

Health Technology Review

# Health System Readiness for Disease-Modifying Therapies for Alzheimer Disease

# Key Messages

## What Is the Issue?

- Alzheimer disease (AD) is a chronic neurologic degenerative disease and 1 of the most common causes of dementia. It affected an estimated 368,200 people in Canada in 2020.<sup>1</sup>
- Mild cognitive impairment (MCI) is a clinical condition involving memory loss that can progress to dementia and is often due to underlying AD. It was estimated to affect around 917,000 people in Canada aged 60 and older in 2020.<sup>1,2</sup>
- Disease-modifying therapies (DMTs) are being developed that target underlying pathologic processes of AD to slow disease progression, unlike contemporary treatments that focus on managing symptoms. A prominent target of these therapies is amyloid-beta, a protein known to contribute to amyloid plaques. Many of the anti-amyloid-beta DMTs are intended for people with early-stage AD, which includes MCI and mild dementia due to AD.
- At least 7 countries have approved a therapy from this treatment class, and, at the time of writing, 2 therapies are undergoing regulatory review by Health Canada and reimbursement review by Canada's Drug Agency (CDA-AMC).
- DMTs demand more frequent health care visits and higher use of medical imaging for safe treatment and monitoring. This would greatly impact current care pathways for early-stage AD, necessitating an examination of health system readiness in Canada.

## What Did CDA-AMC Do?

- CDA-AMC sought to examine health system readiness in Canada and care pathways for early-stage patients with AD in preparation for the potential use of these anti-amyloid-beta DMTs in Canada.
- CDA-AMC reviewed publicly available data and literature about health systems and AD treatment pathways for improving dementia care to prepare for the possible introduction of DMTs in health systems in Canada.

## What Did CDA-AMC Find?

- CDA-AMC found that, if DMTs were approved by Health Canada and provincial and territorial drug plans, a new model of care for AD in Canada would be necessary. The new care pathway would require:
  - earlier screening and diagnosis, at the MCI or mild dementia

# Key Messages

- stages of AD
- guidance for optimal use of diagnostic imaging and biomarker-based tests, as well as an increase in equitable access to PET-CT units for amyloid PET exams or cerebrospinal fluid (CSF) testing to assess treatment eligibility
- increased capacity to administer IV infusions
- guidance for optimal use of MRI to avoid overuse and increase equitable access to MRI to monitor individuals through treatment
- a combination of reliable and validated methods and tools for evaluating cognitive decline in diverse populations, including Indigenous Peoples and racialized groups, presenting with cognitive symptoms or undergoing treatment
- clear criteria for discontinuing treatment.
- CDA-AMC found that assessment and diagnosis of early-stage AD and timely access to DMTs could be delayed due to:
  - a lack of education and awareness of symptoms of early-stage AD among the general public and care providers, as well as cultural barriers, including a fear of stigma or cultural perceptions of the condition<sup>3</sup>
  - staffing shortages in care providers capable of assessing and treating dementia and other supporting staff, including primary care providers (PCPs), dementia specialists, nurses, imaging staff, and social care providers
  - limited capacity of medical imaging (e.g., PET-CT and MRI) and laboratory services (i.e., CSF analysis) to confirm early-stage AD and treatment eligibility and to monitor drug response and disease progression.
- A variety of new technologies are in development, including new AD biomarker testing methods, that may alleviate some capacity concerns in dementia detection, treatment eligibility screening, treatment administration, and patient monitoring.
- Alternative DMTs that target other AD pathologic processes are also in development.

## What Does This Mean?

- There may be challenges in providing equitable and timely access to DMTs for AD, given the geographic distribution of the population (especially in rural and remote locations), cultural barriers, and lack of awareness of the condition in the population in Canada.

# Key Messages

- Not all individuals with mild dementia due to early-stage AD or MCI who are eligible for treatment may have timely access to screening and diagnosis, which could prevent them from receiving DMTs.
- Additionally, an increased number of individuals — some of whom may not be eligible for DMTs — may be motivated to seek screening, leading to higher demand and potential delays in the screening process.
- Health system decision-makers may want to consider system-wide adaptations to enhance screening and care for individuals with suspected early-stage AD, given the projected rise in AD prevalence, which is expected to exceed 1.1 million people by 2050.<sup>1</sup> This may include:
  - adding more health and social care staff
  - providing enhanced training to effectively assess and diagnose early-stage AD
  - improving access to diagnostic imaging to screen and monitor patients using anti-amyloid-beta DMTs.

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## Abbreviations

<b>AD</b>	Alzheimer disease
<b>AI</b>	artificial intelligence
<b>ARIA</b>	amyloid-related imaging abnormalities
<b>CADRO</b>	Common Alzheimer's Disease Research Ontology
<b>CCCDTD</b>	Canadian Consensus Conference on the Diagnosis and Treatment of Dementia
<b>CSF</b>	cerebrospinal fluid
<b>DMT</b>	disease-modifying therapy
<b>GFAP</b>	glial fibrillary acidic protein
<b>LP</b>	lumbar puncture
<b>mAb</b>	monoclonal antibody
<b>MCI</b>	mild cognitive impairment
<b>MINT</b>	multispecialty interprofessional team
<b>NfL</b>	neurofilament light chain
<b>NICE</b>	UK National Institute for Health and Care Excellence
<b>p-tau</b>	phosphorylated tau
<b>PCP</b>	primary care provider

## Background

New DMTs using monoclonal antibodies (mAbs) may provide new treatment options for people with MCI and mild dementia due to early-stage AD. Unlike existing treatments that focus on managing the symptoms of AD or MCI, DMTs are intended to slow disease progression.<sup>4</sup>

Currently, no DMTs are approved for use in Canada for any type of dementia, but, if DMTs are approved by Health Canada, a surge in demand is possible. Resource implications are anticipated, as DMTs would place new requirements on the health care system for their optimal use.<sup>4,5</sup>

## Objective

This report examines the readiness of health care systems in Canada for the potential introduction of anti-amyloid-beta mAb DMTs. While there are several new AD therapies on the horizon, this report focuses on mAb DMTs targeting amyloid-beta in patients with early-stage AD, including MCI or mild dementia due to AD. In some countries, these therapies have received regulatory approval and positive recommendations for reimbursement and are being implemented in the health care system.

This report also explores emerging technologies that could enhance health systems' efficiency in implementing anti-amyloid-beta mAb DMTs for AD and provides an estimate of the number of patients with incident early-stage AD who could receive treatment with anti-amyloid-beta mAb DMTs.

## Approach

Information specialists conducted a tailored literature search, balancing comprehensiveness and relevance, across various sources, including a focused internet search conducted on March 8 and 9, 2024, as well as regular search updates. Content experts were consulted for input and peer review. This document delineates the current patient pathway for AD and outlines 4 domains of a potential future AD treatment pathway for novel anti-amyloid-beta mAb DMTs: assessment and diagnosis of early-stage AD, treatment eligibility assessment, treatment administration, and patient monitoring.

## What Is the Context?

### Alzheimer Disease and Mild Cognitive Impairment

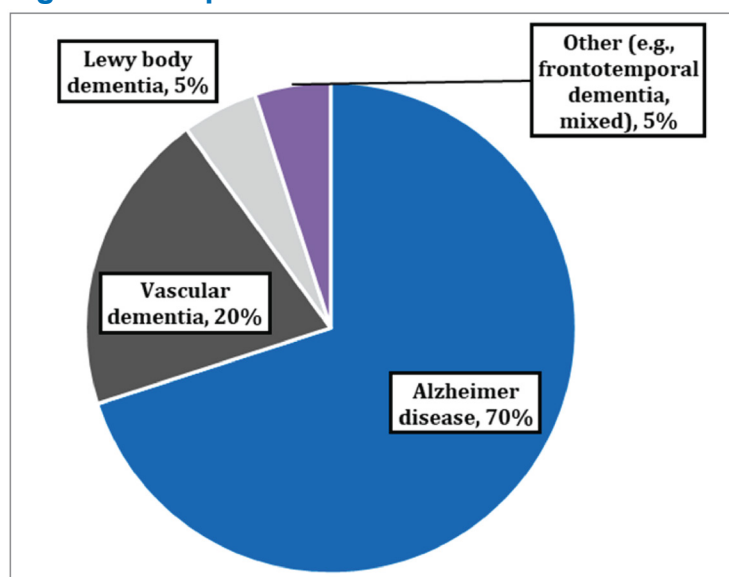
- Dementia is a condition characterized by symptoms such as memory loss and difficulties with attention, language, and problem solving resulting from specific disruptions to brain function, reducing a person's ability to perform everyday activities.<sup>1</sup>
- AD is a chronic neurologic degenerative disease that results in a progressive loss of cognition, function, and social capabilities.<sup>6,7</sup> AD can cause changes to brain structures years before any



symptoms develop and is 1 of the most common causes of dementia, contributing to 60% to 70% of dementia cases (Figure 1) and often affecting people aged older than 65.<sup>1,4,5</sup>

- MCI is a neurocognitive disorder that is characterized by mild symptoms such as memory impairment but that does not functionally affect everyday activities.<sup>7,9</sup> MCI frequently goes undetected until symptoms become more severe.<sup>10</sup>
- MCI is often described as an intermediate stage of cognitive impairment between the changes in cognition associated with aging and the onset of dementia. Around 10% to 15% of MCI diagnoses progress to dementia caused by underlying AD annually.<sup>2,9</sup> Not all MCI diagnoses result from AD pathology, as MCI can be caused by a variety of conditions.<sup>7,9</sup> Early-stage AD includes both MCI due to AD and mild dementia due to AD.<sup>1,2,11</sup>

**Figure 1: Proportions of Common Causes of Dementia<sup>8</sup>**



## AD in the Context of Canada

- In Canada in 2020, there were an estimated 368,200 people living with AD, with that total expected to rise to more than 1.1 million people by 2050.<sup>1</sup>
- Applying US estimates of MCI prevalence to the population in Canada, approximately 917,000 individuals aged 60 and older in Canada would have been affected by MCI in 2020.<sup>2,12</sup>
- In 2020, the total annual economic burden of dementia in Canada was estimated at \$40.1 billion, an average of \$67,200 per person with dementia, and this cost is projected to rise to approximately \$65.2 billion by 2030.<sup>13</sup> According to the Alzheimer Society of Canada and the Public Health Agency of Canada, the total health care system costs and out-of-pocket costs of caring for people with dementia are 5.5 times greater than for those without dementia.<sup>14</sup> The latter stages of AD involve the largest health care costs due to loss of independence, necessitating more attentive and intensive care, typically provided in long-term care or assisted-living residences.<sup>15,16</sup>

- AD diagnosis currently relies on clinical presentation and family history, complemented by clinical assessment of cognition and functional impairment. Neuroimaging and AD biomarker testing are recommended only when initial evaluations are inconclusive in identifying the underlying cause of cognitive impairment.<sup>17</sup> Routine screening of asymptomatic older adults with cognitive testing or diagnostic imaging is not recommended by the 5th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD) guidelines,<sup>17</sup> although there is some disagreement on this recommendation.<sup>17,18</sup>
- Current AD treatment focuses on primary care, where available, and involves psychosocial interventions and pharmacological therapies (e.g., cholinesterase inhibitors and memantine). These approaches are not intended to slow disease progression and instead are intended to manage symptoms and late-stage disease.<sup>17,19</sup> Currently, MCI is treated with preventive lifestyle measures, such as regular physical exercise, mentally stimulating activities, and improved nutrition. These lifestyle adjustments may reduce the risk of progression to dementia, but there are no recommended pharmaceutical treatments for MCI.<sup>17,20</sup>

## Recent Developments in DMTs Using Monoclonal Antibodies for AD

- The development of several novel mAb DMTs is predicated on recent advances in the understanding of AD biomarkers, which are indicators of pathological change of the disease.<sup>4</sup> These therapies are designed to target protein accumulation associated with these biomarkers, thereby aiming to slow disease progression.<sup>21,22</sup>
- One such target of these mAb DMTs is amyloid-beta, a protein believed to contribute to the formation of amyloid plaques in the brain, a signature biological milestone of AD that can lead to brain cell death. The amyloid hypothesis posits that removal of amyloid-beta can slow plaque formation and AD progression, prompting the development of anti-amyloid-beta mAb DMTs.<sup>23</sup>
- Six anti-amyloid-beta mAb DMTs have advanced to or completed phase III clinical trials: aducanumab, donanemab, gantenerumab, lecanemab, remternetug, and solanezumab. Eligibility for these treatments requires early diagnosis of MCI or dementia due to AD.<sup>24</sup> While 2 of these therapies have received FDA approval, others are still under evaluation in clinical trials, with additional treatments in active development.<sup>21,25,26</sup> For the anti-amyloid-beta mAb DMTs that have been approved in the US and other countries, at least 3 MRI neuroimaging exams were required to monitor for adverse events during early phases of treatment, to allow treatment regimens to be tailored accordingly.<sup>27-30</sup> However, if adverse events occur, additional MRI exams would be needed until symptoms resolve.<sup>27-30</sup>
- A reported limitation of this approach to anti-amyloid-beta mAb DMT development is that cognitively healthy individuals will sometimes have abnormal biomarker results. Abnormal biomarker levels do not necessarily indicate that patients will develop AD in the future, meaning that some individuals may receive treatment that is not needed.<sup>31,32</sup> There is also some uncertainty as to whether clearing amyloid-beta accumulations actually improves memory and cognition.<sup>32,33</sup>

- If regulatory bodies and provincial and territorial formularies approve the use and reimbursement of these novel anti-amyloid-beta mAb DMTs, the current paradigm for treatment and management of AD in Canada may need to change. Potential gaps in the current system would need to be addressed so that:<sup>5,20,32,33</sup>
  - individuals with cognitive symptoms receive timely and equitable access to dementia specialists for an early cognitive assessment of AD and to imaging specialists for neuroimaging
  - there is increased capacity and equitable access to amyloid PET scans or lumbar puncture (LP) procedures to determine levels of abnormal amyloid-beta required to assess treatment eligibility and there are standardized optimal-use guidelines for amyloid PET and LP procedures
  - staffing capacity, particularly of dementia specialists, matches expected demand for services
  - there is timely access to MRI scans for screening that follows standardized optimal-use guidelines and for monitoring adverse events during treatment and health care systems are equipped to manage effectively and address any adverse events that may arise.

## Health System Readiness

### The Patient Pathway

Currently, the diagnostic and treatment pathway for people with early-stage AD, which includes MCI and mild dementia due to AD, typically begins with the presentation of symptoms. However, a significant portion of the general public remains unaware of the symptoms of early-stage AD.<sup>34,35</sup>

Patients and their caregivers initially seek care from social care services or from a PCP who can recognize, assess, and diagnose AD, possibly collaborating with a dementia specialist if their expertise is required. Upon confirmation of early-stage AD, current treatments primarily focus on managing symptoms.

It is anticipated that a new model of care and clinical pathway for early-stage AD and additional public education and outreach campaigns may be needed for the successful implementation of anti-amyloid-beta mAb DMTs, if they are approved in Canada. The potential disease treatment pathway for anti-amyloid-beta mAb DMTs could encompass 4 clinical domains ([Figure 2](#)): assessment and diagnosis of early-stage AD, treatment eligibility assessment, treatment administration of anti-amyloid-beta mAb DMTs, and patient monitoring.

### Assessment and Diagnosis of Early-Stage AD

The assessment and diagnosis domain of the clinical pathway may include identifying individuals at risk of AD who are experiencing cognitive symptoms in social care services or primary care settings and administering cognitive assessments through trained care providers. The expertise of dementia specialists and medical imaging professionals to confirm suspected diagnosis of early-stage AD via cognitive assessments and neuroimaging (i.e., MRI or CT exams) may also be required.

### **Treatment Eligibility Assessment**

The treatment eligibility assessment domain of the clinical pathway may involve assessing whether people with early-stage AD are eligible to receive anti-amyloid-beta mAb DMTs. In countries where these therapies have been approved, assessment of individuals includes LP or amyloid PET scans to determine amyloid-beta positivity. Additionally, individuals are evaluated for susceptibility to adverse events, such as brain hemorrhages, using MRI and genotyping.

### **Treatment Administration of Anti-Amyloid-Beta mAb DMTs**

The treatment administration domain of the clinical pathway would involve travel to and from an outpatient clinic. Individuals are administered anti-amyloid-beta mAb infusions at these clinics every 2 or 4 weeks.

### **Patient Monitoring**

The treatment monitoring phase of the clinical pathway would be concurrent with treatment administration and involves regular MRI monitoring for adverse events, supervised by a specialist. The frequency of MRI monitoring may increase if symptoms of adverse events develop.

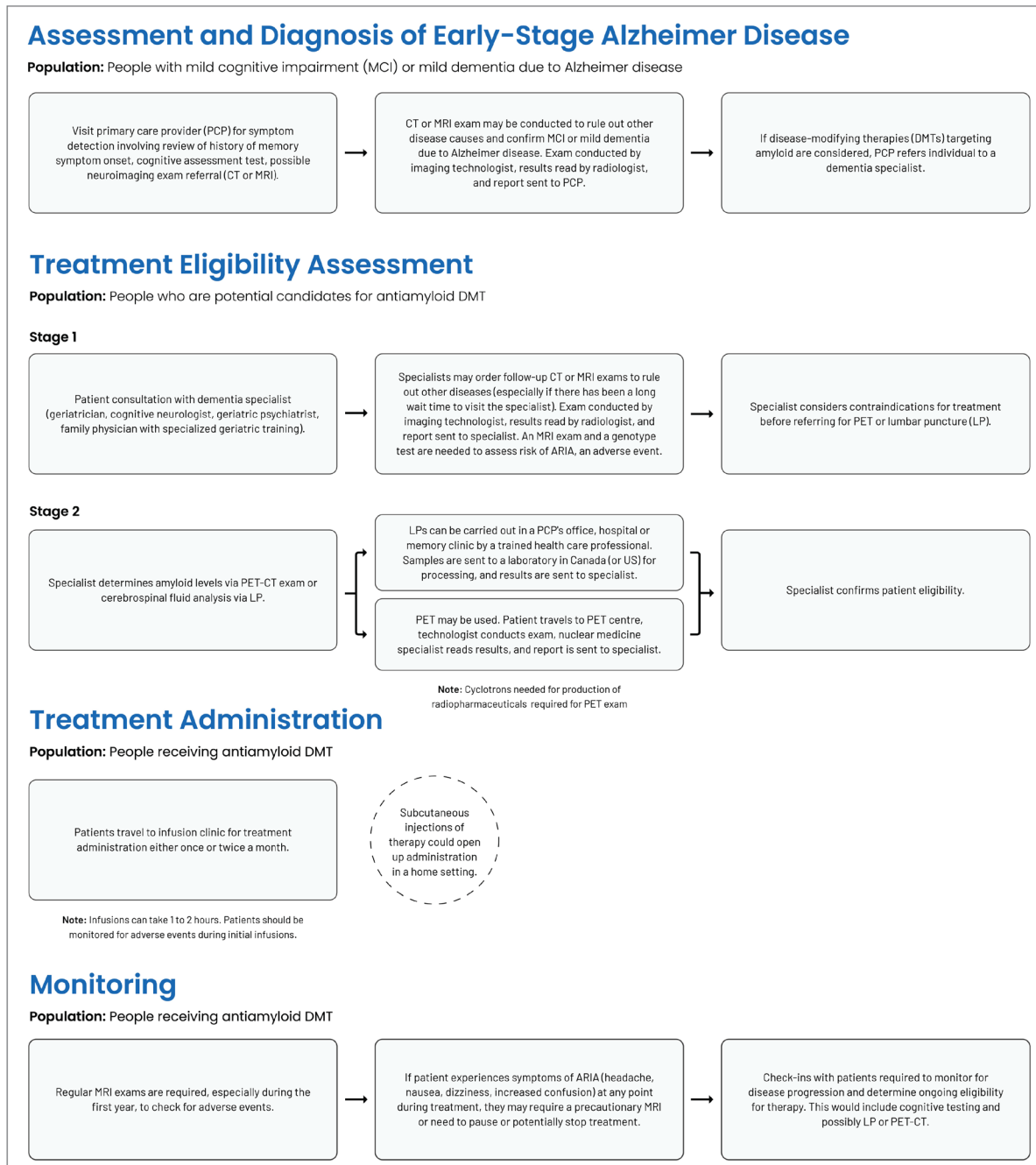
In addition, disease progression could also be monitored with cognitive tests and repeat amyloid PET and LP exams, to determine whether patients are still eligible for the therapy.

## **Assessment and Diagnosis of Early-Stage AD**

### **Identifying MCI and AD and Seeking Help**

Currently, clinical diagnosis of early-stage AD, encompassing MCI and mild dementia due to AD, involves a comprehensive evaluation by a trained primary health care professional, such as a family doctor or primary care nurse. This assessment requires a careful corroborated history of the onset of symptoms and progression from both the patient and caregiver, using pen-and-paper psychometric screening tools, in addition to neurologic exams.<sup>17,36,37</sup> Novel anti-amyloid-beta mAb DMTs were designed for people with early-stage AD, underscoring the importance of diagnosing MCI or AD at an early stage to optimize treatment effectiveness.<sup>26</sup>

**Figure 2: Potential Model of Care With DMTs for Patients With AD**



Current guidance from the CCCDTD does not recommend routine cognitive testing to screen older adults who are asymptomatic.<sup>17</sup> However, these guidelines were published before the advent of anti-amyloid-beta mAb DMTs, and it is unclear how these recommendations would change in this new context. Up to 60% of dementia cases worldwide remain undetected, suggesting that many individuals with early-stage disease may be unaware of or are overlooking symptoms associated with early-stage AD.<sup>34,35</sup> Public education

and advocacy campaigns as well as additional support resources may create better public awareness and understanding of early-stage AD, its symptoms, and how it can be managed.<sup>38</sup>

With the potential introduction of new therapies offering the promise of slowing disease progression, more individuals may be motivated to seek screening, including those who may not necessarily be eligible.<sup>39</sup> A recent survey from Alzheimer’s Disease International has reported that more than 90% of carers and the general public would be more likely to seek a diagnosis if DMTs were available.<sup>40</sup> Jurisdictions in Canada may not be fully prepared for an increase in screening demand, given the challenges in accessing both primary and specialist care, as well as gaps in physician training for diagnosing early-stage AD. This highlights a significant gap in readiness to diagnose individuals at an early enough stage, should anti-amyloid-beta mAb DMTs be approved.<sup>7</sup>

Implementation considerations for identifying early-stage AD include the following:

- There is a lack of awareness among the general population regarding symptoms of early-stage AD. Symptoms such as forgetting names and places, as well as disorientation, are often conflated with “normal” aspects of aging rather than being seen as symptoms that warrant further investigation.<sup>41</sup> The survey from Alzheimer’s Disease International found that 80% of the general public and 65% of health and care providers believe that dementia is a normal part of aging.<sup>40</sup>
- Caregivers, whether paid or unpaid, often play a pivotal role in recognizing symptoms and supporting individuals with early-stage AD.<sup>42-44</sup> A 2011 survey of caregivers in Canada reported that up to half of their family members waited a year or more before seeking help for their symptoms, which included frequent memory loss, disorientation of time and location, or personality changes.<sup>45</sup>
- The stigma associated with MCI or AD diagnosis has been reported to cause hesitancy among individuals with new-onset symptoms to speak about the condition and seek help from social care services or a PCP. A 2017 Alzheimer Society survey found that 1 in 5 Canadians would avoid seeking help for as long as possible if they thought they had dementia.<sup>46,47</sup> A different survey conducted by Alzheimer’s Disease International found that approximately 24% of people with dementia concealed their diagnosis due to the stigma associated with the disease.<sup>40</sup>

### Accessing Primary Care

The diagnostic pathway for early-stage AD begins when individuals or their caregivers recognize symptoms and seek medical attention. Current guidance in Canada suggests the pathway to diagnosis should begin at the primary care level.<sup>17</sup>

Implementation considerations for diagnosing early-stage AD and accessing primary care and treatment include the following:

- **Limited primary care:** As of 2023, an estimated 5.4 million people (17%) living in Canada lack stable access to a PCP, who serve as the initial point of contact for beginning the diagnosis of early-stage AD.<sup>17,48,49</sup> These individuals and their caregivers are often forced to seek care from family doctors or general practitioners at walk-in clinics or emergency departments, or they may go without treatment

altogether. An absence of an established relationship with a PCP is associated with decreased likelihood of the care provider noticing symptoms of early-stage AD.<sup>50,51</sup>

- **Geographic disparities:** People living in rural or remote areas, constituting around 18% of Canada's population, and who tend to be older, encounter challenges in accessing primary care. These regions are served by only 8% of practising PCPs.<sup>52,53</sup> Furthermore, people living in rural or remote areas often rely on caregivers for transportation to health care services, further complicating access to timely care.<sup>54</sup>
- **Barriers to care for Indigenous Peoples:** Indigenous communities in rural and remote areas encounter unique challenges, such as difficulties in recruiting and retaining health care professionals. Additionally, there is a lack of consistent access to PCPs for at least half of First Nations people living off-reserve, as well as Métis and Inuit populations in remote communities.<sup>55,56</sup> Furthermore, although research indicates that Indigenous Peoples may have higher rates of dementia, it is important to note that structural barriers, a lack of trust in colonial institutions, and fears of experiencing racism or discrimination in the health care system may contribute to reluctance in seeking care as well as to underdiagnosis or misdiagnosis in this population.<sup>3</sup>
- **Health care system navigation:** Many jurisdictions in Canada do not have a comprehensive system of care navigators or case managers who could assist prospective patients with dementia in finding the care they need, which often spans multiple health care services and programs. There is also inequitable access to individual care navigators, which may affect certain groups more than others, including people living in rural communities, as well as newcomers to Canada who may lack familiarity with navigating the health care systems in Canada.<sup>42,57,58</sup> As a result, these patients and their caregivers are often left to navigate a fragmented health care system on their own.<sup>59</sup>
- **Lack of equitable access to care:** Racialized groups and some newcomers to Canada may encounter obstacles in accessing culturally appropriate care or locating primary care services.<sup>60-62</sup> In addition, people from racialized communities may have different cultural views and stigma about dementia, making it challenging for individuals from these communities to seek help or accept a dementia diagnosis.<sup>3</sup> There is a wide variation in dementia rates among different racialized groups, which may necessitate further study to understand these differences and to ensure that health care systems provide equitable treatment for these groups.<sup>3,63</sup> These groups may require caregivers, often family members and friends, to assist in navigating the health care system while providing translation between patients and health care providers.<sup>3</sup>
- **Patient and caregiver advocacy:** Individuals with symptoms, along with their caregivers, have reported a need to advocate for access to services to determine an early-stage AD diagnosis and subsequent treatment. This advocacy stems from reported challenges; some PCPs may struggle to recognize symptoms of early-stage AD. As well, there are instances of PCPs being perceived as dismissive of patient concerns regarding these symptoms.<sup>41,64-67</sup> This can result in patients and their caregivers coordinating different appointments to obtain an accurate diagnosis, while keeping multiple care providers informed, requiring both time and effort.<sup>65,68,69</sup> However, this can deepen inequities in access to care, as only those who are persistent and have the necessary resources may

be able to navigate the system effectively and receive timely care, which could include anti-amyloid-beta mAb DMTs.

- **Additional training for physicians:** There are a variety of different methods for diagnosing early-stage AD, including a large range of cognitive assessment tools (e.g., Montreal Cognitive Assessment [MoCA], the General Practitioner Assessment of Cognition [GPCOG], the Canadian Indigenous Cognitive Assessment [CICA], and the Mini-Mental State Examination [MMSE]). The accuracy of a diagnosis depends on the PCP's knowledge of MCI and dementia and their proficiency in administering and interpreting results of cognitive assessment tools for diagnosing these conditions.<sup>17,70</sup> In addition, it was reported in an Alzheimer's Disease International survey that 65% of health care professionals believed that dementia was a normal part of aging.<sup>40</sup> The survey also highlighted a phenomenon known as "therapeutic nihilism," in which some providers refrain from making diagnoses because they believe there are no effective treatments for dementia. Increasing training on the symptoms, causes, and available treatments for dementia could help health care providers better identify and diagnose symptoms.
- **Difficulty in identifying early-stage AD:** Clinical trials for anti-amyloid-beta mAb DMTs used a research framework based on biological definitions of early-stage AD, which were not intended for real-world clinical practice to diagnose people with early-stage AD.<sup>17</sup> This can make it challenging to determine how many patients can be identified with early-stage AD in routine primary care practice.<sup>17</sup> Studies of PCPs in Canada indicate variability in awareness of guideline details and the overall purpose and use of these tests.<sup>64,66</sup> According to the 2019 Commonwealth Fund Survey of Family Physicians, 40% of doctors in Canada felt adequately prepared to care for individuals with dementia.<sup>71</sup>
- **Equitable cognitive assessments:** The cognitive assessment tools used for diagnosing early-stage AD can be administered by any trained professional, such as family physicians and nurses. However, these tools were originally designed for Western populations and may have cultural biases that can result in poor test accuracy in ethnically diverse populations.<sup>72-74</sup>
  - In Canada, there are numerous Indigenous Peoples and racialized groups who may have different cultural perspectives and understandings of early-stage AD.<sup>75-77</sup> Culturally sensitive cognitive assessment methods, screening tools, and care may provide more reliable results and help prevent inequities in diagnosis in these populations.<sup>78,79</sup>

### Accessing Specialist Care and Receiving a Diagnosis

After seeking help in a primary care setting, individuals with symptoms of early-stage AD typically receive a final diagnosis from their PCP, without referral to a specialist, unless the cause of symptoms remains unclear or neuroimaging is required.<sup>17,41</sup> However, if anti-amyloid-beta mAb DMTs are being considered as a treatment option for these individuals, confirmation of the diagnosis and evaluation of treatment eligibility would likely require the involvement of a dementia specialist. To facilitate shared decision-making, the benefits and risks of treatment should also be discussed between the patient and their caregiver, on the one hand, and a dementia specialist, on the other. The specialist would oversee the coordination of care and administration of treatment to ensure appropriate management.<sup>17,41</sup>



Accessing dementia specialists in Canada presents several challenges:

- **Geographic disparities:** Specialized clinics are often located in urban settings, posing challenges for individuals living in rural or remote areas to equitably access specialist care, diagnostic imaging, and support services.<sup>7,80,81</sup> This disparity necessitates additional costs for travel and time away from home and work to receive treatment.<sup>82,83</sup> Programs such as the multispecialty interprofessional team (MINT) memory clinics and Saskatchewan’s Rural and Remote Memory Clinic demonstrate efforts to enhance care accessibility in rural and remote areas, aiming to mitigate geographic barriers.<sup>84-87</sup>
- **Wait times:** Referral times for specialist care can be lengthy, with estimated average wait times of 28 months from diagnosis to specialist assessment. Symptoms will continue to progress while patients await care, potentially closing the window of patient eligibility for anti-amyloid-beta mAb DMTs.<sup>7</sup> The development of a standardized approach to assessing potential patients — including checklists of cognitive tests and assessments, to be completed by PCPs before specialist referral — could reduce delays in early diagnosis.<sup>88</sup>
- **Limited human resources:** Long referral times stem, at least in part, from a shortage of dementia specialists with training and experience in diagnosing early-stage AD (i.e., geriatricians, cognitive neurologists, family physicians with specialized geriatric training, and geriatric psychiatrists). As well, there are challenges with timely access to diagnostic equipment (e.g., PET-CT and MRI machines) to diagnose patients due to high demand and limited capacity.<sup>88-91</sup> These factors collectively contribute to delays in diagnosis and access to specialized care for individuals seeking evaluation and treatment for cognitive symptoms.
- **Lack of multidisciplinary care coordination:** Multidisciplinary teams that incorporate PCPs, AD specialists, nurses, social workers, and other health care providers, with specialized training and cross-collaboration among staff, may allow for quicker detection and coordinated care of early-stage AD by focusing specifically on patients with cognitive symptoms. The Family Medicine Groups in Quebec and MINT memory clinics across Canada are examples of multidisciplinary teams that allow for the administration of cognitive tests and focused care.<sup>4,84,92-94</sup>
- **Imaging capacity:** The method for AD diagnosis recommended in the current CCCDTD guidelines depends on ruling out alternative causes of symptoms.<sup>17,19</sup> Family physicians or specialists may order MRI or CT scans to exclude other causes of dementia unrelated to AD. If underlying pathological processes remain unclear, PET-CT or single-photon emission CT exams may also be ordered. However, accessing medical imaging often entails substantial wait times due to general high demand for these services, potentially delaying diagnosis.<sup>95-97</sup>

### Future Diagnostic Technologies

A variety of new and emerging technologies have been developed or are currently in development to improve the identification of early-stage AD. The adoption of digital cognitive tests, ocular biomarkers, and artificial intelligence (AI) has the potential to enhance health system efficiencies by replacing pen-and-paper psychometric screening methods. While these technologies are showing promise in research settings, their

widespread clinical adoption depends on further validation, regulatory approvals, and integration into health care systems.

### ***Digitization of Cognitive Tests***

The digitization of cognitive screening tools has the potential to transform patient screening by enabling broader access, integrating real-time data, tracking cognitive trends, and reducing clinician workload.<sup>36,98</sup> A shift toward digital platforms has the potential to improve early diagnosis and monitoring, facilitating more effective management of early-stage AD.

Developments in the digital administration of cognitive screening tools include:

- adapting traditional psychometric screening tools to computer platforms, including remotely administered tablet- and smartphone-based cognitive assessments, which may expedite in-clinic or remote administration, automate scoring, and allow data integration<sup>36</sup>
- the introduction of new digital cognitive screening tests aimed to mitigate the effects of language, cultural, racial, and ethnic biases in cognitive assessment<sup>36,99</sup>
- wearable devices that track sleep and activity patterns continuously, facilitating detection of presymptomatic functional decline without having to rely on participant self-report.<sup>100</sup>

While these digital platforms have the potential to enhance early diagnosis and monitoring, particularly in early-stage AD, traditional cognitive testing may still play an important role, especially for patients and care providers who may not have access to, or be comfortable operating, digital devices. Ensuring equitable access to cognitive assessments will likely require a balance between digital innovations and traditional approaches.

### ***Ocular Biomarkers and Retinal Imaging Technologies***

In recent years, some AD research has focused on potential biomarkers correlated with AD development that occur biologically in the eye or are related to functionality of the eye. AI use in conjunction with ocular biomarkers of AD, including tears, corneal nerves, retina, visual function, and eye movement tracking, may be able to detect early-stage AD. This technology may improve the accuracy of identifying AD and could become a screening tool to detect AD before symptoms develop.<sup>101</sup>

Recent developments to advance ocular diagnostics in MCI and AD include the following:

- A machine-learning model uses retinal imaging technologies to differentiate between normal cognition and MCI. By analyzing specific features in the images along with demographic and quantitative data, the model aims to provide a noninvasive approach for the early detection of MCI. Researchers plan to further validate and potentially enhance the model's clinical utility by collecting images from a larger and more diverse cohort of representative individuals.<sup>102</sup>
- An eye-tracking technology uses a tablet-based camera to analyze eye movement parameters. Health Canada has approved an application for use in clinics or remotely through self-testing in patients with multiple sclerosis.<sup>103</sup> The manufacturer is currently conducting trials to evaluate this technology for tracking progression and cognitive changes in patients with AD.<sup>104</sup>

Despite these advances, barriers to implementing ocular diagnostics may persist. These include a lack of consensus on clinical integration strategies and limited understanding of the relationship between retinal changes and AD, underscoring the need for further research.<sup>105</sup> Additionally, challenges such as the need for specialized training for eye care professionals and variations in optometrists' scope of practice across provinces would need to be addressed.

### ***AI Detection and Machine Learning***

AI and machine-learning models, especially those that optimize MRI scans, have the potential to improve diagnostic processes. These technologies have the capability to analyze neuroimaging data with greater precision, detecting subtle brain changes that indicate AD and standardizing pattern identification for radiologists, potentially reducing the need for specialized training. This capability could lead to earlier and more accurate AD diagnoses, distinguishing it from other neurologic conditions.<sup>106-110</sup> However, an important consideration, discussed later in this report, is the need to address implementation challenges associated with MRI access.

Additionally, other key considerations and challenges include the following:

- **Biases in predictive models:** Identifying and mitigating potential biases in predictive machine-learning models is important to ensure they maintain accuracy across diverse populations, including multicultural groups.<sup>107</sup>
- **Privacy safeguards:** Implementing appropriate safeguards to protect patient data privacy is essential when using AI and machine learning in clinical settings.<sup>111</sup>
- **Further research:** Continued research is necessary to develop reliable and clinically applicable AI and machine-learning models for diagnosing and monitoring AD.<sup>111</sup>

These advances underscore the potential of AI to support AD diagnosis and care and highlight the importance of addressing ethical, technical, and practical challenges to maximize their benefits in health care settings.<sup>111</sup>

Recent developments in AI detection and machine learning include the following:

- The FDA has granted De Novo approval of a clinical test that uses AI and standard MRI to predict progression from MCI to AD in individuals within 5 years.<sup>109</sup>
- Other novel AI models that use machine-learning techniques are also being developed to analyze neuroimaging data to detect subtle brain changes, assess disease risk, and differentiate AD from other conditions.<sup>106,108,110</sup>

### **Treatment Eligibility Assessment**

Once diagnosed with early-stage AD, which includes MCI and mild dementia due to AD, individuals would undergo assessment for treatment options, including anti-amyloid-beta mAb DMTs, if approved by Health Canada. In countries where these therapies are approved, regulatory authorities typically require patients to have abnormal levels of amyloid-beta pathology to be eligible for treatment.<sup>28,29</sup> For example, 21% to 40% of people with MCI do not display enough amyloid-beta biomarker load to confirm a diagnosis of AD.<sup>112,113</sup> These

amyloid-beta levels are currently determined by an amyloid PET exam or an analysis of CSF obtained via LP.<sup>114</sup> The required amyloid-beta levels for eligibility may vary among different anti-amyloid-beta mAb DMTs, and clinicians would need training to discern the nuances among these therapies.<sup>115</sup>

The CCCDTD does not currently recommend amyloid PET exams or LPs as a regular part of the diagnosis pathway for early-stage AD unless there is diagnostic uncertainty. However, the CCCDTD recommendations were made in 2020, before the introduction of anti-amyloid-beta mAb DMTs as a potential AD treatment.<sup>17</sup> Integrating these forms of testing may involve considerations of appropriate use, equitable access, and additional training for PCPs and dementia and neuroimaging specialists in the health care systems in Canada.

In addition to determining biomarker levels, regulatory authorities in countries that have approved anti-amyloid-beta mAb DMTs have also required an MRI scan within 12 months before treatment initiation and suggested *APOE* genotyping to evaluate patients' predisposition to adverse events.<sup>114</sup> After patients complete treatment eligibility testing, dementia specialists would have to review the results and determine the treatment plan.<sup>4</sup>

### CSF Analysis and LPs

CSF collection via LP is considered a convenient and cost-effective method to determine amyloid-beta levels compared to amyloid PET exams, primarily due to its lower resource requirements.<sup>116</sup> The procedure requires basic equipment, consisting of a LP kit, which includes a needle and collection tube, making it more accessible for individuals living in rural or remote areas.<sup>117</sup> In some provinces, both PCPs and nurses can perform LPs, although additional training would likely be required.<sup>118-121</sup>

Most often, LPs are performed in the hospital setting by neurologists.<sup>118</sup> While these procedures could be conducted in outpatient settings, which could improve access in the health care system, this would necessitate appropriate training to ensure the procedure is conducted safely.<sup>117,122</sup> An additional advantage of LP, compared to amyloid PET, is that CSF assays can examine multiple different biomarkers concurrently.<sup>117</sup> However, the CCCDTD does not recommend CSF testing and LPs as part of the routine diagnosis pathway unless there is diagnostic uncertainty in people under the age of 65.<sup>17</sup>

Implementing CSF analysis via LPs may present several challenges, and these include the following:

- **LP safety:** Common patient complaints following LP include headaches and back pain, which are generally mild and manageable. Approximately 0.7% of patients experience serious adverse events that require hospitalization, such as cerebral or spinal hemorrhaging; cerebral thrombosis, hematomas, or herniation; or infection.<sup>117,123,124</sup> Additionally, in approximately 10% of cases, LPs do not draw sufficient CSF fluid, necessitating subsequent amyloid PET imaging to determine biomarker load.<sup>125</sup> Amyloid PET exams may also be used after LPs if CSF results do not match clinical diagnosis.<sup>126</sup>
- **PCP acceptance:** Some PCPs have expressed that they feel unprepared or would require training to perform LPs to reduce the risk of adverse events.<sup>64,117</sup> Others have expressed that the procedure is invasive for their patients and there is difficulty in coordinating with specialists to perform LPs.<sup>127</sup> This

hesitancy may push PCPs and people with early-stage AD toward seeking this procedure in hospitals or specialized memory clinics. While the performance of LPs in these settings may be perceived as safer, it could strain resources and increase demand at these facilities. While amyloid PET exams are an alternative option, they are less available.<sup>64,117</sup>

- **Patient comfort and acceptance:** While research has shown that LPs are well tolerated and are generally safe for older people, patient acceptance of the procedure, particularly among those who are frail or have symptoms of confusion, can present a barrier to its widespread implementation.<sup>117</sup> Some people, particularly in certain racialized communities, may feel hesitant about undergoing LP due to concerns about the procedure's invasiveness.<sup>126,128</sup> Effective communication and comprehensive shared decision-making with health care providers regarding the safety, effectiveness, and other aspects of the procedure are crucial to increasing patient and caregiver comfort and acceptance.<sup>129,130</sup>
- **Laboratory capacity:** Currently, Canada has at least 3 laboratories capable of processing CSF samples, with an expected turnaround time ranging from 5 to 28 days. Alternatively, samples can be sent to the US for processing.<sup>4,131-133</sup> However, these CSF samples require specific storage conditions, which raises the risk of spoilage during transition to the laboratories.<sup>134,135</sup> Furthermore, there is a lack of clarity on the number of laboratories that have the capability to process CSF samples beyond these 3 laboratories. With projected annual dementia prevalence rates expected to increase by 51% by 2030 compared to 2020, this projected demand could overwhelm the capacity of laboratories in Canada to process these tests. In scenarios such as equipment failures or when demand exceeds capacity, the necessity to send excess CSF samples to the US for processing could lead to extended wait times for pathological confirmation. Moreover, this process introduces additional complexities regarding the privacy of patient data.<sup>4,136</sup> An expansion of the current CSF processing infrastructure, as well as inclusion of newer automated platforms, could increase the capacity to deliver timely results and system resilience.<sup>137</sup>
- **Reimbursement pathways:** Reimbursement for LPs currently varies across provincial and territorial health care systems in Canada.<sup>4,117</sup> For instance, some jurisdictions do not reimburse LPs related to AD, whereas others require a special approval for reimbursement, creating inequitable access to this procedure.<sup>4,138</sup> Studies have indicated that LPs can be financially burdensome for PCPs, as reimbursement may not adequately cover the time and resources required to perform the procedure. This financial aspect, especially when considering large workloads, may serve as a disincentive for PCPs to offer LPs, potentially impacting patient access to timely diagnostic assessments for AD.<sup>125</sup>

### Amyloid PET Imaging

PET-CT is an advanced, hybrid, diagnostic imaging modality that combines PET and CT imaging in a single unit. This modality uses radiopharmaceuticals to attach to AD biomarkers, such as amyloid-beta plaques in the brain, allowing medical imaging specialists to determine the biomarker load of patients in a noninvasive manner. PET-CT can be used in cases where LP is contraindicated.<sup>7,139-141</sup> However, PET-CT exposes people to ionizing radiation and requires specialized equipment and staff.<sup>142,143</sup>

Amyloid PET imaging is not part of the routine AD diagnosis pathway in Canada and is not recommended for use in those who show no clinical symptoms. Amyloid PET imaging is primarily used in an AD research setting, although it can be used clinically under special authorization, and is usually ordered by a dementia expert, as indicated by the CCCDTD.<sup>17</sup> PET-CT does not currently allow for concomitant tracking of multiple biomarkers, unlike CSF analysis.<sup>118</sup>

Implementing amyloid PET imaging presents several challenges. These include:

- **Capacity:** There are 60 PET-CT machines in Canada, located in 9 provinces and all in urban centres.<sup>144</sup> There are no PET-CT machines in the territories. Expanding PET-CT capacity is complex; it can take up to 5 years to introduce new PET-CT units due to regulatory and licensing requirements, as well as the need to develop or modify facilities to support PET-CT units with proper radiation shielding.<sup>142</sup> The distribution of PET-CT units raises concerns about equitable access for individuals residing outside urban areas. People who do not live close to a PET-CT would need to travel to urban settings or out of their province or territory for imaging, incurring additional cost and logistical challenges.
- **Radiopharmaceutical availability:** Radiopharmaceuticals, a necessity for PET-CT imaging, are in short supply due to a limited number of cyclotrons that generate these reagents.<sup>7</sup> Some radiopharmaceuticals have a very short active half-life; if a cyclotron is farther away, more reagents would need to be purchased in order for a usable amount to remain active by the time the reagents arrive at the imaging unit.<sup>142</sup> Additionally, if a cyclotron experiences downtime, this could lead to rebooking or cancelling appointments, disrupting the continuity of service.<sup>145</sup> Addressing these challenges requires strategies to enhance cyclotron infrastructure and supply chain logistics. This might involve increasing the number of cyclotrons, improving distribution networks, and implementing contingency plans to minimize disruptions in radiopharmaceutical supply.
- **Regulatory approvals:** Currently, 1 radiopharmaceutical is approved in Canada for amyloid imaging. Others are used in the research setting but are unavailable for clinical use in Canada.<sup>145,146</sup>
- **Competing priorities:** Existing PET-CT units are primarily allocated for oncology exams in Canada and frequently operate at full capacity.<sup>144</sup> The prioritization of oncology exams can significantly extend the waiting times for non-oncology exams, including those that would be needed for AD. A 2021 survey of PET-CT clinicians reported that average wait times for non-oncology exams were more than 1 year.<sup>147</sup> This extended wait period underscores the challenges faced by individuals requiring PET-CT scans for diagnoses other than cancer.
- **Limited human resources:** There is a shortage of trained staff capable of operating PET-CT units and specialists capable of interpreting the images.<sup>144,148,149</sup> Staffing shortages may be increasing and have been noted to contribute to long wait times to access PET-CT imaging.<sup>147,150</sup>

### **Amyloid-Related Imaging Abnormalities, MRI, and APOE Genotyping**

In addition to testing for biomarker levels, regulatory authorities and appropriate-use guidelines also require prospective patients to undergo an MRI examination and *APOE* genotyping for their susceptibility to amyloid-related imaging abnormalities (ARIA), an adverse event related to anti-amyloid-beta mAb DMTs.<sup>28,114</sup>

In countries that have already approved anti-amyloid-beta mAb DMTs, regulatory authorities require an MRI scan within the 12 months before treatment initiation. This precaution ensures potential patients can begin treatment safely.<sup>28,29</sup> This scan identifies patients with microhemorrhages in the brain, which puts them at higher risk of ARIA.<sup>114,151</sup> ARIA can be categorized as 2 different subtypes, which can co-occur: ARIA-E (presenting as edema and effusion) or ARIA-H (presenting as microhemorrhages). An MRI exam and reporting of the intensity of symptoms is used to grade the severity of ARIA.<sup>152</sup>

If an MRI examination was conducted within the 12-month period to assess early-stage AD symptoms and included sequences to evaluate the risk of ARIA, a second MRI scan may not be necessary as a baseline before initiating treatment with anti-amyloid-beta mAb DMTs. This is because the initial MRI would have already captured the necessary imaging sequences to determine ARIA risk. However, if a CT exam was used to confirm diagnosis of AD, an MRI would still be required because the CT scan would not have sufficient resolution to identify ARIA.<sup>114</sup>

Implementing MRI may present several challenges, and these include the following:

- **Capacity:** There are 432 MRI units in Canada, in all provinces and 1 territory, with approximately 80% located in urban facilities. This geographic concentration forces patients living in rural and remote areas, especially in the territories, to travel for these scans, incurring additional costs.<sup>153</sup> Limited capacity places strain on wait times, with the national median wait time for an MRI exam in 2023 reaching up to 3 months, although this varies by jurisdiction.<sup>96</sup> Increasing MRI capacity would take time because MRI exams must be carried out in dedicated rooms with sufficient radiofrequency shielding to prevent electromagnetic interference, and a supply chain must be in place to support the advanced cooling systems needed to operate the units.<sup>154</sup>
- **Limited human resources:** According to a survey by the Canadian Association of Medical Radiation Technologists, there is a shortage of staff trained to operate MRI units, with 11% of positions for MRI technologists being vacant as of 2021. This staffing gap contributes to longer wait times for imaging.<sup>148,149,155</sup> This highlights the importance of appropriate use of diagnostic imaging to reduce unnecessary exams and optimize the use of limited MRI capacity.<sup>156</sup>
- **Education and training:** Radiologists may need additional training in MRI acquisition protocols that are optimized to detect and monitor brain structures susceptible to ARIA.<sup>4,157</sup> For example, measuring for ARIA-H on baseline MRI exams can be difficult due to its similarities to other brain microbleeds.<sup>151</sup> Standardized MRI protocols and clear criteria for how ARIA could affect treatment plans should be included as part of this training.<sup>152</sup>

Along with the MRI examination before treatment initiation, regulatory authorities and appropriate-use guidelines have recommended that patients undergo genetic testing to determine whether they are carriers of *APOE4* alleles.<sup>28,114</sup> It has been found that people carrying *APOE4* alleles are especially at risk for ARIA events. *APOE* genotyping can allow better-informed discussions of the risk of anti-amyloid-beta mAb DMTs and ensure better patient monitoring.<sup>114</sup>

Currently, AD genotyping is offered only for patients who have young-onset familial AD; it involves a detailed review of family history by a genetic counsellor or physician and does not include *APOE* genotyping.<sup>158</sup>

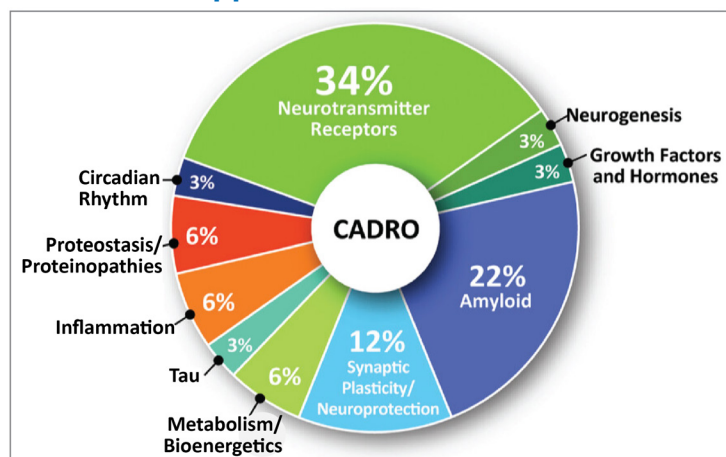
Genetic testing is conducted at research laboratories in Canada or commercial laboratories in the US.<sup>158</sup> While commercial genetic testing is available at clinical laboratories in Canada, it may not be covered by public health plans.<sup>158,159</sup> If anti-amyloid-beta mAb DMTs were approved in Canada, ensuring equitable access to *APOE* genotyping would be important for ensuring the safety of patients receiving this class of treatment. Such genotyping tests could be undertaken at community laboratories in the future, mitigating the need to travel to hospitals for patients and caregivers.<sup>160-162</sup>

### Future Biomarker Detection Technologies

As of January 1, 2024, 164 clinical trials evaluating 127 drugs for AD were registered on clinicaltrials.gov, an international voluntary database of clinical research studies from 200 countries, with DMTs constituting 76% of drugs for AD in the database. These drugs are designed to target nearly all disease processes mentioned in the Common Alzheimer's Disease Research Ontology (CADRO) approach, a method of classifying AD processes into key categories reflecting different aspects of AD pathology and progression.<sup>24</sup> [Figure 3](#) illustrates the mechanisms of action of drugs in phase III clinical trials for AD, classified according to the CADRO approach. The increased use of biomarkers, refined target identification, and enhanced methodologies in clinical trials could improve the success rate of AD drug development.<sup>24</sup> Ongoing research has identified several promising AD-related biomarkers.

[Table 1](#) presents the emerging fluid biomarkers linked to the drugs in [Figure 3](#), categorized by their clinical development stage: FDA breakthrough-device designation, research-only use, and emerging biomarkers needing further clinical validation. This is not an exhaustive list, as drugs and biomarkers in development are evolving rapidly.

### Figure 3: Mechanisms of Action of Drugs in Phase III Clinical Trials for AD, Classified Using the CADRO Approach



Source: Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2024. *Alzheimer's Dement* (N Y). 2024;10(2):e12465. Available from: <https://www.ncbi.nlm.nih.gov/38659717/>. Reprinted in accordance with Creative Commons Attribution 4.0 International License (CC BY 4.0): <https://creativecommons.org/licenses/by/4.0/50.24>



**Table 1: Emerging Fluid Biomarkers Linked to the Drugs in Phase III Clinical Trials for AD**

CADRO category of drugs in phase III clinical trials <sup>24</sup>	Fluid biomarkers <sup>163</sup>	Stage of clinical development
Amyloid	CSF and plasma amyloid-beta	FDA breakthrough-device designation <sup>164</sup>
Tau	CSF and plasma p-tau	FDA breakthrough-device designation <sup>164</sup>
Growth factors and hormones	BDNF	Emerging biomarker requiring further clinical validation <sup>165</sup>
	HSD1, trial-specific hormones	Research use only <sup>166</sup>
Proteostasis or proteinopathies	Proteomics	Research use only <sup>166</sup>
Inflammation	GFAP	Research use only <sup>166,167</sup>
	YKL-40, sTREM2, MCP-1	Emerging biomarker requiring further clinical validation <sup>167-169</sup>
Synaptic plasticity or neuroprotection	Neurogranin, synaptotagmin, and SNAP-25	Emerging biomarker requiring further clinical validation <sup>163,170</sup>
Metabolism or bioenergetics	Metabolomics	Emerging biomarker requiring further clinical validation <sup>163,171</sup>
Neurotransmitter receptors	None identified	—
Neurogenesis	None identified	—
Circadian rhythm	None identified	—

AD = Alzheimer disease; BDNF = brain-derived neurotrophic factor; CADRO = Common Alzheimer's Disease Research Ontology; CSF = cerebrospinal fluid; GFAP = glial fibrillary acidic protein; HSD1 = hydroxysteroid dehydrogenase type 1; MCP-1 = monocyte chemoattractant protein-1; p-tau = phosphorylated tau; SNAP-25 = synaptosomal-associated protein 25; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; YKL-40 = chitinase-3-like protein 1.

### Blood-Based Biomarkers

Blood-based biomarkers, collected through a blood draw, offer a promising alternative to CSF analysis via LPs or amyloid PET exams, potentially reducing reliance on invasive and resource-intensive methods.<sup>172,173</sup> Such biomarkers are intended to complement comprehensive clinical assessments rather than serve as standalone diagnostic tools. While the clinical applications of these biomarkers may introduce some challenges, including scalability, accuracy, robustness, and standardization, they may be less resource-intensive than current options.<sup>164,172,174</sup> Notable biomarkers nearing clinical implementation include plasma amyloid-beta<sub>42/40</sub> ratio, various tau and phosphorylated tau (p-tau) isoforms, plasma neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP).<sup>164,172</sup> There are potential benefits and challenges associated with these biomarkers ([Appendix 1](#)).

### Composite Panels

Several manufacturers are also exploring the use of panels that combine multiple biomarkers to improve diagnostic accuracy, such as:<sup>164,166</sup>

- C2N's PrecivityAD (amyloid-beta<sub>42/40</sub>, APOE, age)
- Roche's Amyloid Plasma Panel (p-tau<sub>181</sub> + APOE4)
- Labcorp's ATN Profile (amyloid-beta<sub>42/40</sub>, p-tau<sub>181</sub>, NfL)
- Fujirebio's AD-BBB testing (amyloid-beta<sub>42/40</sub>, p-tau<sub>181</sub>, p-tau<sub>217</sub>)

- C2N's PrecivityAD2 (amyloid-beta42/40, p-tau 217, np-tau217)
- Quanterix's ALZpath (p-tau181, p-tau217, p-tau231, YKL-40, GFAP)
- Luminex (21-protein panel)
- Alamar (p-tau217 and large multiplex assays)
- Meso Scale (p-tau181, p-tau217, p-tau231).

### ***Fingerprick Blood Sample and Remote Collection***

A fingerprick blood test for measuring NfL, GFAP, p-tau181, and p-tau217 has been developed. In a study involving patients at a memory clinic, both vein and fingerprick blood samples were transferred onto dried blood spot cards and transported without temperature control to a laboratory for interpretation. Upon arrival, biomarkers were successfully detected in both sample types.<sup>175</sup> In the vein blood spots, levels of GFAP, NfL, p-tau217, and p-tau181 closely matched those found in standard blood tests. Similarly, the fingerprick blood samples showed results that closely matched standard blood tests for these biomarkers, indicating the potential of fingerprick blood sampling and remote collection as alternatives to traditional blood draws.<sup>175</sup> This approach could improve access for patients in remote and underserved communities across Canada, where limited capacity and the absence of standard laboratory facilities make traditional blood draws challenging.

### ***Further Development of Blood-based Biomarkers***

Research into plasma protein changes that precede the onset of dementia has identified potential blood-based biomarkers in the immune, lipid, metabolic signalling, and hemostasis pathways. These findings may allow for earlier preclinical AD detection.<sup>176,177</sup> RNA sequencing analysis of blood samples has also identified biomarkers for early diagnosis of AD.<sup>178</sup>

### ***Considerations for Clinical Use***

There are some considerations for the clinical use of biomarkers for AD that may support their successful integration into the management of AD. These include the following:

- **Standardization:** Widespread implementation of AD blood biomarkers in clinical settings may require not only analytical standardization, but also compatibility with laboratory analyzers used in smaller, nonspecialized hospitals, along with standardized sample-collection, processing, and storage procedures.<sup>172</sup> Variations in sample processing — such as time of collection, fasting status, temperature, time from collection to centrifugation, and centrifugation parameters — can introduce measurement variations, reducing clinical reliability and complicating result comparisons across laboratories.<sup>179</sup> With numerous tests under development, harmonizing efforts across laboratories, such as establishing references and quality-control programs, as well as promoting interlaboratory collaboration (for sharing best practices and troubleshooting challenges) would be important for ensuring consistent and reliable assay results.<sup>164,179</sup>
- **Implementation:** Integration of blood-based biomarkers into routine clinical practice may require clear guidelines for use and interpretation.<sup>174</sup> If standardizations and guidelines are sufficiently clear, blood biomarker tests could be implemented at community laboratories, expanding access for patients, especially those in rural or remote areas.<sup>164</sup>

## Treatment Administration of Anti–Amyloid-Beta mAb DMTs

The main method of treatment administration for anti–amyloid-beta mAb DMTs is infusions at regular intervals, ranging from biweekly to monthly.<sup>114,180</sup> These infusions can take between 1 and 2 hours to complete. Individuals are often required to remain at the treatment administration centre immediately after the initial infusions to monitor for any adverse reactions.<sup>4,114</sup> Over time, infusions could be administered at home if the therapies prove to be sufficiently safe and patients respond without adverse reactions.<sup>181</sup> Administration for anti–amyloid-beta mAb DMTs may also be possible via subcutaneous injections in the future, which could also be administered in the home setting. However, mAbs have limited bioavailability beyond the injection site, and a large volume injection may be difficult to administer.<sup>182,183</sup>

### Infusion Clinics

In Canada, there is increased reliance on private infusion clinics, funded by pharmaceutical companies, to provide early access to new therapies, before public drug plan approval.<sup>184-187</sup> Of the outpatient infusion clinics identified in Canada, 573 (52.2%) are owned by private entities and are funded by patient support programs from pharmaceutical companies, or private insurance; or required out-of-pocket patient payments to cover services.<sup>187</sup> It is unclear whether these clinics have capacity or are authorized to administer anti–amyloid-beta mAb DMTs, as they are not required to publicly identify their available capacity or the clinical indications and therapies they support.<sup>188</sup> A coordinated system for collecting and maintaining information on publicly and privately funded infusion clinics would allow for assessment of the regional availability and capacity to administer anti–amyloid-beta mAb DMTs.

There may be several considerations for the successful implementation of treatment administration. These include the following:

- **Geographic disparities:** Individuals living in rural and remote areas would need to travel to infusion clinics for each treatment administration, presenting a potential challenge for equitable access to treatment.<sup>188</sup> This would incur substantial costs and effort for patients and their caregivers and may make coordinating care between the clinics and PCPs more challenging.<sup>82,83</sup>
- **Capacity:** Public infusion clinics may not have the capacity to administer a new therapy to a new and large patient population.<sup>185,189</sup> A 2018 survey of medical oncologists reported wait times of up to 3 weeks to initiate treatments in public infusion clinics.<sup>190,191</sup> Capacity would be limited by the availability of health care professionals, such as nurses and pharmacists, to administer these therapies.<sup>4</sup> Some reports have raised the concern of nurses and other staff moving to work in private infusion clinics, which could further impact capacity in publicly funded infusion sites.<sup>192-194</sup>
- **Education and training:** Reports indicate that infusion-related adverse events occur in 8% to 25% of patients, with the most common symptoms being fever, headache, nausea, or vomiting.<sup>114</sup> Clinic staff would need training to recognize and treat these reactions. Patients may need to stay at infusion clinics longer to monitor for early adverse events.<sup>4,114</sup> Staff may also require additional training to interact with cognitively impaired patients.<sup>180</sup>
- **Continuity of care:** Patient care may be difficult to coordinate when patients are treated by both nurses and on-call physicians at private infusion clinics and by specialists and PCPs in publicly

funded health systems. There may also be concerns that private infusion clinics may lack connections to trained medical staff to monitor ARIA-related reactions.<sup>195,196</sup>

- **Regulatory compliance:** The oversight and regulation of private infusion clinics in Canada can be challenging due to ambiguity regarding which jurisdiction — federal or provincial — holds primary responsibility. This uncertainty particularly pertains to areas such as licensing, inspections, data protection, public safety, and patient advocacy, complicating effective regulation and oversight.<sup>185</sup>
- **Data privacy:** Data privacy concerns of individuals treated at private infusion clinics are an emerging area of concern. It has been noted in other areas of for-profit health care in Canada that patient data may be collected and used to market products and services.<sup>197,198</sup> Patient consent for data collection and transparency around data storage and use could help to address these concerns.

### Future Administration Technologies

New and emerging technologies may play a role in enhancing the operational capacity of infusion clinics, and some of these technologies have already been adopted in other care settings. Integrating smart IV pump technology and remote IV monitoring in infusion clinics, for example, may help to streamline drug-administration processes and workflows and reduce medication errors.

Developments in treatment administration include the following:

- Smart pumps are advanced, programmable infusion devices with built-in drug libraries to set dosage limits and alerts. They have been reported to improve the accuracy of drug delivery and reduce medication errors.<sup>199,200</sup>
  - Bidirectional IV smart-pump interoperability enables real-time, two-way communication between the pump and the centralized hospital software, automating programming and documentation. Implementation considerations include a need to integrate diverse technologies, establish reliable wireless networks, and maintain detailed drug libraries.<sup>201,202</sup>
- Remote monitoring of multiple infusion metres using a device that combines software applications with infusion technology could reduce workload and increase operational capacity.<sup>203</sup>

### Patient Monitoring

When patients begin anti-amyloid-beta mAb DMT, they require monitoring over the course of the treatment, by both caregivers and clinicians, to ensure safe drug administration and to watch for serious adverse effects.<sup>4</sup> Monitoring can lead to dose adjustments, temporary pauses, or discontinuation in therapy, and may require regular MRIs and routine cognition tests administered by a health care provider.<sup>4</sup>

### MRI Monitoring

The most common adverse effect of anti-amyloid-beta mAb DMTs is ARIA. Studies have found that most cases of ARIA are transient and asymptomatic, but ARIA can on occasion lead to serious adverse events such as swelling in the brain (ARIA-E) or hemorrhagic brain bleeds (ARIA-H).<sup>157,204</sup> If an individual experiences ARIA, treatment is suspended until symptoms resolve or treatment is discontinued permanently.<sup>157</sup>

In countries that have approved anti-amyloid-beta mAb DMTs, regulatory authorities require patients receiving treatment to undergo routine MRI scans at set infusion intervals to monitor for ARIA.<sup>27-30</sup> In addition to these routine scans, if patients exhibit symptoms of ARIA (noticed by the patient, caregivers, or clinicians), a precautionary MRI scan could be clinically indicated based on the severity and intensity of the symptoms, as determined by their care provider. If ARIA is confirmed, repeated scans would be required until the ARIA symptoms have resolved.<sup>27-30</sup> Symptoms of ARIA are broad and can include headaches, nausea, dizziness, or increased confusion.<sup>205</sup>

A recent meta-analysis of anti-amyloid-beta mAb DMTs found that approximately 6.5% to 7.8% of trial patients developed ARIA, although the incidence of ARIA has been found to be as high as 30%, depending on the specific therapy.<sup>206</sup> While 80% of these cases are asymptomatic and transient, typically occurring early in treatment with reduced incidence after the first year of treatment, ARIA can still occur at any time, and recurrences are possible.<sup>157,206</sup> In rare cases with severe symptoms, hospitalization may be necessary, and there is a risk of death.<sup>206</sup>

There may be several considerations for the successful implementation of MRI monitoring. These include the following:

- **Capacity:** There are 432 MRI units in Canada, with 87.5% of units concentrated in Ontario, Quebec, British Columbia, and Alberta.<sup>153</sup> Almost 80% of MRI units are in urban facilities, limiting equitable access for those living in rural and remote areas. Travel costs to receive routine MRI monitoring exams would also represent an additional burden of care for patients and their families, if they live far from imaging sites.<sup>82,83,153</sup>
- **Limited human resources:** Based on data from the Canadian Medical Imaging Inventory 2022–2023 national survey, the number of full-time medical imaging staff has not kept pace with the growing volume of exams.<sup>149</sup> Medical imaging staff shortages can lead to longer wait times or service disruptions, with vacancies increasing five-fold from 2019 to 2021, potentially affecting capacity to monitor patients as well as increasing exhaustion among staff.<sup>4,149,155,207</sup> Efforts to streamline credentialing and licensing processes, recruit foreign-trained medical imaging staff, invest in and adopt information technologies and AI to eliminate repetitive tasks, cross-train staff for interoperability, and support existing staff may help to retain and increase available staff capacity.<sup>155</sup>
- **Education and training:** Radiologists may need training to apply appropriate MRI acquisition protocols for ARIA screening as well as training to detect ARIA in MRI images and ensure that baseline and monitoring MRI scans are comparable.<sup>4,157</sup>
- **Wait times:** In 2023, median wait times for an MRI exam peaked at more than 3 months, although this was dependent on the urgency of the exam.<sup>96</sup> The additional volume of MRI exams for scheduled monitoring or unscheduled precautionary scans, would, in the absence of changes to streamline or address appropriate use of diagnostic imaging, almost certainly increase current MRI wait times.<sup>4</sup>
- **Patient safety:** It has been observed that patients with AD and *APOE4* alleles receiving anti-amyloid-beta mAb DMTs are more susceptible to ARIA.<sup>4,208</sup> *APOE4* alleles are most common in people with European or African ancestry.<sup>209,210</sup> *APOE4* testing is not currently routine in Canada, as

*APOE4* mutations indicate susceptibility to AD rather than confirm development of the disease.<sup>158,211</sup> However, given the susceptibility of patients with AD and *APOE4* to ARIA, regulatory agencies and appropriate-use guidelines recommend that *APOE4* testing is warranted to better assess patient risk of developing ARIA and identify those who may require closer and more frequent MRI monitoring.<sup>4,28-30,114,212</sup> Such *APOE4* tests could be combined with other blood-based AD biomarker tests.<sup>164,166</sup>

## Continuation of Treatment

It is unclear how long patients should continue to use anti-amyloid-beta mAb DMTs, as clinical trials have been conducted over a relatively short period. Additionally, clinical trials included patients with early-stage disease, which was assessed by experts using cognitive tests, and it remains unclear what benefits are gained by continued treatment when AD progresses beyond the early stage.<sup>21,213</sup> This may necessitate routine check-ins with a care provider to monitor disease progression.<sup>21</sup>

There are several considerations related to monitoring for disease progression. These include the following:

- **Recurrent cognitive assessments:** Assessment of cognitive decline during anti-amyloid-beta mAb DMT use would require routine administration of cognitive tests. Given that many people in Canada do not have access to a PCP, routine monitoring of cognitive decline may be difficult.<sup>48</sup> Additionally, clinical trials used tests such as the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) and the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) to measure cognitive decline, which are not recommended by CCCDTD for use in clinical practice, as most clinicians are not familiar with these tests.<sup>17,21</sup> Therefore, optimal use of anti-amyloid-beta mAb DMTs would require training PCPs or other care providers on the use of cognitive tests or the development of an alternative validated test that can sufficiently measure cognitive decline in patients using anti-amyloid-beta mAb DMTs.
- **Repeat treatment eligibility assessments:** According to clinician engagement by the National Institute for Health and Care Excellence (NICE), the UK health technology assessment agency, patients may also need repeated amyloid PET exams or LPs to confirm ongoing eligibility for treatment, which could contribute to longer wait times for PET-CT scans and increase radiation exposure. Additionally, CSF analysis following LPs could place added strain on laboratory processing networks.<sup>21</sup>
- **Emerging blood-based biomarkers:** New blood-based biomarkers may play an important role in determining the cessation of treatment.

## Future Monitoring Technologies

Advances in MRI technology could ease current capacity constraints in imaging centres and provide a lower-cost and more accessible alternative to conventional MRI. Some current and emerging MRI technologies include the following:

- Modular MRI systems are designed to be smaller and more portable than traditional MRI machines, enabling them to be used in a variety of settings, including smaller clinics and remote areas. This capability has the potential to enhance equitable access to MRI.<sup>214</sup> However, their smaller size, lower

magnetic field strength, and portability might limit the scope of imaging capabilities, as currently the CCCDTD recommends full-size MRI units with sufficient field strength (1.5 or 3.0 Tesla) for neuroimaging.<sup>17</sup> Investigations are under way to determine whether these portable units with low magnetic field strength have sufficient resolution to reliably detect ARIA.<sup>215</sup>

- Remote MRI operation, like virtual cockpits, could provide support to facilities that have MRI machines but lack specialized MRI operators. A key consideration is the need for robust and secure communication networks to ensure data privacy and prevent interruptions during remote operations.<sup>216,217</sup> It should be noted that technologists would still be required to ensure safety protocols are followed and patients receive care and support.
- Integrating telemedicine with MRI services may streamline workflows by allowing remote prescan and postscan consultations, as well as potentially supporting specialists from different jurisdictions to assist in MRI interpretations if local expertise is unavailable. Challenges for integration of telemedicine with MRI services include ensuring the safety and privacy of patient data, addressing billing issues for specialists, and resolving cross-jurisdictional licensing (5 jurisdictions permit teleradiology services from outside their borders).<sup>95,218</sup>

Blood-based biomarkers have also shown promise for monitoring treatment effectiveness, particularly in anti-amyloid-beta mAb DMT trials. The use of biomarkers such as amyloid-beta42/40, p-tau 217, and p-tau181 have been correlated with reductions in use of amyloid PET across various trials, suggesting the potential of these biomarkers for dynamic monitoring and in determining treatment cessation. However, further research is needed to establish the relationship between biomarker changes and clinical outcomes, particularly at the individual level, to support personalized treatment decisions and to better demonstrate treatment effectiveness.<sup>219</sup>

## Estimation of Treatable Population With Incident Early-Stage AD and Medical Imaging Demand

CDA-AMC estimated the size of the treatable population (those eligible for treatment with anti-amyloid-beta mAb DMTs) with incident cases of early-stage AD in 2020 and the associated demand on medical imaging. In addition, the treatable population and medical imaging demand were projected over a 5-year period from 2020 to 2025. Data availability limited calculations and estimation to this period. Incident cases were used instead of prevalent cases to estimate the number of patients for capacity planning. This approach assumes that prevalent cases of AD would be too advanced to benefit from anti-amyloid-beta mAb DMTs, although this may not accurately reflect all prevalent cases in a real-world setting. The methodology used was adapted from a NICE report that examined potential issues and challenges in evaluating DMTs.<sup>21,220</sup>

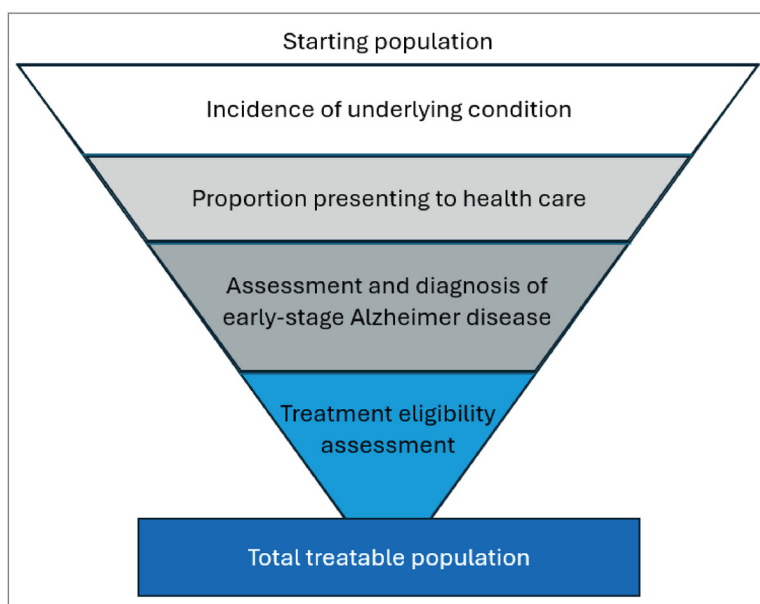
## Treatable Population Estimation

A funnel approach was used to estimate a treatable population with incident cases of early-stage AD by narrowing down a starting population of people aged 65 years or older in Canada in stages, as follows ([Figure 4](#)):

- those who develop dementia of any kind
- those who present to health care services
- those who are assessed and diagnosed to have early-stage AD
- those who have sufficient amyloid-beta to be eligible for treatment with anti-amyloid-beta mAb DMTs.

A literature scan was undertaken to find incidence rates and proportions for each calculation stage. Details on specific methodology and calculations at each stage are provided in [Appendix 2](#).

**Figure 4: Funnel Approach for Determining Treatable Population**



In 2020, the total estimated incident treatable population in Canada was 22,652 people, representing 0.3% of people aged 65 years or older in Canada (6,809,521; [Table 2](#)). This number reflects only 1 year of newly diagnosed cases and provides a conservative estimate of the potential treatable population if anti-amyloid-beta mAb DMTs were available in Canada. It does not account for patients with existing early-stage AD who might also seek treatment, potentially increasing the total treatable population. Additionally, not everyone with sufficient amyloid-beta to qualify for the DMTs may choose to pursue treatment due to comorbidities, frailties, or concerns about potential serious adverse effects, for example.



**Table 2: Combined Estimated Incident Treatable Population With Early-Stage AD in Canada for Anti–Amyloid-Beta mAb DMTs in 2020**

Stage	Mild cognitive impairment		Mild dementia due to AD		Total incident treatable population	
	N	% of starting population	N	% of starting population	N	% of starting population
People 65 years or older in Canada	6,809,521	—	6,809,521	—	6,809,521	—
Incidence of underlying condition	347,286	5.1	86,000	1.3	433,286	6.4
Proportion presenting to health care	46,189	0.7	32,938	0.5	79,127	1.2
Assessment and diagnosis of early-stage AD	25,404	0.4	11,621	0.2	37,025	0.5
Treatment eligibility assessment	14,506	0.2	8,146	0.1	22,652	0.3

AD = Alzheimer disease; DMT = disease-modifying therapy; mAb = monoclonal antibody.

A 2023 report examining current health system capacity found that less than 2% of potential patients would be able to access the health care resources required to be treated with anti–amyloid-beta mAb DMTs, with eligibility assessment creating the largest capacity gap to treat patients.<sup>5</sup> This further reinforces the need to modify the current patient pathway to treat AD should anti–amyloid-beta mAb DMTs be approved, as well as to prepare for the adoption of emerging technologies such as blood-based biomarkers.

The estimate used here limited the treatable population to those 65 years of age or older. In clinical trials of DMTs, the average age of trial participants skewed older, exceeding 70 years of age. However, if anti–amyloid-beta mAb DMT were approved in Canada, it is likely that those under the age of 65 with symptoms would also seek assessment and treatment, increasing the treatable population beyond what was estimated. Additionally, this report relies on publicly available information from a literature scan, including studies from a variety of countries, which may affect its accuracy in reflecting the context of Canada. Much of the literature was published before the introduction of DMTs, so the values underpinning the calculation stages may change as new data and studies examining how patient behaviour is affected by DMTs are made available.

## Estimation of Medical Imaging Demand

Using the estimated incident treatable population with early-stage AD, the number of PET-CT and MRI exams required for anti–amyloid-beta mAb DMTs was calculated and matched to the domains of the patient pathway for AD. This is a novel extension to the work done in the NICE report.<sup>21,220</sup> Details on specific methodology and assumptions are listed in [Appendix 2](#).

In 2020, an estimated 7,475 PET-CT exams and 70,900 MRI exams would be required to support the 22,652 patients with incident early-stage AD eligible for anti–amyloid-beta mAb DMTs for 1 year ([Table 3](#)). This represents 6% and 3% of the 2019 to 2020 exam volumes for PET-CT and MRI, respectively, adding an

additional volume to medical imaging capacity, which would be expected to further contribute to long wait times.<sup>144,153</sup> As previously mentioned, eligibility assessment, including PET-CT exams, was 1 of the largest identified capacity gaps in the current health care system, leading to a reduced access to anti-amyloid-beta mAb DMTs for the treatable population.<sup>5</sup>

**Table 3: Estimated PET-CT and MRI Exams Required Based on Estimated Incident Treatable Population in Canada With Early-Stage AD for Anti-Amyloid-Beta mAb DMTs in 2020**

Domain	PET-CT exams	MRI exams
Treatment eligibility assessment	7,475	22,652
Treatment administration of anti-amyloid-beta mAb DMTs	NA	NA
Patient monitoring	NA	48,248
Total	7,475	70,900

AD = Alzheimer disease; DMT = disease-modifying therapy; mAb = monoclonal antibody; NA = not available.

These exam volumes also represent a conservative estimate of potential exams, as it was assumed only patients contraindicated for LPs (33%) would receive PET-CT exams, whereas patient preference may lead to more PET-CT exams than projected.<sup>221</sup> In addition, it may be necessary to conduct recurrent PET-CT exams each year to confirm continued eligibility for anti-amyloid-beta mAb DMTs. The estimated MRI exam volumes include a baseline exam and 2 scheduled monitoring exams for all patients and the associated exams needed for the 6.5% of patients who experience ARIA. However, the estimated MRI exam volumes did not take into account the need for precautionary MRI exams when symptoms of adverse events appear that do not progress to full cases of ARIA, which could significantly inflate the exam volume. Additionally, if people with existing early-stage AD were to seek treatment, the subsequent exam volume would increase as well.

## Estimating Future Demand

The 5 years from 2020 to 2025 were examined by combining the estimation of the treatable incident population with the estimated medical imaging demand to aid in potential capacity planning. Details on specific methodology and assumptions are provided in [Appendix 2](#).

Over the 5-year period, an initial jump in the number of patients, from 22,625 patients to 71,249, was seen in the first 3 years as anti-amyloid-beta mAb DMTs were introduced. The health system may not be able to handle a large influx of patients and medical imaging exams within a relatively short period of time. With patients remaining on treatment for 2 years before being taken off, a steadier increase of patients was projected, increasing by approximately 4,000 annually.

**Table 4: Estimated Incident Treatable Population With Early-Stage AD in Canada for Anti–Amyloid-Beta mAb DMTs From 2020 to 2025 and Estimated Demand on Medical Imaging**

Year	Total annual number of patients eligible for treatment	Annual number of incident cases	Annual PET-CT exams	Annual MRI exams
2020	22,625	22,625	7,475	70,900
2021	46,357	23,732	15,307	75,752
2022	71,249	24,892	23,521	79,456
2023	74,733	26,109	24,662	83,339
2024	78,387	27,386	25,868	87,415
2025	82,220	28,725	27,133	91,689

AD = Alzheimer disease; DMT = disease-modifying therapy; mAb = monoclonal antibody.

This projection assumes a constant demand for anti–amyloid-beta mAb DMTs, which may not reflect reality, as demand could grow as the treatment becomes more established. In addition, the projection assumes the treatment period lasts 2 years based on clinical trial parameters, but it remains unclear how long patients would remain on anti–amyloid-beta mAb DMTs, as open-label extension studies are ongoing.<sup>222,223</sup> Additionally, a constant increase in the incidence rate was assumed over the 5-year period, which may not reflect the potential future demand, as more patients with symptoms may seek assessment if anti–amyloid-beta mAb DMTs become more established as a treatment option. Finally, health care providers may be cautious concerning adverse events and limit patient eligibility, or the health system may limit where treatments will be offered during the early phases of anti–amyloid-beta mAb DMTs implementation, lowering the number of patients who will be treated. For instance, 6 months after regulatory approval, it has been reported that only 2,000 to 3,000 people in the US have received treatment with anti–amyloid-beta mAb DMT because treatment was mainly being provided at large neurology centres.<sup>224</sup>

## Future Considerations for Anti–Amyloid-Beta mAb DMTs

With numerous potential treatments for AD in development, the current care pathway may not provide the range of health care resources required for optimal patient support. If these therapies are approved, substantial changes to existing patient care pathways may be necessary to ensure equitable access to them. This may include:

- enhancing care by implementing interdisciplinary teams to better support and manage patients presenting with cognitive symptoms as well as coordinating care while patients receive anti–amyloid-beta mAb DMTs
- increasing health system capacity to treat patients with AD, including dementia specialists, AD care providers, lab capacity, and infusion sites to meet the needs of a growing aging population
- increasing medical imaging capacity, with consideration for staffing levels and the number and location of MRI and PET-CT units, as well as supporting medical imaging staff with education and training

- improving equitable access to primary and social services for underserved groups — such as racialized communities and Indigenous populations — which requires expanding culturally appropriate care, addressing structural barriers, implementing equitable cognitive-assessment tools, and educating and training health care providers to better support these communities to ensure they receive the care and support they need
- increasing outreach and awareness of cognitive decline symptoms among PCPs, patients, and the general public, especially in racialized groups that may be less aware of AD
- establishing criteria for accessing limited medical imaging resources without disrupting access for current patients (i.e., oncology patients receiving PET-CT exams)
- conducting postmarket drug evaluations to assess long-term safety and effectiveness of anti-amyloid-beta mAb DMTs, including their impact on AD progression and potential side effects over time
- ensuring appropriate follow-up and monitoring, potentially with a patient registry, to determine when patients should discontinue treatment.

The landscape of anti-amyloid-beta mAb DMTs implementation is already evolving, with the development of blood-based AD biomarker testing. As well, the adoption of portable or remote operating MRI units may play a role in alleviating some equity and travel concerns for patients living in rural or remote areas in the future. These developments may greatly increase access to anti-amyloid-beta mAb DMTs, and care needs to be taken to ensure that these advances can be deployed in a timely and equitable manner. This includes:

- developing a standardized threshold for determining AD using blood-based biomarker tests as well as accrediting labs throughout the country to ensure timely analysis of biomarker tests
- combining newly developed technologies and key alterations in how patients with AD receive care to improve patient care and health system readiness and resilience to treat patients with anti-amyloid-beta mAb DMTs if they are approved in Canada.

## Limitations

The aim of this report is to provide a high-level overview of considerations for health care systems in relation to the potential market entry of anti-amyloid-beta mAb DMTs. Some of the challenges may differ in magnitude across different provinces and territories. Additionally, this report specifically focused on anti-amyloid-beta mAb DMTs, as they are the most developed treatment option, they have been approved in some countries, and they share many considerations for potential effects on the treatment pathway and the health care system. Other DMTs for AD that target alternative pathologic processes or use different administration methods (e.g., oral intake) are still in earlier stages of development and may involve additional considerations not covered here. However, these other DMTs for AD may have considerations that overlap with some of the proposed changes to the current treatment pathway for potential uptake of anti-amyloid-beta mAb DMTs.

This report is also limited by information that is publicly accessible via a literature search. Access to provincial and territorial health systems data could provide key information about demographic aspects and the clinical profile of people with early-stage AD, current processes of care, and outcomes of the disease, which would assist in projections and planning to optimize care.

## Conclusions

CDA-AMC has highlighted some key considerations in relation to the readiness of health care systems if emerging DMTs were adopted in Canada.

The regulatory approval and public reimbursement of DMTs for AD in Canada would require a new pathway of care to ensure equitable and timely access to these novel therapies.

Implementing the changes to the clinical pathway for the use of anti-amyloid-beta mAb DMTs will require considerations for adaptations across the continuum of care, including health and social human resources planning and additional clinical training, increased capacity for diagnostic imaging, laboratory networks, and IV infusion. Careful consideration of processes and systems would be needed to promote best clinical practice and appropriate use of finite health care resources.

Across different provincial and territorial health care systems, challenges will vary, necessitating open communication and multidisciplinary collaboration between health system partners to facilitate the optimal delivery of patient care. It would take time to design, plan, and operationalize models of care for novel DMTs, and careful consideration would need to be given to emerging technologies that may support their delivery. New blood-based biomarkers, for example, could largely obviate the need for LP via CSF and PET-CT to assess amyloid positivity. An ongoing awareness of emerging health technologies in relation to screening, diagnosis, treatment, monitoring, and assessment of their benefits and limitations would be important to support optimal care and health system sustainability.

This report highlights that certain groups of people in Canada may face challenges in accessing the technologies, services, and clinicians needed to diagnose the presence and severity of the disease, determine eligibility for treatment, administer therapies, and provide ongoing monitoring. Rural and remote populations, newcomers to Canada, Indigenous Peoples, and other groups may experience barriers in accessing and navigating the health care systems, challenging the principle of health equity.

Pan-Canadian alignment among the provinces and territories, as well as input from patients and caregivers, is required to promote a standardized, patient-centred approach to screening, diagnosing, treating, and monitoring patients. Such an approach may help achieve long-term success in expanding capacity and ensuring the delivery of optimal and sustainable care.

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## Appendix 1: Additional Information on Blood-Based Biomarkers for AD

Please note that this appendix has not been copy-edited.

Examples of some of the strengths and weaknesses of emerging biomarkers:

- Plasma Amyloid-Beta
  - While CSF amyloid-beta42/amyloid-beta40 ratios are associated with amyloid plaques in the brain, plasma amyloid-beta42/amyloid-beta40 testing encounters challenges related to accurate blood sampling and variability in diagnostic utility. Studies have shown that integrating genotyping and age into plasma amyloid-beta42/amyloid-beta40 testing may enhance its performance.<sup>164,166,172</sup>
- Plasma p-tau
  - Studies have suggested that plasma phospho-tau (p-tau) isoforms, including p-tau181, p-tau217, and p-tau231, elevate early in the AD disease process and increase with disease progression.<sup>164,172</sup> While some comparative studies have reported that p-tau217 may be a better diagnostic biomarker for symptomatic AD, p-tau181 is easier to measure due to higher levels in plasma.<sup>166,172,173</sup>
  - Some studies have shown that plasma p-tau231, when combined with plasma amyloid-beta42/amyloid-beta40, age, sex, and APOE4 status, may detect amyloid-beta pathology earlier in younger individuals who have yet to develop cognitive impairment.<sup>225</sup>
- Plasma GFAP
  - Plasma GFAP concentrations increase following central nervous system injury and have been associated with early amyloid-beta pathology in some studies, potentially predicting cognitive decline and conversion to AD in cognitively unimpaired individuals and those with MCI.<sup>164</sup>
  - Additionally, significant reductions in plasma GFAP levels have been observed following the removal of amyloid-beta plaques through anti-amyloid-beta AD immunotherapy, suggesting that plasma GFAP may potentially be useful in monitoring treatment response.<sup>172</sup>
- Plasma NfL
  - Studies suggest that serum NfL is a sensitive, nonspecific biomarker for neuronal damage across conditions such as dementia, brain injury, cardiovascular diseases, and multiple sclerosis.<sup>164</sup>
  - NfL offers limited utility for specific detection of AD pathology, but it may hold prognostic value in predicting future cognitive decline in patients with MCI or dementia.<sup>172</sup>

## Appendix 2: Methodology for Estimation of Treatable Population With Incident Early-Stage AD

Please note that this appendix has not been copy-edited.

### Treatable Patient Population Estimation

To facilitate the adaptation of the NICE model to the context of Canada, a literature scan was undertaken to find incidence rates and proportions for each calculation stage, from individuals aged older than 65 through to those receiving treatment. Where updated studies could not be found, the same studies in the NICE report were used for their equivalent calculation stage. These estimates could increase if those who have prevalent AD and those under the age of 65 with cognitive symptoms sought treatment.

To accommodate ranges of incidence and proportions, upper and lower estimates were calculated for each stage of the patient pathway using the NICE approach for MCI and mild dementia due to AD (Tables A1 and A2, respectively). The midrange results were presented in the Treatable Patient Population Estimation section with methodology detailed in this section for MCI and mild dementia due to AD.

### Mild Cognitive Impairment

For calculating stage I (incidence of underlying condition), an annual MCI incidence of 5.1% was applied to the 2020 starting population of Canadians aged 65 years or older. This value comes from a table in Roberts et al. that reported a variety of incidence rates among different age cohorts.<sup>226</sup> The listed 5.1% annual MCI incidence rate was from Manly et al. from a racially diverse cohort of people aged 65 years or older in the US.<sup>227</sup> Calculating MCI incidence is a novel addition to the methodology used in the NICE report which only examined prevalence of MCI.<sup>21</sup>

For calculating stage II (proportion presenting to health care), Anstey et al. reported that 13.3% of those with MCI presented to health care.<sup>228</sup> Anstey et al. was used in the NICE report and is a study following a cohort of Australian participants who were assessed every 4 years for MCI.

For calculating stage III (assessment and diagnosis of early-stage AD), Glynn et al. reports 55% of MCI cases are amnesic.<sup>229</sup> Amnesic MCI is a subtype of MCI that progresses to AD and is likely caused by underlying AD etiology. Glynn et al. is a 20-year retrospective study of MCI patients at a memory clinic.<sup>229</sup>

For calculating stage 4 (treatment eligibility assessment), Petersen et al. reports 57.1% of MCI cases show amyloid positivity.<sup>230</sup> Petersen et al. examined a cohort of amnesic MCI patients from the Mayo Clinic Study on Aging and examined AD biomarkers, including amyloid positivity.<sup>230</sup>

### Mild Dementia Due to AD

For calculating stage I (incidence of underlying condition), this statistic comes from the Government of Canada's web page on dementia and had the same parameters (statistic was for those aged 65 years or older in 2020 to 2021 with dementia of any kind).<sup>236</sup>

For calculating stage II (proportion presenting to health care), Lang et al. reported that 38.3% of those with dementia presented to health care.<sup>34</sup> Lang et al. was used in the NICE report and is a systematic review and meta-analysis examining the prevalence of undetected dementia in communities.<sup>34</sup>

For calculating stage III (assessment and diagnosis of early-stage AD), a two-step process was done. First, it was assumed that 70% of dementia cases were due to underlying AD etiology from the 2020 Alzheimer's Association fact sheet.<sup>237</sup> Second, Yuan et al. found that 50.4% of Alzheimer patients had mild dementia due to AD.<sup>238</sup> Yuan et al. was a study examining the distribution of Alzheimer severity among participants of the Framingham Heart Study.<sup>238</sup>

For calculating stage 4 (treatment eligibility assessment), Rabinovici et al. reports 70.1% of mild dementia cases due to AD show amyloid positivity.<sup>239</sup>

**Table 5: Upper and Lower Ranges of Estimates for Treatable Population in Canada With Incident MCI From 2020 to 2021**

Stage	Upper Estimate	% of starting population	Source	Midrange Estimate	% of starting population	Source	Lower Estimate	% of starting population	Source
<b>2020</b>									
<b>People 65 years or older in Canada</b>	6,809,521	—	StatsCan 65+ (2020) <sup>12</sup>	6,809,521	—	StatsCan 65+ (2020) <sup>12</sup>	6,809,521	—	StatsCan 65+ (2020) <sup>12</sup>
<b>Incidence of underlying condition</b>	522,971	7.7%	Ravaglia et al. (76.8/1000 person-years) <sup>231</sup> from Roberts et al. <sup>226</sup>	347,286	5.1%	Manly et al. (5.1% annual incidence) <sup>227</sup> from Roberts et al. <sup>226</sup>	146,405	2.2%	Solfrizzi et al. (21.5/1000 person-years) <sup>232</sup> from Roberts et al. <sup>226</sup>
<b>Proportion presenting to health care</b>	69,555	1.0%	13.3% from Anstey et al. <sup>228</sup>	46,189	0.7%	13.3% from Anstey et al. <sup>228</sup>	19,472	0.3%	13.3% from Anstey et al. <sup>228</sup>
<b>Assessment and diagnosis of early-stage Alzheimer disease</b>	52,166	0.8%	75% from Knopmann et al. <sup>233</sup>	25,404	0.4%	55% from Glynn et al. <sup>229</sup>	10,710	0.2%	55% from Glynn et al. <sup>229</sup>
<b>Treatment eligibility assessment</b>	33,751	0.5%	64.7% from Lee et al. <sup>234</sup>	14,506	0.2%	57.1% from Petersen et al. <sup>230</sup>	4,391	0.1%	41% from Kim et al. <sup>235</sup>
<b>2021</b>									
<b>People 65 years or older in Canada</b>	7,045,990		StatsCan 65+ (2021) <sup>12</sup>	7,045,990		StatsCan 65+ (2021) <sup>12</sup>	7,045,990		StatsCan 65+ (2021) <sup>12</sup>
<b>Incidence of underlying condition</b>	541,132	7.7%	Ravaglia et al. (76.8/1000 person-years) <sup>231</sup> from Roberts et al. <sup>226</sup>	359,345	5.1%	Manly et al. (5.1% annual incidence) <sup>227</sup> from Roberts et al. <sup>226</sup>	151,489	2.2	Solfrizzi et al. (21.5/1000 person-years) <sup>232</sup> from Roberts et al. <sup>226</sup>

Stage	Upper Estimate	% of starting population	Source	Midrange Estimate	% of starting population	Source	Lower Estimate	% of starting population	Source
<b>Proportion presenting to health care</b>	71,971	1.0%	13.3% from Anstey et al. <sup>228</sup>	47,793	0.7%	13.3% from Anstey et al. <sup>228</sup>	20,148	0.3	13.3% from Anstey et al. <sup>228</sup>
<b>Assessment and diagnosis of early-stage Alzheimer disease</b>	53,978	0.8%	75% from Knopmann et al. <sup>233</sup>	26,286	0.4%	55% from Glynn et al. <sup>229</sup>	11,081	0.2	55% from Glynn et al. <sup>229</sup>
<b>Treatment eligibility assessment</b>	34,924	0.5%	64.7% from Lee et al. <sup>234</sup>	15,009	0.2%	57.1% from Petersen et al. <sup>230</sup>	4,543	0.1	41% from Kim et al. <sup>235</sup>

**Table 6: Upper and Lower Ranges of Estimates for Treatable Population in Canada With Incident Mild Dementia Due to AD From 2020 to 2021**

Stage	Upper Estimate	% of starting population	Source	Midrange Estimate	% of starting population	Source	Lower Estimate	% of starting population	Source
<b>2020</b>									
<b>People 65 years or older in Canada</b>	6,809,521	—	StatsCan 65+ (2020) <sup>12</sup>	6,809,521	—	StatsCan 65+ (2020) <sup>12</sup>	6,809,521	—	StatsCan 65+ (2020) <sup>12</sup>
<b>Incidence of underlying condition</b>	124,000	1.8%	Alzheimer Society of Canada Landmark Report (likely includes those under 65) <sup>1</sup>	86,000	1.3%	Government of Canada 'Dementia: Overview' <sup>236</sup>	82,872	1.2%	Crude incidence rate of dementia (1,217/100K) from CCDSS for 2020 to 2021 <sup>240</sup>
<b>Proportion presenting to health care</b>	55,800	0.8%	45% from Lang et al. <sup>34</sup>	32,938	0.5%	38.3% from Lang et al. <sup>34</sup>	20,718	0.3%	25% from World Alzheimer Report 2021 <sup>60</sup>

Appendix 2: Methodology for Estimation of Treatable Population With Incident Early-Stage AD

Stage	Upper Estimate	% of starting population	Source	Midrange Estimate	% of starting population	Source	Lower Estimate	% of starting population	Source
<b>Assessment and diagnosis of early-stage Alzheimer disease</b>	25,891	0.4%	(80% from 2020 Alzheimer's Association fact sheet) <sup>237</sup> x (58% from Jonsson et al.) <sup>241</sup>	11,621	0.2%	(70% from 2020 Alzheimer's Association fact sheet) <sup>237</sup> x (50.4% from Yuan et al.) <sup>238</sup>	5,967	0.1%	(60% from 2020 Alzheimer's Association fact sheet) <sup>237</sup> x (48% from Jonsson et al.) <sup>241</sup>
<b>Treatment eligibility assessment</b>	22,007	0.3%	85% from Jansen et al. <sup>242</sup>	8,146	0.1%	70.1% from Rabinovici et al. <sup>239</sup>	4,183	0.06%	70.1% from Rabinovici et al. <sup>239</sup>
<b>2021</b>									
<b>People 65 years or older in Canada</b>	7,045,990		StatsCan 65+ (2021) <sup>12</sup>	7,045,990		StatsCan 65+ (2021) <sup>12</sup>	7,045,990		StatsCan 65+ (2021) <sup>12</sup>
<b>Incidence of underlying condition</b>	92,725	1.3%	Crude incidence rate of dementia (1,316/100K) from CCDSS for 2021 to 2022 <sup>240</sup>	92,091	1.3%	Crude incidence rate of dementia (1,307/100K) from CCDSS for 2021 to 2022 <sup>240</sup>	91,527	1.3%	Crude incidence rate of dementia (1,299/100K) from CCDSS for 2021 to 2022 <sup>240</sup>
<b>Proportion presenting to health care</b>	41,726	0.6%	45% from Lang et al. <sup>34</sup>	35,271	0.5%	38.3% from Lang et al. <sup>34</sup>	22,882	0.3%	25% from World Alzheimer Report 2021 <sup>60</sup>
<b>Assessment and diagnosis of early-stage Alzheimer disease</b>	19,361	0.3%	(80% from 2020 Alzheimer's Association fact sheet) <sup>237</sup> x (58% from Jonsson et al.) <sup>241</sup>	12,444	0.2%	(70% from 2020 Alzheimer's Association fact sheet) <sup>237</sup> x (50.4% from Yuan et al.) <sup>238</sup>	6,590	0.1%	(60% from 2020 Alzheimer's Association fact sheet) <sup>237</sup> x (48% from Jonsson et al.) <sup>241</sup>
<b>Treatment eligibility assessment</b>	16,457	0.2%	85% from Jansen et al. <sup>242</sup>	8,723	0.1%	70.1% from Rabinovici et al. <sup>239</sup>	4,620	0.07%	70.1% from Rabinovici et al. <sup>239</sup>



## Estimation of Medical Imaging Demand

After estimating the incident treatable population eligible to receive anti-amyloid-beta mAb DMTs for early-stage AD, estimates of the number of PET-CT and MRI exams were calculated and matched to the domains of the patient pathway for AD. This is a new extension to the work done in the NICE report. It should be noted that while CT exams may be used to rule out other causes of dementia in patients, it is insufficient for determining treatment eligibility, so it was excluded from the estimation.

For PET-CT exams, Verger et al. reported that up to 33% of patients are not able to receive LP to determine amyloid positivity and will need a PET-CT exam.<sup>221</sup> This was applied to the estimated incident population eligible for treatment (22,652) to get 7,475 potential PET-CT exams. Verger et al. is a position paper put forward by the European Association of Nuclear Medicine Neuroimaging Committee which cites a study noting that up to one-third of patients may require amyloid PET over LP to determine amyloid positivity.<sup>221</sup>

For MRI exams, a baseline MRI exam is required during treatment eligibility assessment to ensure that patients' brain structures are not at high risk of adverse events, leading to 22,652 baseline scans. This has been a requirement in countries that have approved anti-amyloid-beta mAb DMTs.<sup>28,29</sup> In addition, at least 2 MRI exams are taken within the first year of treatment to monitor for the development of adverse events, leading to an additional 45,304 scans, for a total of 67,956 exams if no adverse events occur. In some countries that have approved the use of anti-amyloid-beta mAb DMTs, this can be up to 3 MRI exams, potentially adding another 22,652 exams.<sup>28,29</sup>

However, if an adverse event were to occur, MRI monitoring exams would increase to once every 2 to 4 months. Jeong et al. reports an adverse event incidence rate of 6.5%, with the majority of cases resolving within 4 months.<sup>206</sup> Assuming an incidence rate of 6.5% and that cases resolve within 4 months with a monitoring rate of 1 MRI scan every 2 months, this leads to an additional 2,944 MRI exams. This leads to an estimated 70,900 MRI exams.

## Estimating Future Demand

After estimating the incident treatable population eligible to receive anti-amyloid-beta mAb DMTs for early-stage AD, and the number of PET-CT and MRI exams to support treatment, a 5-year projection was estimated. This is a new extension to the work done in the NICE report to assist in capacity planning.

Several key assumptions underpin the 5-year projection. Subsequent changes to these assumptions would affect the numbers. The assumptions used to create the initial treatable incident population estimate and medical imaging demand estimate were carried forward into the calculations made for the projection.

The percent increase in incidence rate between 2020 to 2021 was calculated and applied to each subsequent year. This assumes a constant incidence rate increase which may not necessarily be accurate as more people with cognitive symptoms could seek health care if there was a treatment available for them. Additionally, it was assumed that patients would receive anti-amyloid-beta mAb DMTs for 2 years before AD progression removed them from treatment eligibility. It remains unclear how long patients will be able

to remain on anti-amyloid-beta mAb DMTs.<sup>21,213</sup> Furthermore, it was assumed that patients would undergo annual treatment eligibility assessments to ensure they are still able to receive treatment.<sup>21</sup> This means that those who received PET-CT exams previously would receive another for each year of treatment. It was also assumed that those who experienced an ARIA event within the first year of treatment will require an additional MRI exam 1 year after treatment initiation.



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