Chapter 25
New challenges and opportunities in the diagnosis of dementia

Claire Webster

- Clinicians recognise the need to make their practice more efficient in the diagnosis of dementia.
- New blood biomarkers may facilitate diagnosis of the causes of dementia.
- Medical and health science university faculties must integrate new insights and knowledge about diagnosis and management of dementia.
General background

This concluding Chapter summarises some of the important emerging themes based on the survey responses and expert essays. This is encouraging news, as primary care physicians express interest in adapting their clinical practice to incorporate biomarker screening and become more specialised in the diagnostic and post diagnosis management process. Unfortunately, the current reality is that there are roadblocks still in place that prevent individuals from obtaining a diagnostic assessment easily. These include a lack of awareness regarding the signs and symptoms of the condition; public fear and stigma associated with the diagnosis; problematic geographical locations, lack of adequate transportation to reach clinicians; insufficient numbers of trained healthcare experts in dementia; limited access to free public healthcare and the financial costs related to medical care.
Survey results

Among the 1,111 multidisciplinary clinicians who responded to the survey, most (75%) ranked the increased numbers of people who will seek a diagnosis given the ever-ageing population as the major challenge facing dementia diagnosis in the future. This was followed by people seeking a diagnosis based on self-testing results from web-based symptoms checklists or cognitive tests (44%), new disease-modifying therapies (43%), and direct-to-consumer genetic testing (22%). When asked what would make clinical practice more efficient when diagnosing people with cognitive decline, validated blood tests to confirm the aetiology of dementia was first (71%), followed by cognitive scales better adapted to various cultures and languages (67%), validated on-line algorithms taking into account clinical, laboratory and brain imaging information (59%), cognitive scales validated for telemedicine (52%) and self-screen cognitive, functional and behavioural scales completed prior to the clinical assessment (44%) were the top answers (Table 1).

Many of the 101 national Alzheimer associations who completed the survey indicated that their country has (37%), or is developing (23%), a National Dementia Plan. Most of the existing National Dementia Plans have a segment devoted to diagnosis, but few include a specific target for diagnosis rates or collect information about the number of newly diagnosed people with dementia (25%). Only 33 countries have easy access to healthcare professionals for all people concerned about their memory or cognitive changes, with 55 of the 101 associations citing that access is limited due to: a lack of clinicians (47%); people’s fear of a dementia diagnosis (46%); costs (33%); or other reasons (16%) (Table 2).

In terms of knowledge sharing with the populations they represent, nearly all associations provide information about the warning signs of dementia (98%) and about reducing the risk of dementia (95%). Many provide information about diagnosis on their website (61%).

### Table 1. List of choices by clinicians to make clinical practice more efficient in the diagnosis of dementia in order of priority

- Validated blood test to confirm aetiology of dementia.
- Cognitive scales better adapted to various cultures and languages.
- Validated on-line algorithms to combine clinical and laboratory data for individuals.
- Cognitive scales validated for telemedicine.
- Self-screening for cognition, function and behaviour prior to the clinical assessment.

### Table 2. Alzheimer associations’ list of reasons to explain the limited access to healthcare professionals, in order of importance

- Lack of clinicians.
- People’s fear about a dementia diagnosis.
- Costs.
The first point of contact in healthcare for people with symptoms that make them question whether they have an emerging dementia disorder is, in most cases, a primary care physician (GP, family practitioner, family physician) (1,2). Primary care can be organised and financed in many different ways — it can be public or private. Primary care physicians can work more or less alone or in teams with many variations of staff, and the out-of-pocket expenses can be low or high. The commission for primary care can be broad or rather narrow. Being a primary care physician can be a speciality like other specialities (neurology, internal medicine, etc.), but physicians can also start working in a primary care setting after completing medical school.

The prerequisites for this first contact can vary quite a bit, depending on where in the world you live. In general, primary care physicians work with and follow patients regularly, and, when needed, refer them to specialists. Thus, primary care should be the optimal care level for this first appointment.

In an ideal scenario, the primary care physician has known the individual and the family well for many years. The physician is experienced and well-educated in dementia. They have blocked off plenty of time for the appointment (approximately, one hour). A family member or friend should accompany and be present, termed medically as an ‘informant’ (this is with the patient’s consent). A structured case history is collected. A set of cognitive tests, such as Mini-Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA), or clock drawing test is conducted, perhaps by another member of the dementia care team at the primary care centre. A base laboratory test is analysed and following a CT scan, a follow-up visit takes place. If needed, the individual is referred to a specialist. Unfortunately, this ideal scenario is rarely the case, and dementia often goes under-diagnosed in primary care (3).

**Barriers to a making a diagnosis**

Lack of competence, training and skills in dementia as well as negative attitudes towards dementia diagnostic work-ups by primary care physicians are often regarded as significant barriers (4). This is, of course, a problem, although to varying degrees (5). Dementia education geared towards primary care physicians is essential and has proven effective (6). However, there are still two other aspects that needs attention.

First, in many countries, primary care physicians see several patients per hour, perhaps 6–10, and it is not possible to make an accurate dementia diagnosis in 10 minutes. This way of working is often related to significant demands and pressure caused by extensive patient lists (5).

Second, the remuneration system is often linked to a payment per visit structure. The more patients seen, the more money the practice earns. Such payment systems are extremely counterproductive for proper dementia management in primary care (4).

To date, there are many primary care physicians who can manage the assessment and post diagnosis process of their patients with a suspected dementia without needing to make referrals, as they have an ideal structure in place.

However, we are now facing a new situation with two arms which are closely linked: the diagnostic process is moving from dementia to pre-dementia states. Currently in primary care clinical practice, a diagnosis such as mild cognitive impairment (MCI) is not actually the goal, but rather a consequence of the diagnostic process that results in an MCI diagnosis. This is because the individual did not fulfil the criteria for dementia. However, in research, and at many memory clinics, there is a particular focus on the...
pre-dementia Alzheimer’s disease diagnosis. Besides the current diagnostic tools (brain imaging with MRI, PET, CSF, neuropsychology), blood-based markers for Alzheimer’s disease are on their way, and such markers will likely be made available in primary care (7). However, for the moment, it is difficult to anticipate their role. The second arm is the hope for disease-modifying treatments (DMT), particularly for Alzheimer’s disease (8). Since we know that the brain damaging process has been ongoing for many years before criteria for a dementia diagnosis are fulfilled, the arrival of disease-modifying treatments will demand a pre-dementia diagnosis of Alzheimer’s disease.

Since the US Federal Drug Administration has recently (June 2021) given aducanumab a conditional approval for the treatment of Alzheimer’s disease, the situation will likely change in a dramatic way, at least in the US. We have yet to know how it will change in other parts of the world. We also do not know if ‘filters’ or restrictions will be applied to the accessibility of aducanumab. Nevertheless, this new US situation, combined with improved techniques, particularly for pre-dementia Alzheimer’s disease diagnosis, will undoubtedly change the role of primary care in the diagnosis of dementia. If we assume that US approval will be followed in other parts of the world, or that other disease-modifying treatments will enter the market, people with subjective and/or slight memory problems may seek primary care more frequently, with the hope and demand for treatment for an eventual Alzheimer’s disease diagnosis. The use of blood markers in combination with some cognitive tests in primary care (hopefully also responsive in pre-dementia states), may make referrals to specialists for additional assessment increase dramatically. However, and as shown in the reports from RAND (9,10), the readiness for such a heightened demand is inadequate in most countries. The diagnostic infrastructure is not prepared for a large increase in demand for pre-dementia (and early dementia) Alzheimer’s disease diagnostics. The fact that there have been no disease-modifying treatments on the market is perhaps the main reason primary care physicians are sceptical about pre-dementia Alzheimer’s disease diagnostics along with, for example, blood-based biomarkers (11). The argument that an early diagnosis is not only linked to drug treatment, but also presents possibilities for early prevention (12), is probably not a solid argument for many primary care physicians. Prevention of dementia is, to a great extent, linked to cardiovascular risk factors, and this is already a major aspect of the work conducted in primary care. Therefore, even if the risk of dementia is appended, it does not impact the work all that much.

Be aware that this is the situation in high income countries. In low- and middle-income countries, the situation is entirely different. The primary care infrastructure is limited, the diagnostic capacity for dementia is scarce, and primary care physicians are more engaged in managing conditions other than dementia. The accessibility to current Alzheimer’s disease related drugs is already limited (13), and the expected price of a disease-modifying treatment will probably make it more or less impossible to obtain for the vast majority of people with Alzheimer’s disease in low- and middle-income countries.

Another aspect to consider is that even if the sensitivity and specificity of new blood-based diagnostic tests is high (say 90%), the positive predictive values on a population level (with a prevalence of, say 10%), such as in primary care, is low (about 50%) (14). Though the arrival of blood-based biomarkers (in combination with cognitive tests) is considered progress for those of us who work in primary care, the label is important: ‘at risk’ of Alzheimer’s disease does not conclude that people have Alzheimer’s disease before the diagnosis is confirmed with more comprehensive tests. The accessibility to current Alzheimer’s disease related drugs is already limited (13), and the expected price of a disease-modifying treatment will probably make it more or less impossible to obtain for the vast majority of people who are referred to memory clinics, where the Alzheimer’s disease diagnosis was yet to be confirmed, will be referred back to primary care, in an anxious state.

References


Expert essay

Defining Alzheimer’s disease biologically

Clifford R. Jack

Mayo Clinic, Rochester, MN, UNITED STATES

Diagnostic criteria for Alzheimer’s disease

The first formal, widely accepted diagnostic criteria for Alzheimer’s disease were the NINDS-ADRDSA (National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer’s Disease and Related Disorders Association) criteria published in 1984 (1). A diagnosis of probable Alzheimer’s disease could be made in life after certain exclusions, while a diagnosis of definite Alzheimer’s disease could only be made at autopsy. These criteria made complete sense at the time because they were developed in the pre-biomarker era. Because they were well-formulated, they have been widely used in both research and clinical practice for over a quarter of a century. They are still widely used in modern clinical practice. Unfortunately, the critical distinction between probable and definite Alzheimer’s disease made by the NINDS-ADRDSA workgroup is often ignored and, as a result, a non-specific clinical syndrome (typically an amnestic dementia) is commonly equated with Alzheimer’s disease which is a specific disease with a specific pathological definition (2).

Biomarker era

Biomarkers for Alzheimer’s disease are either fluid or positron emission tomography (PET) imaging. It is difficult to pick a specific date marking the beginning of the era of Alzheimer’s disease biomarkers, but review articles describing cerebrospinal fluid (CSF) biomarkers already appeared in the early 2000s (3,4). Magnetic resonance (MR) and fluorodeoxyglucose-positron emission tomography (FDG-PET) had been used since the 1980s to study dementia; however, these modalities are not specific for Alzheimer’s disease, thus the first true disease-specific Alzheimer’s disease imaging biomarker was amyloid PET introduced in 2004 (5). Tau PET was introduced some years later (6). Many research groups around the world have incorporated Alzheimer’s disease biomarkers into their research programmes which has resulted in a large literature base relating observed clinical symptoms in research participants to contemporaneous biomarker indicators of neuropathology. These clinical-biomarker studies revealed three important discrepancies between the 1984 NINDS-ADRDSA (1) definition of probable Alzheimer’s disease and biomarker findings. First, what was labelled probable Alzheimer’s disease on clinical grounds was often not supported by biomarkers. Second, individuals given non-Alzheimer’s disease clinical diagnoses sometimes had Alzheimer’s disease by biomarker findings. Third, many cognitively unimpaired individuals had considerable Alzheimer’s disease pathology by biomarkers. These clinical-pathologic discrepancies had been noted in neuropathologic studies (7,8), but the advantage of biomarkers is the ability to link contemporaneous clinical and biological findings (rather than waiting, sometimes years, for autopsy), as well as the ability to follow individuals over time with serial biomarker-clinical correlations.

The application of biomarkers to clinical research led to the formulation of biomarker-based disease models. A common model holds that different pathologic features of Alzheimer’s disease do not arise simultaneously but rather co-evolve in a staggered offset manner (9). Specifically, Alzheimer’s disease biomarker abnormalities begin with those of amyloid, then tau, then neurodegeneration. Overt clinical symptoms appear last in the sequence, many years after the onset of biomarker evident amyloidosis, and symptoms are most closely linked with tau and neurodegeneration (9).

Revised diagnostic criteria incorporating biomarkers

Two different groups have published revised diagnostic criteria for Alzheimer’s disease that incorporate biomarkers. The International Work Group (IWG) has published a series of criteria centred around the idea that a diagnosis of Alzheimer’s disease requires biomarker evidence of the disease plus overt clinical symptoms (10–12). Individuals with abnormal biomarkers who are asymptomatic (except for familial mutation carriers) are labelled ‘at risk’ for Alzheimer’s disease. The second group to publish diagnostic guidelines was the National Institute on Aging-Alzheimer’s Association (NIA-AA). Three different NIA-AA work groups each published guidelines in 2011, one for preclinical Alzheimer’s disease, for mild cognitive impairment, and one for dementia (13–15). Each of these three documents was internally consistent; however, there were conceptual inconsistencies between them.
NIA-AA research framework

The NIA-AA commissioned another working group in 2016 to address inconsistencies between the three 2011 documents and to incorporate advances in the field (for example, the development of tau PET) that had not been present when the 2011 guidelines were developed. The document produced by this group was labelled the NIA-AA research framework (16). Some of the key principles underlying the research framework were the concepts of syndrome and biology should be separated. An amnestic dementia and Alzheimer’s disease are not synonymous. The former is a non-specific clinical syndrome that may be due to a variety of pathologies; in reality, amnestic dementia or mild cognitive impairment in elderly people is usually due to a combination of pathologies (17). In contrast, Alzheimer’s disease is one specific pathologic entity which is defined by plaques and tangles (2). The term Alzheimer’s disease should be used to describe the biologically defined entity which can be ascertained either at autopsy or in living people by biomarkers, not by a clinically defined syndrome(s).

Operationalisation of biomarkers in the NIA-AA research framework was based on the AT(N) construct (18) in which biomarkers are placed into three general groups based on the nature of the pathologic process that each maps onto. Accepted biomarkers at the time the research framework was developed were either CSF or imaging. Biomarkers of β-amyloid plaques (labelled ‘A’) were cortical amyloid PET ligand binding or low CSF Aβ42 (or 42/40). Biomarkers of fibrillar tau (labelled ‘T’) were elevated cerebrospinal fluid phosphorylated tau (P-tau) and cortical tau PET ligand binding. Biomarkers of neurodegeneration or neuronal injury (labelled ‘(N)’) were cerebrospinal fluid total tau (T-tau), FDG PET hypometabolism and atrophy on MRI. The (N) group was placed in parenthesis to denote the fact that these biomarkers, like clinical symptoms, are not specific for Alzheimer’s disease and thus are used for disease staging but not for definitive diagnosis (16).

Plasma Alzheimer’s disease biomarkers

Diagnostic biomarkers that were accepted, validated, and widely used in research and in some clinical settings at the time the NIA AA research framework was being developed were either cerebrospinal fluid or PET imaging; thus, making a biological definition in vivo required testing that was either invasive or expensive. This was explicitly identified in the research framework document 16 as a significant limitation to widespread adoption of a biologically based definition of Alzheimer’s disease. However, around that time and shortly after the research framework was published in 2018, papers began appearing that showed very promising diagnostic performance for plasma biomarkers in the A category, specifically plasma Aβ 42/40 (19–21), and for biomarkers in the (N) category, particularly plasma NfL (22–27). Very recently, plasma measures of ptau181 and ptau217 have shown very promising diagnostic performance (28–33). The development of plasma Alzheimer’s disease biomarkers has ushered in a new age in which a biologically based diagnosis of Alzheimer’s disease can be generally available non-invasively and inexpensively – blood can be drawn anywhere and sent to central labs for analysis – and can be widely implemented for both research and clinical diagnostic purposes.

Disease-modifying therapy

A second major recent development in the field has been the approval by the Federal Drug Administration (FDA) of the first disease-modifying treatment for Alzheimer’s disease. Aduhelm (aducanumab) received accelerated approval for treatment of people with Alzheimer’s disease who are in the mild cognitive impairment or early dementia stage. FDA approval was based on reduction in amyloid PET in treated patients on the assumption that amyloid reduction was likely to be of benefit. Further studies are required to prove clinical benefit. Although specific guidance on how a diagnosis of Alzheimer’s disease should be verified was not provided in the FDA package insert, the phase 3 clinical trials of aducanumab required documentation of Alzheimer’s disease pathology either by amyloid PET or cerebrospinal fluid biomarkers for entry.

In summary, these two transformative developments, plasma biomarkers and disease-modifying treatments, will interact in a reinforcing manner to reshape the field. The first ever disease-modifying treatment is now a reality. It is likely that clinicians will initially use either amyloid PET or cerebrospinal fluid biomarkers to document the presence of Alzheimer’s disease in patients who are being considered for treatment. However, plasma biomarkers are predicted to play an increasingly prominent role in diagnosis once clinicians gain greater experience with them. Thus, it seems reasonable to predict that plasma biomarkers will make a biological diagnosis of Alzheimer’s disease practical on a wide scale at a moment in time when the ability to make a biological diagnosis in clinical practise is needed to indicate which individuals will benefit from newly approved amyloid lowering therapeutically.
References

Conclusions

When reviewing the totality of the information drawn together in this Chapter, and indeed the entire report, it is evident that receiving a diagnostic assessment for dementia should ideally begin at the primary care level. That said, this is precisely where the barriers to getting such a diagnosis exist. All the amassed survey responses converge to offer an inclusive behind-the-scenes look at what physicians, people with dementia and their carers experience.

From a clinician perspective, a lack of competence and training regarding dementia coupled with a high patient load and remuneration systems that do not encourage lengthy consultations contribute to the complications. Alternatively, from an individual’s viewpoint, lack of recognition of potential signs of dementia along with perceived stigma and fear, costs, difficulties with remote locations and scarce transportation also play their part in delaying a diagnosis.

Nonetheless, there is a movement towards change. Primary care physicians have expressed interest in the potential for biomarker screening tests while the proliferation of self-testing kits point to a heightened awareness by people questioning their symptoms.

However, the ageing population and the influx of people seeking a definitive diagnosis based on the genetic risks indicated by these kits will present major challenges for clinicians, including the shift towards diagnosing pre-dementia states. This is why the advent of validated blood tests to confirm aetiology is being so enthusiastically supported. Cost-efficient, non-invasive and easily implemented – it is hoped that this trifecta of benefits will make dementia diagnosis on a wide-scale a new reality.