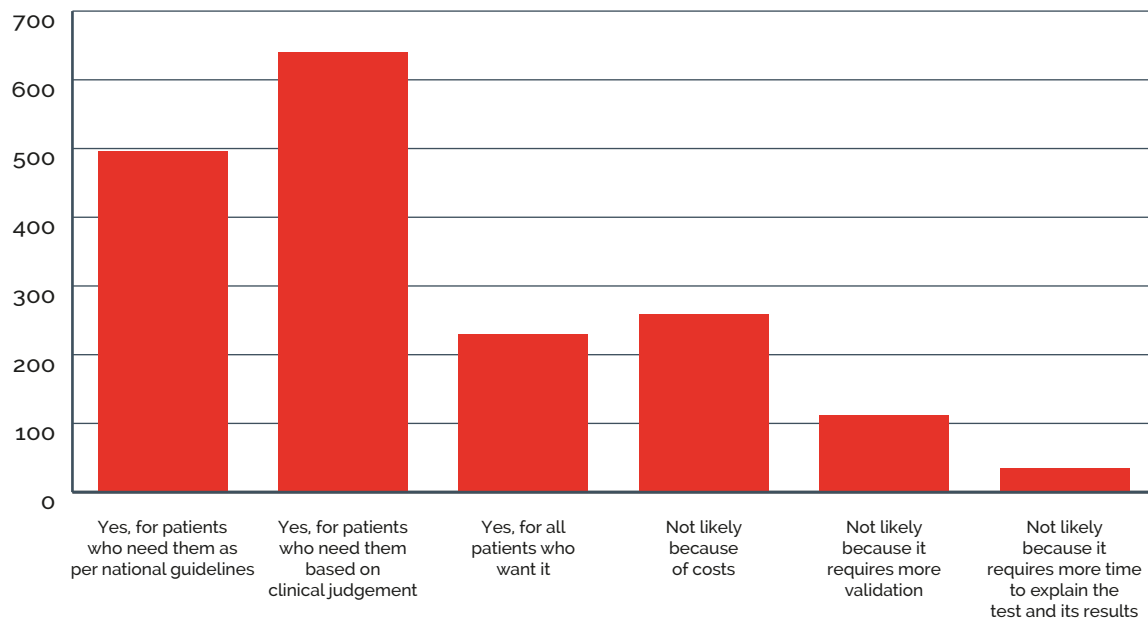


Chart 3. Clinician responses.

Expert essay

Machine learning and artificial intelligence for Alzheimer's disease

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Machine learning and artificial intelligence (AI) have revolutionised many industries and can transform the care of Alzheimer's disease and other chronic conditions. Modern machine learning techniques, when given access to large amounts of patient data, are capable of learning robust, high-performing models for Alzheimer's disease that can identify novel markers of risk, predict disease to help clinicians intervene earlier, model disease progression and even suggest precision-medicine interventions for individual patients. Although the adoption of machine learning to support clinical decisions for Alzheimer's disease is in its infancy, this area has great promise, especially considering the US FDA's recent approval of Aduhelm (aducanumab), the first drug approved to treat people with Alzheimer's disease.

Today there are several research studies involving the use of machine learning, image processing and statistical learning with amyloid PET scans, FDG PET scans and 3D MRI scans from large cohorts such as the Alzheimer's Disease Neuroimaging Initiative (ADNI). Potential applications include early detection (1), classification of diagnosis and staging (2), prognostic prediction of disease (3–5), and differential diagnosis (6,7). Deep learning-based brain segmentation techniques and white matter hyper intensity quantification techniques show promise for early diagnosis and disease staging of Alzheimer's disease (8,9). Although much of this research takes the form of retrospective analyses, an increasing number of clinical trials are using machine learning in conjunction with imaging reads to reduce the burden on radiologists, both to identify candidates for clinical trials and to detect and quantify surrogate markers for trial endpoints.

In addition to plaque, abnormal accumulation of tau protein (detected via tracers, such as MK6240) has been associated with neurodegeneration and cognitive impairment. Using machine learning to detect brain tau burden via in vivo tau imaging, combined with amyloid and MRI imaging, can provide clinical and research biomarkers in a holistic approach to support differential diagnosis (10). Furthermore, the closer association of tau with cognitive impairment as

well as neuronal dysfunction makes it suitable for AI-based methods to automatically monitor disease progression and to identify candidates for clinical trials.

The FDA's recent approval of Aduhelm to treat people with Alzheimer's disease should accelerate the clinical adoption of machine learning for Alzheimer's disease. Aduhelm is the first approved treatment directed at the underlying pathophysiology of Alzheimer's disease, the presence of amyloid beta plaques in the brain. Clinical trials have shown a reduction in these plaques, and the FDA's expectation is that Aduhelm will lead to a reduction in the clinical decline of people with Alzheimer's disease. The current protocol mandates an amyloid scan (or lumbar puncture) to detect the presence of amyloid plaque prior to starting treatment. Further, treatment must be preceded by a baseline MRI scan within one year before treatment and two additional scans prior to successive infusions. As this therapy is rolled out across the Alzheimer's disease population, there will be a tremendous opportunity for machine learning/artificial intelligence to support radiologists via computer-aided diagnosis software to detect the presence of amyloid. Machine learning/artificial intelligence can also help to track the progression of the intermediate clinical endpoint (plaque burden) in post-market studies, gather data to determine the impact of therapy on other surrogate endpoints (for example, the accumulation of tau) and eventually support the potential linkage of treatment with diminishing cognitive decline (in turn, measured by AI-based digital diagnostics).

A recent study identified four different trajectories of tau deposition in people with Alzheimer's disease (11). This is particularly relevant for the development of new therapies. Considering that 'diseases of the blood' were deemed incurable only a century ago; today, these are subdivided into dozens of leukaemias and lymphomas, many of which can be completely cured if detected early. Similarly, one can imagine a future in which Alzheimer's disease, instead of being managed as a single monolithic condition with inevitable progression, is subdivided into different subtypes each with different prognoses and treatment pathways. Machine

learning-based clustering and unsupervised learning methods that analyse imaging and clinical data can play a role in helping automatically identify increasingly fine-grained Alzheimer's disease subtypes with variations in therapy response.

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As Aduhelm and future Alzheimer's disease treatments increasingly move into clinical practice, machine learning can play an amplified role in the proactive and early identification of Alzheimer's disease, potentially even before the presentation of clinical symptoms or imaging evidence. As with all chronic diseases, the earlier the intervention, the greater the potential benefit. It will probably not be feasible to rely on neuroimaging as the primary screen for Alzheimer's disease, namely the ability to perform amyloid scans on the general population at age 50 to detect signs of early Alzheimer's disease. Machine intelligence/artificial intelligence can serve as an initial blunt screening tool, potentially leveraging non-imaging data and even genetic data to identify those at high risk for future Alzheimer's disease, and as candidates for diagnostic neuroimaging scans. However, it is in the use of AI-based blood biomarker panels (possibly augmented with cerebrospinal fluid data) where machine intelligence/artificial intelligence can have an immeasurable impact.

Recent research studies have identified several emerging blood-based biomarkers as potential surrogate markers for amyloid and tau in the brain (12,13). These biomarkers are significantly cheaper and more convenient compared to imaging alternatives. These blood biomarkers, perhaps combined with patient demographics and potentially clinical information, have the potential to identify individuals at high-risk for progression to Alzheimer's disease before symptoms present and possibly even before imaging evidence (14). An AI-based blood biomarker panel could be used to identify patients for trials for new drugs, to track progression of clinical endpoints, predict future cognitive decline, or possibly as a screening test.

There are several ongoing Alzheimer's disease research projects which go beyond the analysis of neuroimaging and fluid data. Research studies are investigating artificial intelligence/machine learning applications for analysing recorded speech and word usage, predict progression from MCI to Alzheimer's disease, as well as predict future disease prior to clinical symptoms. Other data being investigated includes sociodemographic characteristics, clinical and neuropsychological test scores, cardiovascular risk indices, gene expression data, retinal vasculature, and large-scale administrative health data.

Finally, artificial intelligence can be used within interactive tools and mobile/web apps. As treatment guidelines are being developed, there is great interest among physicians to avail themselves of clinical decision-support tools, possibly via cloud-based implementations of these guidelines, that can orient clinicians (and patients) in the early identification and management of Alzheimer's disease. Several start-ups have developed applications (apps) for consumers (and physicians) to conduct cognitive tests. We expect that in the coming decade, an increasing number of digital diagnostics and therapeutics will be prescribed/used by patients, carers and even consumers to help in the management of this disease.

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Conclusions

As a matter of course in today's primary care environment, most clinicians follow the prescribed protocols to formulate and render a diagnosis of dementia and its most likely aetiology. This is necessary to determine what kind of dementia an individual may have, be it a typical form like Alzheimer's disease to rarer, atypical types such as dementia with Lewy bodies that would require specialised and collaborating assessment. This includes taking a family history and laboratory testing data.

However, there are new developments that will impact this routine in due course. Firstly, accelerated changes in the field of biomarkers coupled with people seeking answers to their cognitive complaints much sooner than before will engender changes both in data collection and analysis. The majority of clinicians welcome these changes as they foresee quicker and more detailed analysis results as well as being able to render a diagnosis in the earliest stages of the syndrome.

The advent, but more importantly, the advancements of machine learning and artificial intelligence are inching the world of clinical decision-support tools towards more of a reality in dementia care. This even extends to mobile applications that can administer cognitive tests and provide individuals and their carers with digital diagnostic and therapeutic support. In the future, the prospect of identifying risk markers, forecasting disease to support differential diagnosis and modelling disease progression will likely revolutionise the management of dementia.

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