

# The Right to Know: Accurate and Earlier Diagnosis of Dementia

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**Dementia  
Access  
Taskforce**



**Alzheimer's  
Research  
UK**

Make  
breakthroughs  
possible

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# 1. Executive summary

Dementia is one of our greatest healthcare challenges, with an ageing population and no treatments to delay the onset or slow the progression of the underlying diseases. Investment in research and development has resulted in significant advances in our understanding of the diseases that cause dementia, the development of novel diagnostic tools and the potential for new treatments. In order to capitalise on progress made, we need to ensure people can benefit from the progress in research. Our best chance to affect the course of the disease lies in intervening much earlier, many years before the common symptoms associated with dementia start to be observed. Access to diagnostics, including the latest molecular diagnostics, is a crucial component in achieving this ambition.

Current dementia assessment services are not able to routinely offer the range of diagnostic tests needed to offer accurate and early diagnosis. In this report, we outline a stepwise approach to reform to progressively build our capabilities and better prepare the system for the changes that may come.

Our approach starts with recognising the benefits that a dementia diagnosis can have now in terms of post-diagnostic management and support. Existing diagnostic capabilities need to be strengthened, through investment, to help reduce the high number of unspecified diagnoses currently delivered. Increasing patient recruitment into clinical trials will also be significantly aided by greater access to molecular diagnostics. But we need to go further to translate the potential of early diagnosis into improvements in the lives of those living with dementia, by preparing the health system to enable access to any new treatments. Wider implementation of molecular diagnostics – including of promising tools and tests currently in development, like blood-based biomarkers – will require considerable investment in infrastructure, service redesign and workforce. Furthermore, we need to address the current variations in clinical practice and access to diagnostics across the UK to ensure equity of access.

With a new dementia strategy underway, set against the backdrop of wider health system reform and pandemic recovery efforts, we believe this is the time to more closely examine dementia diagnostics.

This report is also part of a broader programme of work by Alzheimer's Research UK to enable access to treatments. We will use avenues such as the Dementia Access Taskforce to position the issue of diagnostics at the forefront of our discussions with policy makers, as well as with regulatory, health professional and other stakeholder groups.

## **Summary of recommendations**

Turning our vision of the future into reality will require progressively building our capabilities and better preparing the system for the changes that may come.

### **Now, to improve diagnostic accuracy:**

1. The NHS should invest in improving structural imaging capacity so that memory clinics can offer access to these scans in line with NICE guidelines.
2. The NHS should scope out current as well as future needs and invest in improving patient access to FDG PET and/or CSF tests for the diagnosis of Alzheimer's disease, in line with NICE guidelines.
3. The NHS should mandate a national audit of all specialist dementia diagnostic services, beginning with and extending beyond the National Memory Clinic Audit.
4. Government should invest in the development of a network of high-performance dementia clinical trial sites with the capacity and expertise to fully deploy molecular biomarker testing.

**Next, to prepare for earlier diagnosis:**

5. NICE should develop national clinical guidelines on the diagnosis, treatment and follow-up of patients living with Mild cognitive impairment (MCI).
6. The NHS should scope out short-term as well as long-term needs, and invest in infrastructure, resources and clinical workforce to build diagnostic capacity in preparation for the arrival of future disease-modifying treatments.
7. The health community should foster interdisciplinary collaboration between sites that already use molecular diagnostics, to increase relevant expertise across the country and develop a network of initial sites capable of delivering disease-modifying treatments in the short to medium term.
8. The health community should evaluate, and where appropriate, support the potential of innovative service models to offer a new diagnostic pathway.

## 2. Introduction

Dementia is one of our greatest healthcare challenges. There are almost one million people currently living with dementia in the UK.<sup>1</sup> With an ageing population and no treatments to delay the onset or reduce the progression of dementia, this number is set to rise to 1.3 million by 2030.<sup>1</sup> Today, the economic impact of dementia is over £26 billion per year to the UK economy.<sup>1</sup>

Most people living with dementia are only diagnosed when they or a loved one notice the common clinical symptoms associated with it, such as memory loss. However, scientific evidence suggests that changes in the brain associated with dementia occur much earlier than commonly thought. These changes can happen as many as 10-15 years prior to the onset of visible clinical symptoms. Despite this realisation, advances in diagnostics and greater understanding of the diseases that cause dementia, it is still diagnosed too late for too many people. Pre-pandemic, data suggested an average wait time of 2.2 years for patients to be diagnosed with Alzheimer's disease, which is time when people can't access care, plan for the future and participate in research.<sup>2</sup>

The government's Challenge on Dementia has focused on improving diagnosis rates. The national ambition to diagnose two thirds of those estimated to be living with dementia was met since July 2016.<sup>3</sup> However, since March 2020, due to the impact of COVID-19 on access to services, the diagnosis rate for those 65 and over has dropped from 67% at the start of 2020 to 61% in February 2021.<sup>4</sup> These diagnoses are still primarily based on clinical symptoms and many people simply receive a broad diagnosis of 'dementia' rather than a diagnosis specifying its underlying cause. Historically, it has been challenging to diagnose accurately at an earlier stage of disease progression. Our limited access to the brain has also restricted our ability to directly see and understand the early effects of diseases on the brain. The emergence of molecular biomarkers – measurable biological characteristics – have improved our capacity to identify these early changes and have the potential to offer more accurate diagnoses. But these tools are not used widely in routine clinical practice.

There is a common perception that because we don't yet have any disease-modifying treatments (DMTs), there is little benefit to pushing for earlier diagnosis of Alzheimer's disease, which in some cases may be supported by molecular biomarker testing. However, it is the very lack of such diagnostic infrastructure which may be partly to blame for the failure of successive clinical trials. Waiting for this chicken and egg situation to resolve itself will only risk prolonging these trends.

In an era of COVID-19, we are painfully aware that limited access to a confirmed diagnosis has proven to have had wide-ranging consequences across sectors of society, especially for patients and healthcare providers. Even in the absence of life changing treatments, we believe an accurate dementia diagnosis can be, as with COVID-19, just as powerful. It could allow individuals to plan for the future, open access to dedicated support mechanisms and facilitate the opportunity to participate in clinical trials.<sup>5,6,7</sup> An accurate diagnosis can also potentially positively influence patient management, identify eligible patients for potential treatments and help to utilise healthcare resources as effectively as possible.<sup>8,9,10</sup> We also know the importance of a negative test - it can be hugely significant for a patient to be told they don't have Alzheimer's disease.

We know the public appreciate the value of timely access to diagnosis, as 74% of the population would want to know before the appearance of visible clinical symptoms, if they or a family member had developed Alzheimer's.<sup>11</sup> This recognition extends to the political sphere, where government is investing to support early detection in a range of conditions including dementia, through initiatives such as Our Future Health. This research initiative will recruit a new cohort of up to five million volunteers to find new ways of detecting and preventing diseases potentially before symptoms occur.

This report, looking at accurate and earlier diagnosis of dementia, is part of Alzheimer's Research UK's advocacy work around access to treatments. Our 2018 'Thinking Differently' report assessed the impact of potential future treatments on the existing health system. We recommended NHS and government begin preparing the health system to diagnose dementia causing diseases much earlier, and raise awareness of

molecular diagnostics, in part to enable timely access to future life-changing treatments.<sup>12</sup> We also launched the Dementia Access Taskforce, an ambitious multi-year initiative bringing together patients, government, NHS, NICE, clinicians and the pharmaceutical industry to help prepare the health system for future treatments.<sup>13</sup>

There is a pressing need for these same stakeholders to come together again and accelerate these conversations. Molecular biomarkers are increasingly being employed to recruit people for clinical trials assessing treatments for use in the earlier phases of Alzheimer's. Brain health clinics are being set up in different parts of the country, proposing an alternative, novel and integrated approach to diagnosis and treatment. Perhaps most importantly, we are potentially on the cusp of life-changing treatments for Alzheimer's disease becoming a reality. The 2025 ambition set at the 2013 G8 summit to find a cure or disease-modifying treatment for dementia, may soon be achieved.<sup>14</sup> Because of these reasons and more, we need to invest in infrastructure and diagnostic capacity or run the risk of encountering significant barriers and delays to patients accessing and benefitting from new treatments.

Equally, this report details the case for addressing existing challenges in the clinical landscape to enhance the provision of timely and accurate dementia diagnoses. Even in the absence of life-changing treatments, investing in our infrastructure, capabilities and diagnostic resources, is integral to supporting access to quality care. The association between socioeconomic deprivation and less accurate diagnosis also suggests that improving diagnostic infrastructure is important from an equity perspective.<sup>15</sup> We also pay particular attention to the potentially advantageous role that greater access to molecular biomarkers could play in research and clinical settings. In developing our recommendations, we bring together evidence, action and gathering momentum that are already contributing to bringing these changes about.

The current COVID-19 pandemic has demonstrated the importance of available diagnostics capability to identify relevant patient groups as quickly as possible. A recent NHS England review into the state of diagnostics in the country underlined how the diagnostics landscape was already in need of reform before the pandemic.<sup>16</sup> It recommended the need for investment in diagnostic workforce, equipment and service delivery, to address the current service issues. Considering the setbacks incurred by COVID-19 on dementia diagnoses and diagnostic services, the need for investment has become even more pressing. Investing in diagnostics to overcome current limitations, as well as prepare the healthcare system for future dementia treatments, is integral to making the UK the best country in the world for people living with dementia.

We believe that everyone should expect access to a health system that enables them to find out whether they are developing the diseases that cause dementia. We need to work towards a long-term ambition of having a health system where everyone can find out at the earliest stage whether they are developing any of the underlying diseases that cause dementia and have access to the appropriate interventions to minimise or reduce disease progression. Access to diagnostics, including the latest molecular diagnostics, is a crucial component in achieving this ambition. This paper sets out our views on how investment in diagnostics could help to achieve this vision of the future.

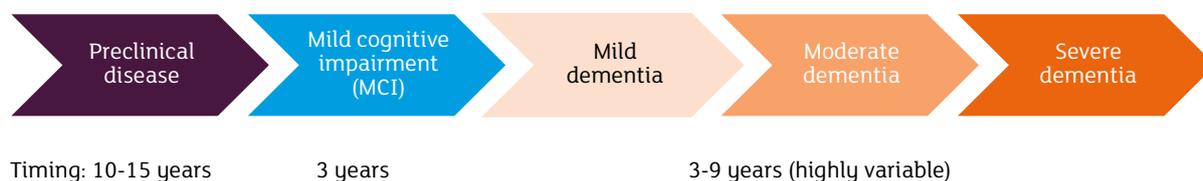
As we work towards this future, there are concrete actions we can take now to progressively build our capabilities and better prepare the system for the changes that may come. There is a case for change now, to improve diagnostic accuracy by ensuring services can offer NICE recommended diagnostics. There is also a case for change for what we know is likely coming next. Namely, to prepare for earlier diagnosis in clinical settings, as well as for the arrival of potential disease-modifying treatments. Only after these steps are progressed, is there a case to be made for the future, with much wider implementation of novel diagnostics and a move towards pre-symptomatic diagnosis.

## 2.1. The Alzheimer's disease continuum

This paper seeks to consider diagnosis for the underlying diseases that cause dementia. However, the focus is on Alzheimer's disease, given that it is the most common dementia causing disease and the most likely to have the first disease-modifying treatment. We recognise many of the principles apply to all the underlying diseases that cause dementia. We also acknowledge that for people who develop dementia at a younger age, many of the current diagnostic services have not been set up to meet their needs. We also note that many people with dementia, especially those with late-stage onset, show evidence of several diseases, also known as mixed dementia.

The spectrum of the underlying diseases that cause dementia, such as Alzheimer's disease, span from an asymptomatic stage through to the symptomatic stages. There is much debate within the field around the nomenclature and definitions for each stage of disease and figure 1 presents one possible approach:

- Preclinical disease: the earliest stage, possibly decades before symptoms. At this stage there are no clinical symptoms but there is evidence of changes in brain pathology, such as the build-up of hallmark proteins amyloid and tau.
- Mild cognitive impairment (MCI): the next stage is where subtle changes in cognitive abilities may be evident, but these symptoms are not severe enough to diagnose dementia.
- Dementia due to Alzheimer's disease: the latter stages are when symptoms have started to impact on people's day to day lives, with changes in memory, orientation or behaviour, such that they are clinically diagnosed as dementia.



*Figure 1: Stages of progression for dementia.*

### Box 1: Overview of current dementia diagnosis pathway for suspected dementia patients

A range of clinical pathways and service configurations exist currently for dementia diagnosis in the UK, with one example set out below. While it is not representative of all potential pathways a patient may go through, the principles are broadly similar throughout. This example is drawn from the Royal College of Psychiatrists and begins with an initial assessment in primary care. But we recognise that diagnosis can also happen elsewhere, such as in neurology and geriatric-led services and also within primary care, emergency departments and within inpatient settings.

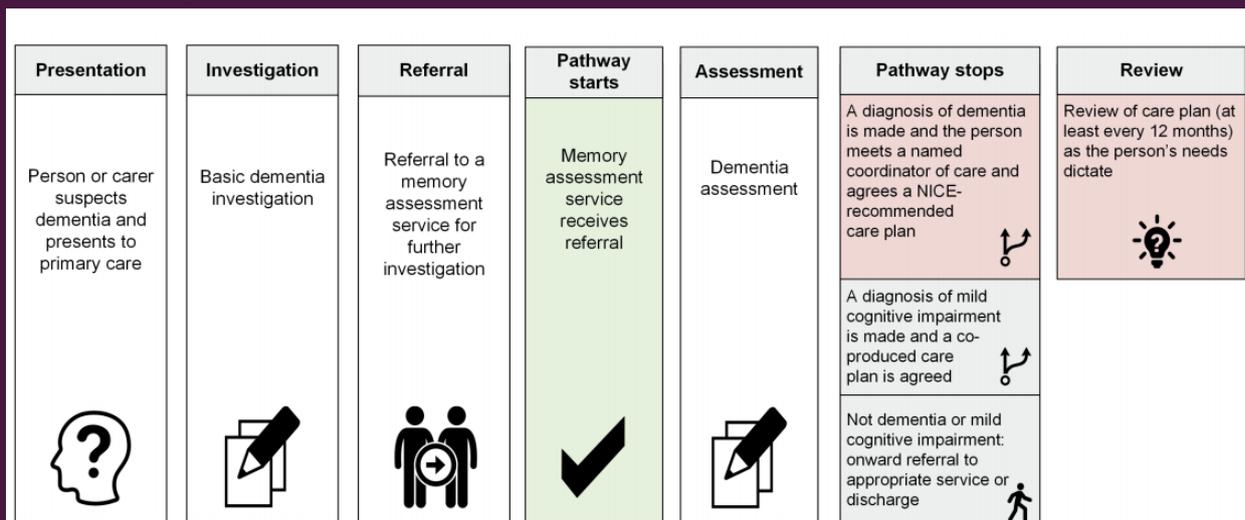


Figure 2: Example dementia diagnosis pathway in England.<sup>17</sup>

### 3. Diagnostic toolbox overview

A clinical evaluation of Alzheimer's disease can incorporate a variety of tests and tools. In this document, we focus on the role of neuroimaging and cerebrospinal fluid sampling (CSF). This is because of the key role they play in offering a more accurate diagnosis and are likely to play in the prescription of a disease-modifying treatment. A range of other imaging, fluid and digital biomarkers, currently at various stages of development, also hold potential to increase early and accurate diagnosis.

The complexity and inaccessibility of the brain, alongside historic underfunding of dementia research, has hampered our ability to understand and diagnose the diseases that cause dementia. There are few opportunities to see or touch a brain. More broadly, there is limited public understanding of mechanisms and processes taking place inside the brain. This inaccessibility has meant that diagnostic approaches have historically used clinical symptoms to diagnose the diseases that cause dementia, particularly using cognitive testing. However, such an approach does not provide information about the underlying disease mechanisms. This type of insight is essential if we are to affect the onset and course of the disease beyond the clinical presentation.

In recent years, there has been recognition of these diagnostic limitations and there are now concerted efforts to develop new diagnostics. Such efforts are starting to offer new techniques and the opportunity to identify biological markers of disease. More recently, research has discovered detectable biological changes in the brain which can be used to increase the specificity of a diagnosis. The development of molecular diagnostics has opened the possibility of diagnosing and intervening years before the dementia stages of Alzheimer's disease, when substantial damage to the brain has already occurred.

Advances in imaging techniques have played a crucial role in allowing us to indirectly look at the brain. Structural and functional brain imaging has been a significant support to more accurately diagnosing the underlying diseases that cause dementia. They have also helped in identifying possible alternative explanations for someone's cognitive decline.

Below, we outline key selected diagnostic methods available for Alzheimer's disease now and potentially in the future.

#### Cognitive tests

Many tests measuring cognitive decline are available to assist in the detection and diagnosis of Alzheimer's disease. These usually form part of an initial assessment. They are often brief, easily administered and used in both clinical and research settings. They are common across the health system (primary care, memory assessment services and neurology clinics). The proprietary Mini-Mental State Examination (MMSE) is perhaps the most widely used screening test for dementia.<sup>18</sup>

#### Structural imaging

Structural imaging is used to visualise anatomical features of the brain. Structural imaging using computerised tomography (CT) or magnetic resonance imaging (MRI) is typically a first line imaging tool used in the clinical assessment of Alzheimer's disease. It is helpful in detecting areas where the brain has lost volume, which can be an indication of neurodegeneration.

NICE guidelines recommend the use of structural imaging in specialist diagnostic settings like memory services.<sup>19</sup> This serves to rule out causes of cognitive decline which may potentially be resolved. It can also assist in dementia subtyping: the identification of the underlying disease(s) responsible for the dementia symptoms.

## Functional imaging

Further tests are possible if previous diagnostic tests, including structural imaging, have not led to a confirmed diagnosis. Functional imaging is used to visualise the underlying processes of brain tissue. NICE recommends fluorodeoxyglucose-positron emission tomography (FDG PET) as an additional test to help confirm suspected Alzheimer's disease.

## Molecular diagnostics

Molecular diagnostic tools, currently amyloid PET scans and cerebrospinal fluid tests, can detect the presence of specific proteins characteristic of Alzheimer's disease which cause damage to brain cells. Tracers have been developed that bind to amyloid proteins in the brain. Using a PET scan with these tracers, we can detect the presence of amyloid and other proteins, something which structural and functional imaging cannot do. A lumbar puncture is used to collect CSF, in which we can measure concentrations of specific proteins, like amyloid and tau. Currently, molecular diagnostics are predominantly carried out in research or academic-led settings, reflecting the recent innovation and development in the field. There is limited access to molecular diagnostics in NHS clinical settings.<sup>20</sup>

The clinical use of CSF, unlike amyloid PET scans, is recommended by NICE in suspected Alzheimer's disease cases where the cause of symptoms remains uncertain after a more traditional diagnostic evaluation.<sup>19</sup> Other expert groups recommend the use of molecular diagnostics in some atypical cases and where the diagnosis is uncertain.<sup>21,22,23</sup> But as amyloid positivity can be common in older individuals who may be cognitively healthy, such results need to be carefully interpreted.<sup>24</sup> Also, interpreting molecular biomarker results by themselves to arrive at a diagnosis is not currently recommended as there are still developments needed, namely in the sensitivity and specificity of these tools.

Within the UK, there is some public reluctance for lumbar punctures. 40% of the UK public are willing to undertake this test to identify their risk of developing Alzheimer's disease, compared to ~80% who are willing to undertake scans or blood tests.<sup>11</sup> We found people were willing to be guided by their clinician to undertake a CSF sample by lumbar puncture, suggesting that a key aspect to acceptability of diagnostic tests will be clinical perception of a given technique.<sup>11</sup> CSF is rarely used for dementia diagnosis in UK clinical practice, in contrast with much of the rest of Europe, thus reflecting wider geographical differences in clinical training and practice.<sup>25,26</sup>

## Promising advances ahead

### *Blood*

The effectiveness of the blood-brain barrier means that until recently blood tests have not been able to accurately measure the hallmark Alzheimer's disease proteins of amyloid and tau. The last few years have seen advances in technology that now enable us to measure these proteins in blood to much greater precision. We can detect amyloid and tau at lower levels than before, which opens up blood as a potential diagnostic. Blood-based biomarkers are highly sought-after tests because they could be a cheaper, more scalable and accessible way to diagnose Alzheimer's disease.

Blood tests are still a relatively novel technique and need to be validated against existing diagnostic techniques before they can be used more widely. Blood tests are starting to be used in clinical trials and it is anticipated that it will be a few years before they could be available within clinical practice. When first available, it is likely that blood tests will offer a first stage filtering process, identifying those with some degree of protein pathology, but not with the sensitivity and specificity needed to be a standalone test. It is likely that CSF or amyloid PET scanning will supplement the blood test. Therefore, a blood test in the short term at least could reduce, but not remove all, demand for CSF or amyloid PET scanning.<sup>27</sup>

## Digital

The current progress in digital health technology is opening new avenues for detecting subtle changes in behaviour that may be associated with the earliest stages of diseases affecting the brain. Proof of concept initiatives are underway, such as Early Detection of Neurodegenerative Diseases (EDoN), spearheaded by Alzheimer's Research UK.<sup>28</sup> The initiative looks to identify behavioural and other measures indicative of the early changes caused by diseases like Alzheimer's. By combining data from multiple measures, it will develop a digital fingerprint that can identify people at the earliest stages of disease. If such approaches are validated, they will offer a highly scalable tool.

### How could this all fit together?

We believe these emerging innovations mean there is a case to reconsider the diagnostic pathway for Alzheimer's disease as a diagnostic funnel (figure 3). Those tests offered earliest are currently the least specific but likely to be the most scalable. Much of the funnel is not currently available in clinical practice and many tests for the very earliest stages of disease still have important research development phases to progress through. The diagram also highlights the importance of balancing scalability, specificity, cost and capacity.

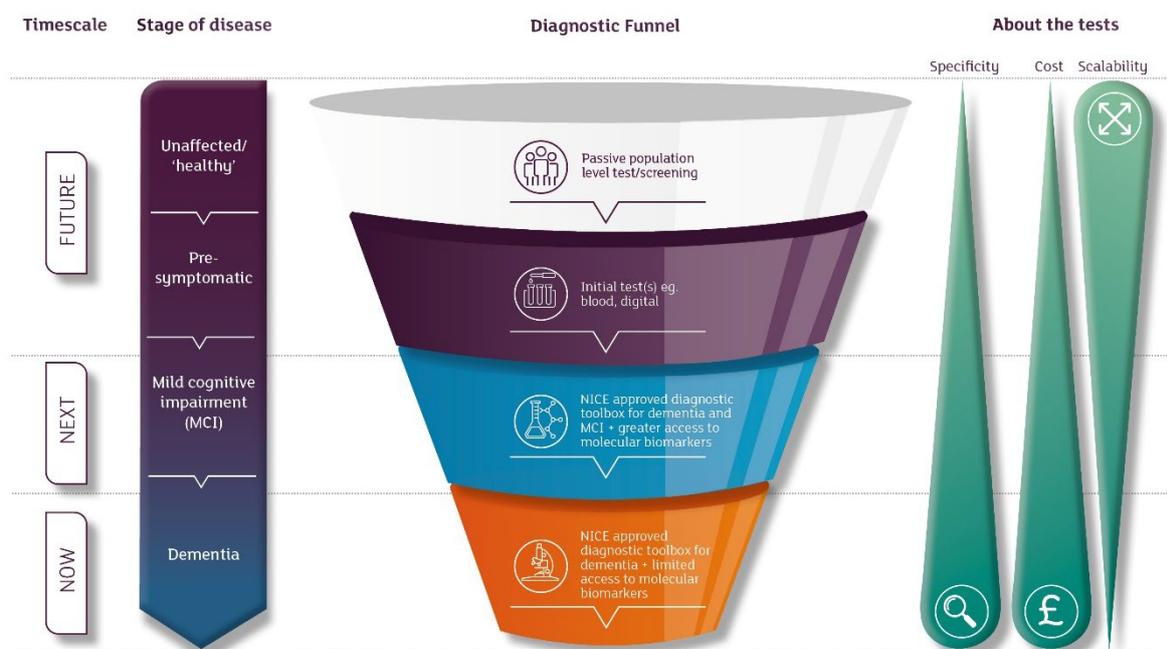


Figure 3: The potential diagnostic funnel for dementia.

Our understanding of dementia is at a turning point. Previously, a definitive diagnosis of Alzheimer's disease could only be made by examining the effects of disease on a brain only after someone had died. Progress in the field of diagnostics means we can now use molecular biomarkers to detect these same effects in the brain while someone is alive. This enables us to move from a diagnosis of exclusion to one of inclusion. This represents a fundamental reinterpretation of our current approach to diagnosing Alzheimer's disease. It also means molecular diagnostics have an important role to play in moving towards earlier and more accurate diagnosis, the success of clinical trials and patient access to future treatments.

## 4. Case for now - improving diagnostic accuracy

The Challenge on Dementia recognised the link between timely diagnosis and access to treatments, care and research.<sup>29</sup> We also believe an accurate diagnosis is of paramount importance to that equation. One of the key achievements of the Challenge on Dementia has been the increase in diagnosis rates of dementia.<sup>3</sup> Despite this progress, there remains considerable variation in diagnostic accuracy between memory clinics. For example, the 2019 memory service audit found diagnosis of “unspecified dementia” for memory clinic patients aged 65 and over varied from 0-50% per service.<sup>30</sup> An unspecified dementia diagnosis can directly affect the type of care and post-diagnostic support a patient receives, for example in terms of accessing potentially important prescription medication. We collectively need to build on the Challenge’s success and ensure even more patients can benefit from an accurate diagnosis of the underlying cause(s) of dementia (their dementia subtype). To that end, NHS England should aim to reduce the level of unspecified diagnoses within the current clinical pathway. This could be addressed by improving diagnostic capacity and infrastructure, thereby raising memory clinics’ access to certain key NICE recommended diagnostic tools.

**Key ask 1: The NHS should invest in improving structural imaging capacity so that memory clinics can offer access to these scans in line with NICE guidelines.**

Limited access to structural imaging lies foremost among the challenges contributing to a high level of unspecified dementia diagnoses. The 2018 NICE guidelines recommend structural imaging is offered as part of memory clinic services, to exclude reversible causes of cognitive decline and help with determining the type of dementia.<sup>19</sup> However, only 26% of memory clinics offered a brain scan (CT or MRI) to patients without a recent scan already.<sup>30</sup> This may be partly because memory clinics are often located in mental health services and the scanners in acute hospitals. It could also be because 60% of the audited memory clinics do not have access to the electronic picture archiving and communication system (PACS) that would enable them to view the brain imaging results.<sup>30</sup>

Access to PACS was concluded by the 2019 Memory Clinic audit to be a key area for improvement. Without PACS the potential to view and interpret scans is limited, reducing the role for scanning within a differential diagnosis. The five-week average waiting time for a CT or MRI scan was also acknowledged to be a key barrier to meeting the six-week patient referral to treatment target.<sup>30</sup> Investment in capacity, as a way to improve overall memory clinics’ access to the results of structural imaging scans in accordance with NICE guidelines, therefore, should begin with investment in this technology.

NHS England should undertake scoping work and invest to statistically and tangibly improve patient access to structural imaging. The scoping should include an assessment of the clinical need for CT and MRI scans, as well as the feasibility of deploying the PACS systems, especially in Mental Health Trusts.

**Key ask 2: The NHS should scope out current as well as future needs, and invest in improving patient access to FDG PET and/or CSF tests for the diagnosis of Alzheimer’s disease, in line with NICE guidelines.**

There is currently limited access to further tests that may help diagnose suspected Alzheimer’s disease. The NICE guidelines recommend FDG PET or CSF as further tests. However, only 77% and 56% of memory services can refer patients for PET scans and CSF testing, respectively.<sup>30</sup> Moreover, it is likely that the services which can access these diagnostics are predominantly located within or near research centres with the necessary infrastructure, thereby creating geographical inequity of access.

As with structural imaging, it is likely that limited access and/or capacity to these further tests is in some cases hindering the accurate diagnosis of the disease(s) causing dementia. The scoping work should weigh the relative benefit of making these tests more widely accessible in the medium term with the specific clinical circumstances under which these tests are recommended. It should also consider the expected unmet clinical need, as well as operational, financial and other hurdles around implementing CSF more widely. The role of

commissioning, including specialist commissioning where appropriate, should be explored to ensure availability of funding for further testing capacity.

**Key ask 3: The NHS should mandate a national audit of all specialist dementia diagnostic services, beginning with and extending beyond the National Memory Clinic Audit.**

The 2019 audit gave us ground-breaking insight into the performance of memory services in the field of dementia diagnosis and care. It provided critical insight into the challenges and discrepancies faced by memory clinics and their patients. The audit concluded that it “demonstrated marked variation in almost every aspect of the memory service pathway, from assessment practices, to the choice of investigations, to the final diagnosis and access to treatment and support”.<sup>30</sup>

The national audit has likewise identified the need for several improvement projects. These include projects to improve diagnostic accuracy, such as by improving access to PACS and limiting the use of “no diagnosis” as a diagnostic endpoint. But they also include key issues discussed later in this document, like improving multi-disciplinary working. The audit needs to be repeated to review the implementation and effectiveness of these proposed changes. We further argue that because of its value, NHS England should mandate this type of audit be regularly carried out at predefined intervals.

#### 4.1. What are the possible implications of molecular biomarkers for clinical trials?

There are currently no approved disease-modifying treatments for Alzheimer’s disease despite numerous clinical trials in recent years. Clinical trials in this field are particularly challenging due to difficulties in recruiting participants at the right stage of disease progression to benefit from a treatment. Screen failure rates are much higher than for other disease areas like oncology and trials take longer to both recruit and read out.<sup>31</sup> We need to find ways of tackling the underlying causes of these challenges and thereby increase our chances of finding life-changing treatments.<sup>32</sup> For example, if some of these potential treatments are based on removing amyloid from the brain, we need to have the tools to demonstrate the presence of such proteins in participants in the first place.

**Key ask 4: Government should invest in the development of a network of high-performance dementia clinical trial sites with the capacity and expertise to fully deploy molecular biomarker testing.**

Patient identification is a major barrier to the successful running of effective and efficient clinical trials. A recent review of phase III trials for Alzheimer’s disease-modifying treatments found the average recruitment period (160 weeks) largely exceeded that necessary to test efficacy and safety (98 weeks).<sup>33</sup> Screening for appropriate patients is also estimated to account for the majority of total per patient trial costs.<sup>31</sup> This difficulty in recruitment may stem from upstream barriers to funnelling appropriate patients into the clinical trial ecosystem. Major barriers include limited public and clinician awareness of the earlier asymptomatic stage of Alzheimer’s disease; public awareness of and understanding of clinical research; healthcare system capacity, notably in primary care; and access to quick and cheap diagnostics.<sup>31</sup>

Limited access to molecular diagnostics, in particular, can be detrimental. Without access to these, participants must undergo a more traditional diagnosis of exclusion, which can be complex and time consuming. This contributes to two significant barriers in recruiting participants for Alzheimer’s disease clinical trials. Trials for disease modifying treatments in the earlier stages for Alzheimer’s suffer from high screen failure rates. These are 88% in the preclinical stage, 78% in the MCI stage and 44% in the mild AD stage.<sup>31</sup> Secondly, evidence from recent trials suggests that even after initial screening, treatments may have failed partly because they targeted the wrong individuals. For example, bapineuzumab and solanezumab are two anti-amyloid treatments that were administered to patients with mild-to-moderate Alzheimer’s disease in phase III clinical trials. But trial findings suggest approximately a third of patients had something other

than Alzheimer's.<sup>34,35</sup> Employing molecular biomarker testing would help alleviate both these issues by ensuring appropriate patients are enrolled who have the relevant underlying disease markers.

We should aim to more widely integrate the use of CSF and/or amyloid PET imaging to enrich trial populations by ensuring only those patients are enrolled who have the correct diagnosis.<sup>36</sup> We are already seeing positive steps taken in this direction, as evidenced by the increasing use of molecular biomarkers in trial entry criteria to confirm the presence of hallmark Alzheimer's proteins.<sup>33</sup>

As part of Alzheimer's Research UK's recommendations for government to deliver its dementia Moonshot commitment, we proposed they invest £15 million pounds over five years to establish a UK network of high-performing clinical trial sites.<sup>37</sup> Such a network would support the government's ambition to make the UK the go-to-place for clinical research by addressing specific challenges encountered in the dementia space. This includes expediting trial set-up times, improving patient recruitment, streamlining contracting procedures and enabling learning via data sharing.

As outlined in our Moonshot action plan, we need to increase clinical trial expertise, tailored recruitment approaches and diagnostic infrastructure. We now further recommend that molecular biomarkers should be considered an integral component to meeting these aims. By enabling the full use of molecular biomarker testing by this network of high-performance clinical trial sites, we can raise our chances of finding potential trial participants at the earliest stages of disease. By increasing access to amyloid PET and CSF, we can increase diagnostic accuracy, facilitate effective and efficient patient recruitment, and improve the likelihood of finding a disease-modifying treatment. This network could also provide a responsive diagnostic capability should a DMT be licensed in the UK and potentially gather invaluable real-world experience via phase IV testing about the ongoing safety and effectiveness of a novel therapeutic pathway.

## 5. Case for next - preparing for earlier diagnosis

To reduce the impact of Alzheimer's disease further, we need to start identifying, treating and caring for people at the earliest possibility. This means we need to gradually transition from diagnosing in the dementia stage of Alzheimer's disease to diagnosing in earlier stages, including Mild cognitive impairment.

### 5.1. The challenge of Mild cognitive impairment (MCI)

We currently have NICE guidelines for the diagnosis, treatment and care of people living with dementia, but these guidelines do not apply to the stages before the established symptoms of dementia, such as MCI. Before we can begin wholly advocating for earlier diagnosis, we first need to agree on what it is that we're looking to diagnose. What should the symptoms, applicable tests and tools, and approach to patient management be for this segment of the population? We should also recognise that the arrival of disease-modifying treatments will inevitably drive changes in the clinical approach to people at earlier stages of disease. But with NICE guidelines, we can seek to minimise the likely variation in service performance and its subsequent impact on patient outcomes.

**Key ask 5: NICE should develop national clinical guidelines on the diagnosis, treatment and follow-up of patients living with Mild cognitive impairment (MCI).**

a) NICE guidelines would ensure greater equity in diagnostic practices and patient management.

Today, MCI is already a widely used clinical diagnosis in England, with 17% of memory clinic patients aged 65 and over diagnosed with MCI.<sup>30</sup> However, there is widespread variation at a service level in the use of MCI as a diagnosis, amounting to between 0 and 47% of patients in memory clinics.<sup>30</sup> It is likely that this variation reflects differences in clinical attitudes and approaches to the use of MCI rather than significant underlying clinical differences in the presenting patients.

The diagnostic challenge around MCI stems in part from two key characteristics. First, MCI can be considered an at-risk state. Per year, approximately 5-15% of those with MCI will go on to develop dementia.<sup>26</sup> After five years, about 50% of those told they have MCI will not have experienced further decline.<sup>26</sup> Evidence also suggests up to 25% may even return to a normal cognitive state.<sup>38</sup> Second, this instability arises partly because the identified issues may be the result of one or more causes, one of which may be a disease that causes dementia. This uncertainty poses significant challenges to MCI's usefulness in clinical settings, especially if there is no standardised approach to patient follow-up and post-diagnostic support.

A recent expert led review of the evidence base for MCI, its clinical utility and role in the future treatment landscape, led to the publication of the Manchester Consensus. Its authors acknowledge the wide variation in diagnosis rates and discuss its several different potential causes.<sup>26</sup> These include a lack of NICE guidance, follow-up duration and, access to imaging technologies and CSF biomarkers. While new guidance from NICE on MCI will not address all the potential sources of variability, it will contribute greatly to minimise variation in the clinical management of patients living with MCI. We therefore join the authors of the Consensus in recommending that NICE guidelines on MCI be urgently developed.

b) NICE guidelines would help define and formalise an early Alzheimer's disease population in the UK.

In the current context, we have limited standardised information about people living with MCI. At an individual level, the assessment of MCI depends on how baseline levels of impairment are defined, which tests are used and consistency in clinical coding.<sup>26</sup> Without standardised guidelines, this creates challenges in terms of reliability and comparability of assessment between patients. At population level, we know that available incidence and prevalence estimates can vary greatly between studies because of differences in population definitions, methodology and diagnostic criteria.<sup>39</sup> The absence of a formally clinically defined

MCI patient population makes it difficult to redress the variability in MCI use and develop a standardised picture of that group's size and features. In turn, this may hinder the understanding and decision-making ability of patients, health professionals and policy makers.

NICE guidelines around MCI would represent an invaluable step towards a widely shared and recognised clinical understanding of MCI. Not only would this drive greater consistency in clinical practice, but it would also enable the health community to firmly establish an MCI patient population. In the longer term, we would be able to more clearly segment patient groups to improve patient management, increase population-level understanding and later identify relevant patients for disease-modifying treatments.

c) NICE's evidence review should cover molecular biomarkers and its guidelines should clearly outline the role of molecular biomarkers in diagnosing MCI due to Alzheimer's disease or other causes of dementia.

The Manchester Consensus recommends that in selected individual cases, molecular biomarkers can play a role in helping diagnose MCI suspected to be caused by AD.<sup>26</sup> Emerging evidence from large-scale studies, like the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study, is showing how tools like amyloid PET can improve diagnostic accuracy and patient management.<sup>8</sup> Separate from NICE, other expert diagnostic criteria also support using molecular biomarkers to help diagnose and predict progression to Alzheimer's, in specific circumstances where MCI is possibly caused by AD.<sup>40,21,41</sup>

This is a rapidly evolving field in which we've made considerable progress in identifying, testing and validating molecular biomarkers in earlier stages of dementia, particularly for Alzheimer's disease. Nevertheless, there are still many questions left unanswered. In the context of developing diagnostic criteria for MCI due to Alzheimer's or other causes of dementia, guidance may be needed on:

- challenges around sensitivity and specificity;
- the need for further evidence of clinical benefit;
- assessing the comparative diagnostic benefit of molecular biomarkers with other Alzheimer's biomarkers; and
- how accurately can existing molecular biomarkers differentiate between Alzheimer's disease, other diseases that cause dementia and ageing.

All this suggests NICE should review the latest evidence and clearly delineate the appropriate use of CSF, amyloid PET and blood-based biomarkers in diagnosing MCI due to Alzheimer's and other diseases that cause dementia. This would formally clarify whether information derived from molecular biomarkers about early changes in the brain could be a useful complement to more traditional means of clinical assessment.

## 5.2. What is the potential impact of a future disease-modifying treatment and what role will molecular biomarkers play?

Based on the current pipeline, it is likely that the first disease-modifying treatments for Alzheimer's disease will work by removing the amyloid protein from the brain. To enable access to such a treatment, clinicians will need to be able to demonstrate a patient has amyloid positivity.

Initial scoping by Alzheimer's Research UK in February 2020 showed that there is currently limited amyloid PET scanning capacity or access to CSF sampling for diagnosing Alzheimer's disease. There are a limited number of clinical services that can analyse CSF samples for amyloid positivity. Existing PET scanning utilisation is already near capacity primarily supporting oncology services. So, there will be limited available capacity to accommodate any increased demand for access to either amyloid PET and/or CSF. Consequently, capital investment will be needed to scale up infrastructure.

Improved diagnostic capabilities and clinical consensus around MCI are important building blocks for earlier diagnosis of Alzheimer's. But we will also need to invest in capacity and infrastructure to respond to a rising

number of patients. This investment should include making molecular diagnostics more widely available, given the likely role of amyloid positivity in enabling access to potential future disease-modifying treatments.

**Key ask 6: The NHS should scope out short-term as well as long-term needs, and invest in infrastructure, resources and clinical workforce to build diagnostic capacity in preparation for the arrival of future disease-modifying treatments.**

In the event of a new disease-modifying treatment, there will be a significant increase in demand for a diagnosis. First, the system will need to identify people living with Alzheimer's disease who would be eligible for treatment based on the licensing label of the treatment. The arrival of a disease-modifying treatment is also likely to result in significant numbers of people seeking a diagnosis who had previously not done so. This might include cognitively healthy people who worry they might have dementia and those who have been experiencing symptoms for some time but hadn't sought a diagnosis previously.

The existing diagnostic pathway, starting with primary care, will need to adapt to face any such increase in demand. Pre-COVID-19, only 26% of memory clinic patients met the 6-week target to be diagnosed with dementia and begin treatment following a GP referral.<sup>30</sup> It is therefore unlikely that current system capacity will be able to adequately cope with the anticipated level of demand created by a disease-modifying treatment. The current diagnostic pathway will need to have the capacity and workforce with the knowledge and skills to successfully adapt to the new diagnostic requirements.

Considerable investment will be required in infrastructure and clinical capacity to both undertake molecular biomarker tests and interpret results. The choice of which molecular diagnostic tool to employ to detect the presence of amyloid is likely to be dependent on cost and availability. In terms of costs, amyloid PET scans are estimated to be more expensive (~£1000 per scan) than CSF sampling (~£630/sample analysed).<sup>42</sup> Exact costs depend on the number of tests performed, as some components of cost, such as purchasing additional PET scanners, will depend on the capacity required. CSF sampling has the potential to be more scalable as it requires less significant infrastructure investment, especially if analysis of CSF samples operates in the form of a centralised service. Clinical capacity will likely need to include radiographers, nuclear medicine radiologists, nursing and administrative staff. We anticipate that blood-based biomarkers may well be clinically available in the near future. However, it is not clear that they will, in the short term at least, be able to fully replace CSF and amyloid PET in terms of clinical utility.

The necessary growth in diagnostic infrastructure and workforce will take time. If we are to ensure timely and equitable patient access to any new DMT, we need to begin considering and addressing these issues now.

**Key ask 7: The health community should foster interdisciplinary collaboration between sites that already use molecular diagnostics, to increase relevant expertise across the country and develop a network of initial sites capable of delivering disease-modifying treatments in the short to medium term.**

If and when a disease-modifying treatment is licensed in the UK, there are likely to be a limited number of locations that have the diagnostic infrastructure, capacity and skills available to be able to diagnose amyloid positivity. Regional collaboration will be needed between these centres, as well as between clinical academics who already employ biomarker testing in clinical and research settings. This will be needed to both inform the development of broader treatment pathways and improve equity of access.

**Key ask 8: The health community should evaluate, and where appropriate, support the potential of innovative service models to offer a new diagnostic pathway.**

Brain health clinics have been proposed as one potential model of an integrated and multidisciplinary approach to care. They would identify and assess all those in the prodementia stages and offer non-

pharmacological and pharmacological interventions to promote brain health, access to support services, and referral to research trials.<sup>43</sup> Since these clinics were articulated in the Edinburgh Consensus, varying models are now in various stages of development in at least Edinburgh, Manchester, Oxford and Bristol. A national programme in Scotland was also established in 2020. While these clinics are still at a proof-of-concept stage, their approach to early diagnosis and intervention could teach us a lot in the short term about how to design services in the long term. The successes of these programmes should be evaluated in due course to determine their longer-term viability and role in dementia patient pathways.

We also need to consider the development of molecular diagnostics within the wider policy context. A recent review of diagnostic services, also proposed the implementation of new service models, including the creation of community diagnostics hubs.<sup>16</sup> These would offer a broad range of diagnostic services targeted towards multiple conditions, allow for ongoing patient monitoring and potentially integrate digitally enabled home-based services. The opportunity, and potentially the challenge, is to make the case to ensure that future diagnostics for dementia integrate with these novel directions.

## 6. Case for the future - anticipating a new diagnostic pathway

### 6.1. Our vision

Our ultimate vision is of a world where people are free from the fear, harm and heartbreak of dementia. We envisage a future health system where everyone can find out at the earliest stage whether they are developing any of the underlying diseases that cause dementia and have access to the appropriate interventions to minimise or reduce disease progression. Access to diagnostics, including the latest molecular diagnostics, is a crucial component in achieving this ambition.

We know that it will take time and effort to get to this vision. As outlined, we need to incrementally build on the current NICE guidance. We need to support clinical trials to find new treatments and research into diagnostic tools that help us to identify patients earlier. Also, we should address the initial challenges of the arrival of the first disease-modifying treatments and finally, engage the public and clinicians in the changes ahead. Clearly, the system will continue to evolve and change over this timescale. Therefore, we need to plan an adaptable approach.

Alzheimer's Research UK is committed to driving forward our vision of this future health system. Our efforts will be underpinned by these six principles:

- 1) Engage with the evolving dementia diagnostics landscape and continue to advocate, where appropriate, for additional investment in the health system's ability to identify and support people living with dementia.
- 2) Evaluate the latest research and innovations that could facilitate early and accurate diagnosis of people living with dementia and support stakeholder engagement with these technologies.
- 3) Consider, support and engage with the development of innovative diagnostic service models.
- 4) Work with stakeholders to develop a new clinical pathway, identifying the skills and competencies required at each stage.
- 5) Work with clinical stakeholders to identify the education and training needs of a new pathway and agree an approach to address these needs.
- 6) Engage the public, health community and other stakeholders in awareness raising around earlier detection and diagnosis.

### 6.2. Innovation will create opportunities

There has been increased investment in dementia research in recent years, and this is likely to result in significant progression in innovation and the development of new technologies which will have impact across the diagnostic pathway. The incentive to progress will largely be driven by when, and if, disease modifying treatments are available. Their presence removes the argument that there is no point in diagnosing earlier.

We anticipate considerable progress in the field of molecular biomarkers that have the potential to revolutionise the diagnostic pathway. This is both in terms of developing the technology to measure biomarkers we already know about, such as amyloid and tau, but also other emerging or yet-to-be identified biomarkers that may bring new insight to diagnostic approaches. For example, there is potential to use neurofilament light as a marker of nonspecific neurodegeneration or the use of retinal or ocular lens scanning to identify the presence of amyloid. As outlined in figure 3, we expect the diagnostic funnel to broaden and identify people developing, or even at risk of developing, Alzheimer's disease at increasingly earlier stages.

There is strong optimism across the field that blood based biomarkers will be clinically available in the next 2-5 years. Work is currently underway to develop standardised tests that are clinically reproducible over time. This will need to be complemented by the development of appropriate use criteria and clinician training to interpret results before clinical implementation is realistic. We also anticipate there will be significant

progress in developing digital markers to identify the earliest indications of disease. Used in conjunction with blood-based biomarkers or other novel diagnostics, digital biomarkers offer scalable tests that are likely to be widely accessible.

The use of blood and digital tools will have significant impacts for clinical practice. We anticipate that the existing clinical specialties of neurology and psychiatry will work in new ways both within and between services. Greater collaboration will enable the range of skills and expertise to offer a holistic and integrated approach to diagnosing Alzheimer's disease.

Also, as we find out more about the influence of genetics in Alzheimer's and dementia, it may be that discussions of genetic risk too become part of a future clinical diagnostic model. For example, polygenic risk scores (PRS) are a way of calculating aggregate risk from different genetic variants associated with Alzheimer's. PRS have been shown to be associated with different markers of Alzheimer's disease (e.g. cognitive decline prior to the onset of clinical dementia symptoms) and with utility in predicting diagnosis.<sup>44,45</sup> PRS thus may become an important way to detect and diagnose earlier.

By broadening the diagnostic funnel to a larger and younger population it is likely that GPs and primary care will play a key role in the utilisation of these new technologies. We appreciate that primary care already faces challenges with workforce shortages and an increasingly complex caseload. However, there is likely to be a significant patient group who do engage with new diagnostic technologies and who will seek health advice from their GP practice. We need to work with primary care professionals to ensure they have the knowledge and skills to support their patients and are able to refer patients on to the most appropriate specialist services.

By identifying people at a much earlier stage there is also the opportunity to offer health and lifestyle advice and interventions to modify and reduce risk of disease progression. By supporting the concept of brain health, we can normalise an approach that looking after your brain should be as important as looking after your physical and mental health.<sup>46</sup>

With earlier diagnosis comes challenges around uncertainty in terms of disease progression and wider implications for the individual. Questions of information disclosure for services such as health insurance and the impact of an early diagnosis on decisions around employment and driving will need to be answered. It is because of questions like these that we may need a long-term model of care for the conditions that cause dementia. This includes recognising the earlier people are diagnosed, the earlier they will need access to post-diagnostic support.

### 6.3. A future diagnostic pathway

With the likely progress in diagnostic technologies coupled with the arrival of disease modifying treatments, there is a strong case to develop a new clinical pathway for Alzheimer's disease. With a younger population being identified at an earlier stage in disease progression, the current pathway (figure 2) is unlikely to be able to meet future needs. We recognise that the first disease-modifying treatments are likely to only be available to those in the earliest stages of disease. Therefore, it is vital that alongside the development of a new pathway, existing services are still available to support people in more advanced stages of disease progression. Ultimately, we may be able to screen for the diseases that cause dementia. There are a clear set of principles for screening, set out by the National Screening Committee and the World Health Organization that would need to be met should we want to take such an approach.<sup>47,48</sup>

While much of the detail is uncertain, depending on the progress with diagnostic technologies and the timing and specific requirements of disease-modifying treatments, there is enough to start considering a new pathway. There is potential to learn from other disease areas who have experienced significant innovation and the arrival of the first disease-modifying treatments, such as multiple sclerosis or HIV/AIDs. We can also evaluate the success of the Brain Health Clinics currently being set up in several locations in the UK to determine whether they offer a viable contribution to a new clinical pathway.

## 7. Next steps

While there is uncertainty over what exactly the future of early diagnosis and treatment of Alzheimer's disease will look like, we are confident there are concrete steps we can already take today to prepare for that future. Alzheimer's Research UK therefore commits to these actions:

- Engage the NHS, NICE and other relevant health stakeholders on the challenges and opportunities highlighted in this document.
- Continue our ongoing leadership of the Dementia Access Taskforce to ensure critical work around access to treatments is kept at pace.
- Engage with the Department of Health and Social Care on the forthcoming dementia strategy to ensure the issue of diagnostics is appropriately addressed.

### **Summary of recommendations**

Turning our vision of the future into reality will require progressively building our capabilities and better preparing the system for the changes that may come.

#### **Now, to improve diagnostic accuracy:**

1. The NHS should invest in improving structural imaging capacity so that memory clinics can offer access to these scans in line with NICE guidelines.
2. The NHS should scope out current as well as future needs, and invest in improving patient access to FDG PET and/or CSF tests for the diagnosis of Alzheimer's disease, in line with NICE guidelines.
3. The NHS should mandate a national audit of all specialist dementia diagnostic services, beginning with and extending beyond the National Memory Clinic Audit.
4. Government should invest in the development of a network of high-performance dementia clinical trial sites with the capacity and expertise to fully deploy molecular biomarker testing.

#### **Next, to prepare for earlier diagnosis:**

5. NICE should develop national clinical guidelines on the diagnosis, treatment and follow-up of patients living with Mild cognitive impairment (MCI).
6. The NHS should scope out short-term as well as long-term needs, and invest in infrastructure, resources and clinical workforce to build diagnostic capacity in preparation for the arrival of future disease-modifying treatments.
7. The health community should foster interdisciplinary collaboration between sites that already use molecular diagnostics, to increase relevant expertise across the country and develop a network of initial sites capable of delivering disease-modifying treatments in the short to medium term.
8. The health community should evaluate, and where appropriate, support the potential of innovative service models to offer a new diagnostic pathway.

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