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An Overview of New and Emerging Technologies for Early Diagnosis of Alzheimer Disease

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Key Messages

- Alzheimer disease is a progressive neurologic condition that leads to the decline of cognitive functioning and eventual death. There is currently no cure.
- Proposed causes of Alzheimer disease include the amyloid hypothesis, which suggests that it is caused by a buildup of amyloid-beta and tau proteins in the brain, leading to cell death. Recent diagnostic tools focus on amyloid and tau proteins as potential markers of the disease, and new treatments are also focusing on amyloid and tau formation.
- Earlier diagnosis of Alzheimer disease allows time for planning for care and support needs before symptoms worsen. It also allows for both drug and non-drug treatments to be used earlier, which may prolong time with a higher quality of life.
- Emerging diagnostic tools include biomarker-based tools, such as MRI, PET, CT, blood-based biomarkers, cerebrospinal fluid-based biomarkers, ocular testing, and salivary biomarkers. The majority of these tools are in the research phase, although imaging is often used in combination with cognitive testing to diagnose Alzheimer disease.
- One blood-based biomarker test is available in the US (paid out of pocket). It is unclear whether testing will be available in Canada or when this will happen.

Purpose

The purpose of this Horizon Scan is to present health care stakeholders in Canada with an overview of information related to emerging technologies to aid in the early identification of Alzheimer disease (AD) and related dementias and a summary of important considerations for the potential implementation of the technology, should emerging evidence demonstrate value. This report is not a systematic review, does not involve critical appraisal, and does not include a detailed summary of study findings. It is not intended to provide recommendations for or against the use of the technology.

Methods

A limited literature search was conducted by an information specialist on key resources, including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were dementia and Alzheimer disease, imaging, biomarker testing, and early diagnosis. No filters were applied to limit the retrieval by study type. If possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2019, and November 24, 2021. The date limit was chosen due to the volume of literature found.

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was an emerging technology to aid in the early identification of AD and related dementias. Conference abstracts

and grey literature were included if they provided additional information to that available in the published studies.

Peer Review

A draft version of this report was reviewed by 1 clinical expert with expertise in neurodegenerative disease and brain injury biomarkers.

Background

Dementia is a set of symptoms related to progressive deterioration of cognitive function, including memory loss; declining executive function, decision-making, and language function; and changes in behaviour and mood.[1] AD is a form of dementia. The most prominent symptom of AD is memory loss, starting as mild cognitive impairment (MCI; i.e., memory problems that do not interfere with everyday life) and progressing to impairment in communication, confusion, and trouble recognizing people. Some people may have paranoia and hallucinations associated with their diagnosis. Eventually, the disease progresses to severe AD, in which a person is entirely dependent on others for care, and then eventually death.[2]

There is currently no cure for AD, and the exact causes of the disease are not known.[1] The leading hypothesis for the cause of AD is the amyloid hypothesis. AD is linked to abnormal protein formation in the brain — amyloid-beta- proteins clump together to form "plaques" and tau proteins clump together to form "tangles." The plaques clump around nerve cells in the brain, which leads to cell death. The tangles prevent essential nutrients from moving through cells.[3] These changes begin before any cognitive symptoms appear, so tests to detect changes in the proteins before symptoms emerge are of particular interest to researchers.[4] These tests are also of interest to health care providers, individuals with AD, and their caregivers because it may allow for early intervention and a prolonged time with a higher quality of life.

In Canada, 25,000 new cases of AD are diagnosed each year.[5] There is currently no single test used to diagnose AD. Diagnosis of AD involves a series of tests performed on an individual to rule out other diseases or causes and to confirm the diagnosis. These tests include blood and urine tests, memory tests, problem-solving and counting tests, and brain scans (MRI, PET, and CT).[2] Risk factors for AD include age, sex, a genetic background for the disease (i.e., family members with AD), unbalanced diet, physical inactivity, brain injuries, and other environmental factors.[1] The rate of progression of the disease varies between people — a person may live for 4 years to 8 years after their diagnosis, especially if diagnosis comes later in the disease progression, or could live up to 20 years after diagnosis.[3]

Current research related to AD focuses on treatment options and early diagnosis. Changes in the brain linked to the buildup of plaques and tangles are irreversible, so much of the current research on AD focuses on early treatment and early diagnosis before there is major damage to the brain.[6] Early diagnosis of AD helps doctors determine a personalized plan for people and optimized treatments.[4] Currently, many people are not diagnosed with Alzheimer-related dementia until later stages in the disease, which represents a missed opportunity for early intervention. These missed or delayed diagnoses are due to multiple factors, such as the

belief that memory problems are normal as people age; a lack of knowledge or recognition of the disease by family, friends, or health care providers; and a lack of consistent biomarkers for diagnosis.[4] Early detection of AD is a challenge because MCI also can lead to other types of dementia or not lead to dementia at all. Deciding who requires in-depth screening is difficult; therefore, any tools that are used for early diagnosis must be sensitive (i.e., no false negatives), practical to use by health care providers, and ideally noninvasive.[7]

A new early AD treatment was approved by the FDA in 2021 and, as of the writing of this document, has been submitted to Health Canada for review.[4,8] This is the first drug for treatment of early AD to receive FDA approval.[9] The drug works by reducing the number of amyloid-beta plaques in the brain. The drug is intended for people with MCI who are in the early stages of AD; therefore, confirmation of the presence of amyloid plaques in the brain is required[9] by brain imaging (e.g., PET) or cerebrospinal fluid (CSF) testing.[9]In preparation for potential new disease-modifying treatments for AD similar to these new treatments that target the removal of amyloid-beta plaques, it is of interest to know about methods of diagnosis of AD, including imaging and other markers. This Horizon Scan examines the emerging technologies to aid in the early identification of AD and related dementias and the potential implications of early detection of AD for diagnosis, treatment, and management.

Methods of Early Diagnosis

There are numerous proposed and tested methods of diagnosis for AD in the early stages of the disease. These include questionnaires, imaging, CSF biomarkers, blood testing, olfactory biomarkers, salivary testing, and retinal and ocular testing. Some methods of diagnosis are in current use, while others are still in development.

Current Methods and Technology for Diagnosis

Diagnosis of Cognitive Impairment

Questionnaires and Cognitive Testing

There are cognitive tests used for the diagnosis of AD, such as the General Practitioner Assessment of Cognition (GPCOG), the Memory Impairment Screen (MIS), the Mini-Cog test, the Mini-Mental State Examination (MMSE) for dementia, the Clinical Dementia Rating scale–Sum of Boxes (CDR–SB), and the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog).[6] The earliest these tests are performed is in the early stage of cognitive decline; therefore, they cannot be used before cognitive impairment. The 5th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, held in 2020, recommends rapid psychometric screening tools such as the MIS and the clock drawing test, the Mini-Cog, the AD8, the 4-item version of the Montreal Cognitive Assessment (MOCA), or the GPCOG. It was also recommended that preference be given to longer and more comprehensive tests such as the MMSE.[10] The full version of the MOCA, which consists of 30 questions related to cognitive functioning,[11] is also used in the diagnosis of AD and dementia.[12]

These cognitive tests are used to monitor cognitive changes post-diagnosis and to determine treatment effectiveness, but they currently cannot diagnose early AD in people who do not show any symptoms.[6] Amyloid-beta and tau protein biomarkers and imaging are

more frequently used in research settings for determining people with "preclinical" AD (i.e., individuals who test positively for the proteins but who do not display any symptoms).

Diagnosis of Neurodegeneration

MRI

One of the common imaging techniques for diagnosing AD is structural MRI. Because AD follows a typical pattern of brain damage, early diagnosis with MRI focuses on brain tissue atrophy (shrinking) in the hippocampus (a part of the brain associated with memory).[13] Other regions that can be looked at because of their association with early AD are the entorhinal cortex and the amygdala.[13] Another option for MRI is to examine the cortical thickness of brain regions, usually in the temporal, orbitofrontal, and the parietal regions of the brain.

Imaging of the hippocampus is considered the best-established biomarker of AD in diagnosis in the stages of MCI. However, reduced volume of the hippocampus is also associated with other brain disorders, such as Parkinson disease, Huntington disease, and epilepsy. Sometimes, in unusual forms of AD, damage to the hippocampus does not occur in the early stages of the disease.[13]

Established Biomarkers for Neurodegeneration and Alzheimer Pathology

Imaging and Biomarkers

There are 4 main diagnostic biomarker types that research for AD focuses on: PET imaging, blood biomarkers, CSF biomarkers, and MRI. Currently, amyloid-beta PET imaging is the most commonly used biomarker in many parts of the world.[14] According to clinical expert input, in Ontario, CSF biomarkers are more commonly used than PET imaging. There are no current guidelines or recommendations that focus on using biomarkers for the diagnosis of AD before symptom onset in current routine practice.[10,15] Diagnosis is focused on standardized criteria for people who have started to develop symptoms of the disease rather than testing of asymptomatic individuals.[10] However, there are some new diagnostic methods that have been offered in other countries, such as the blood-based test PrecivityAD in the US.[16]

PET Imaging

A PET scan is performed using radioactive tracer that is injected into the person; within the body, it attaches itself to specific molecules of interest present in the brain (such as amyloid). The radiation is picked up by the scanner, indicating to clinicians that the molecule of interest is present in the brain.[17]

One type of PET scanning is an amyloid PET scan. Before the development of amyloid-specific PET imaging, plaques could only be seen after death of the person during an autopsy of the brain.[18] The amyloid PET scan allows visualization of the plaques in the brain while the patient is still alive — they light up on the scan of the brain. A second type of PET imaging is tau PET scans, which are used to locate accumulation of tau proteins in the brain, similar to the amyloid imaging.

Fluorodeoxyglucose (FDG)-PET scans are also used for AD diagnosis. FDG-PET scans measure the amount of glucose in the brain, which can indicate the extent of nerve damage (i.e., synaptic damage).[19] Changes in FDG-PET scans occur before detectable changes on MRI, which allows for earlier diagnosis;[13] however, changes in glucose that would be detectable on the PET scan may happen after nerve damage has already occurred and is too severe to treat.[13]

Results from early drug trials for AD may have been limited because people without amyloid clumping may have been included. PET imaging would allow researchers to confirm that every individual included in a trial has these plaques, which may allow for more precise patient selection for the trials and ultimately for these drugs.[17]

Amyloid and tau PET imaging for earlier AD diagnosis is currently not widely available in Canada; their use is mostly limited to research. Table 1 is a list of Health Canada– and/or FDA-approved PET imaging radiotracers. These radiotracers are emerging for use in the US and Canada, but many that are approved for use in the US are not currently approved in Canada.

At the 5th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, it was recommended that because the significance of the presence of amyloid and tau proteins in people without cognitive decline is unclear, amyloid and tau imaging should not be used outside of the research setting.[10] For people with cognitive impairment, the recommendation was that amyloid and tau PET imaging only be ordered by dementia experts.[10] It was also recommended that asymptomatic people should not be routinely screened for MCI or dementia (including people with relevant risk factors), either with clinical or cognitive testing or with imaging.[10]

In Canada, there are 57 PET-CT scanners available for use, which are mostly used for oncology (80% of use). Distribution of these scanners is also heavily focused in urban centres; Prince Edward Island and the territories of Canada do not have PET-CT scanners. New Brunswick does not fund amyloid-specific PET imaging for AD.[20]

CSF Testing

CSF may be more useful than other biomarkers such as those found via blood tests because of its connection to the brain and relative separation from the rest of the body. Similar to PET imaging, CSF biomarkers include amyloid-beta deposition (42 amino acid–long amyloid-beta peptide [amyloid-beta1–42]), tau tangle formation (tau protein phosphorylated at threonine

Table 1: List of Health Canada– and/or FDA-Approved PET Imaging Radiotracers for Alzheimer Disease

Generic name	Trademark name	Health Canada authorization	FDA approval
Amyloid imaging			
Florbetaben F18 injection	Neuraceq (Piramal Imaging SA and Isologic Innovative Radiopharmaceuticals)	Yes (NOC 2017)[21]	Yes (2014)[22]
Florbetapir F18 injection	Amyvid (Avid Radiopharmaceuticals)	No	Yes (2012)[23]
Flutemetamol F18 injection	Vizamyl (GE Healthcare)	No	Yes (2013)[24]
NFT imaging			
Flortaucipir F18 (AV1451)	Tauvid (Avid Radiopharmaceuticals)	No	Yes (2020)[25]
Metabolism imaging			
FDG F18	None	Yes	Yes[26]

FDG = fluorodeoxyglucose; NFT = neurofibrillary tangles; NOC = Notice of Compliance.

181 [P-tau181]), and loss of neuronal function (T-tau). In the CSF, amyloid-beta1–42 decreases throughout the course of the disease, and T-tau and P-tau181 increase. If all these biomarkers are within the normal reference range, it can help rule out AD.[27]

CSF testing for AD-related biomarkers is promising because of its high sensitivity and specificity compared with healthy controls or to autopsied people.[27] However, except for early-onset dementia, CSF testing is not mandatory for all people with dementia although it can be provided to those who wish to undergo testing. CSF biomarker testing is useful if other testing cannot determine the type of dementia. It can also be useful for identifying AD in people with unusual or atypical presentations of the disease.[27]

CSF testing is not routinely recommended for people who do not have symptoms of cognitive decline because a small percentage of people 85 years and older who are cognitively healthy can have similar testing results as people with AD. The earliest use of CSF biomarkers may be in the prodromal stage of AD, when a person has developed the first symptoms of MCI but has not proceeded to more severe disease.[27]

The first testing program for CSF biomarkers in Canada has been launched as part of a study at the University of British Columbia. The study (IMPACT-AD) is currently running, and the testing is available if requested by a clinician that specializes in dementia.[28,29]

Other research-based tests available in other countries include Elecsys β-Amyloid(1-42) CSF (Roche) and Neurology 3-Plex A assay (Quanterix, Massachusetts, US).[30]

Experimental Biomarkers for Neurodegeneration

Other biomarkers at the early research stage include blood-based biomarkers, salivary biomarkers, olfactory biomarkers, and ocular biomarkers.

Amyloid-Based Blood Biomarkers

PrecivityAD is a blood biomarker test advertised and offered in the US (except New York) by C2N Diagnostics (Missouri, US). This test is not covered by US private insurance, Medicare, or Medicaid, although interested individuals can pay for it out of pocket.[31] It currently costs US$1,250, and the company offers a financial assistance program for those who are eligible. The test looks for the apolipoprotein E (*APOE*) genotype (individuals at higher risk for AD), and amyloid-beta- 42/40 ratios to determine the probability of AD.[31] According to a C2N Diagnostics study, when compared with amyloid PET imaging, the PrecivityAD test had a sensitivity of 93% and specificity of 77% under certain cut-off conditions.[31]

Another test that has recently received FDA breakthrough designation is the Soba-AD platform by AltPep Inc. It is designed to detect the toxic forms of the amyloid-beta peptide in earlier stages of AD.[32] AlzoSure Predict by Diadem,[33] a prognostic blood assay intended to be used to predict the onset of AD, is another test that has received FDA breakthrough designation as well as the European Conformity In Vitro Diagnostic Medical Devices certification.[34].

Other amyloid tests in the research phase include Amyblood (ADx Neurosciences, Ghent, Belgium) and Simoa Aβ40 Advantage Kit (Quanterix, Massachusetts, US).[30]

As of the writing of this report, these tests are not available in Canada. In Canada, blood tests are performed to rule out other causes of memory loss or symptoms, such as anemia,

diabetes, thyroid problems, or infection,[35] but are not used to identify amyloid or other biomarkers for clinical diagnoses of AD.

Other Emerging Technologies

Imaging and Biomarkers

Blood Biomarkers

Blood and plasma biomarker tests have been explored as an alternative to the more invasive CSF biomarker tests. Blood tests may also allow for potential tracking of disease biomarkers because repeated collection is relatively easy compared with other methods of biomarker collection.[36] Potential biomarkers include upstream and early biomarkers such as:

- plasma amyloid-beta species (e.g., amyloid-beta peptides, ratio of amyloid-beta peptides, amyloid-beta oligomers)
- plasma tau forms (e.g., total tau proteins, phosphorylated tau protein).

And downstream biomarkers, such as:

- neurodegeneration biomarkers (e.g., plasma neurofilament light, plasma synaptic proteins)
- neuroinflammation biomarkers (e.g., cytokines, chemokines)
- exosome biomarkers (e.g., microRNAs in exosomes, insulin resistance–related biomarkers in exosomes, lysosomal proteins in exosomes, other molecules in exosomes)
- genomic and molecular analysis biomarkers (e.g., sphingolipids, acylcarnitine, and glycerophospholipids of lipids)
- metal-based biomarkers (e.g., copper and ceruloplasmin, iron and ferritin, aluminum, manganese, and zinc).

Other options include genetic biomarkers (e.g., familial genes such as the *APP* gene, *PSEN1* gene, and *PSEN2* gene) or combinations of these.

Genetic testing for AD is used to determine the potential risk of developing AD, but it is not a biomarker for diagnosis. The genes that influence risk of development of AD are called "susceptibility genes," and include *APOE4*, and the other familial genes noted previously.[37]

Blood-based biomarkers have not been as consistent as CSF biomarkers for the early diagnosis of AD.[36] These biomarkers are also not always specific for AD, and will likely need to be revised to be sensitive and specific to AD. Some challenges with blood biomarkers are the lack of diverse data from different countries, lower concentrations of biomarkers in the blood compared with CSF, and the complex nature of blood (i.e., other components of blood may change biomarker levels in different people and comorbid conditions may influence biomarker levels).[36]

Currently, blood-based biomarker research focuses heavily on amyloid and tau proteins; other biomarkers are in very early research stages.[36]

Lipid Biomarkers

APOE4, which codes for a carrier for cholesterol transport, is a gene that has been linked to the development of AD. Cholesterol is linked to amyloid creation, therefore levels of cholesterol are of interest to AD researchers.[38] Plasma lipids, such as cholesterol, are a

proposed blood-based biomarker for AD; there may be an association between different levels of these molecules and AD.[38,39] These proposed markers are:

- high-density lipoprotein
- low-density lipoprotein
- total serum cholesterol
- total cholesterol:high-density lipoprotein ratio
- triglycerides
- 24S-hydroxycholesterol
- lipoprotein A
- phospholipids
- sphingolipids.

Studies examining these biomarkers are mostly association studies and are in very early stages of development.[35]

Salivary Biomarkers

Saliva shares 40% of the diagnostic protein biomarkers with blood but gathering saliva samples is less invasive and often cheaper.[40] Relevant biomarkers include salivary acetylcholinesterase, salivary amylase-beta42, salivary tau, salivary trehalose and lactoferrin, salivary metabolites, and the salivary microbiome (i.e., bacteria and microbes in the mouth). A review by Bouftas (2021)[40] found mixed results for the accuracy of these biomarkers. Salivary amylase-beta42 was the most reliable biomarker, but this research area is still relatively new. More research is required to confirm the usefulness of salivary biomarkers for AD.[40,41]

Olfactory Biomarkers

Issues with a person's sense of smell are common with neurologic conditions, including AD.[42] There is some research ongoing that is exploring changes in sense of smell as an early indicator of AD. Olfactory tests, such as odour identification tests, odour discrimination tests, and odour sensitivity tests, can determine whether a person with AD has issues with their sense of smell and can be differentiated from control groups. However, using olfactory tests is challenging because these tests are currently unable to differentiate between different kinds of neurodegenerative diseases, therefore additional tests are required. More research is required to increase the specificity and sensitivity of olfactory tests for AD.[42]

Retinal and Ocular Changes

The eye is an extension of the central nervous system (a "window to the brain") which is another focus for diagnosis of AD. Eye diseases and AD also share many risk factors.[15] Deposition of amyloid on the retina of the eye is of particular interest to researchers looking into the early identification of AD. Using optical coherence tomography (a noninvasive test that takes photographic cross-sections of the retina), a clinician can look at the layers of cells in the retina and compare the thickness of the cell layer with control groups.[15,43] Individuals with AD often have thinner retinal nerve fibre layers.[15,43] In a large multi-centre study of the retina and cognition, people with retinal nerve fibre layers in the lower 40% of the sample were twice as likely to perform poorly on a cognitive test.[15] Researchers are also using optical coherence tomography angiography to look at the density of blood vessels in the retina as an indicator of AD.[15]

One of the challenges with retinal changes for the identification of AD is creating a consistent test for detection of the disease. Retinal thinning also occurs in other eye diseases, such as glaucoma and diabetic retinopathy, and distinct changes related to AD have not been identified or confirmed.[15]

In Canada, Optina Diagnostics (Montreal) is developing a retinal test — awAIr cerebral amyloid status test — that uses a hyperspectral camera (Optina-4C) and artificial intelligence (AI) to assess cognitive function. The camera takes multiple photos of the eyes at different wavelengths and the AI algorithm then analyzes the data. These eye data are used to assess cognitive function through the presence of amyloid in the eye. The test has been granted FDA breakthrough device designation and is currently available for research but not commercial use.[44] RetiSpec (Toronto) is also developing an ocular test using hyperspectral imaging and AI. This test is also in early stages of research and not commercially available.[45]

Novel Biomarkers

Some newer biomarkers for the detection of AD include:

- synaptic vesicle glycoprotein 2A[13]
- receptor for advanced glycation end products[13]
- iron.[13]

These biomarkers are in very early stages of development. They are currently being researched by various groups exploring new biomarkers for AD through primarily association studies.

Artificial Intelligence

Recently, there has been increased interest in using AI for diagnosis of AD. AI can be used to test multiple biomarkers at once rather than 1 at a time. AI requires a lot of data to create accurate algorithms for diagnosis. With open-source neurological datasets such as the Alzheimer's Disease Neuroimaging Initiative,[46] a large amount of data can be collected and used for AI algorithms to make them more accurate.[7] Additionally, for data that are collected over time, such as longitudinal cognitive data, AI offers a way to analyze this large amount of data.[7] Imaging data (e.g., resting stage functional MRI,18F-FDG-PET, and AV45-PET) with imaging modalities (e.g., structural MRI, functional MRI, T1 weighted image MRI) used in the AI algorithms can be combined with cognitive testing results and genetic data to increase classification accuracy.[47]

Other data proposed to be used by AI to identify AD include home-based motion sensors, handwriting analyses, handwashing tasks, wearable activity monitors, and speech data.[7] These AI algorithms are not proposed to replace clinician-based diagnoses but to support clinicians in the early and timely diagnosis of AD.[7]

Operational Issues

Ethical Considerations

As with other types of screening, there is concern about the ethical and unintended consequences of higher screening volumes for people in preclinical stages of AD.[48] For

example, if AI-based diagnostic algorithms are used, there may be a higher likelihood of false positives (creating unnecessary worry in people), anxiety over the diagnosis because treatments are not available yet, potential for insurance denial due to diagnosis, and increased psychosocial issues (e.g., stigma, increases in "rational suicide").[48] It is not currently recommended to provide screening or testing to people who show no symptoms of AD.[10]

There are also differences in what the appropriate timing for diagnosis is for an individual compared with the appropriate timing for "society." For an affected person, the appropriate timing is likely individualized (such as being in the MCI phase), whereas the appropriate timing for society might be much earlier so that preventive measures can be taken. An ethical dilemma is deciding which timing to prioritize.[27] Testing and disclosing genetic abnormalities that raise a person's risk of AD may not be effective because genetic risk is a difficult concept to understand for many people.[49] Numerical-based risk assessment can be difficult for both doctors and their patients for many health conditions — referred to as *collective statistical illiteracy* — and may affect how individuals receive risk profiles related to AD.[50] However, people have a right to know and a right to autonomous decision-making regarding their health.[48]

Additionally, the current approach to AD diagnosis assumes that we know enough about AD to make decisions regarding diagnosis. AD is likely more heterogenous in presentation than initially thought, so it may not be ethical to lump all AD diagnoses into 1 type of disease with 1 method of diagnosis.[49] There is also an ethical dilemma when considering the treatments that are available for AD. Currently, there is not an effective way to prevent AD progression or to reverse damage, so it is important for those undergoing testing to provide informed consent and have the autonomy to choose to be tested or not.[48,51,52] Many people fear the stigmatizing language and negative association with "dementia," and practitioners have mentioned the potential for people to feel devastated by an official diagnosis. An earlier diagnosis may lead to more years of worry.[52] Some individuals may not want to know their diagnosis until later. However, early diagnosis does not always prompt negative emotions in people and may provide relief.[53]

There have also been criticisms of the use of amyloid testing for the general population because the burden of proof has not been reached that these tests are valid and useful. In addition, amyloid-based treatments are also fraught with controversy regarding the proof of their effectiveness.[49] Therefore, it is debated whether amyloid-based biomarker testing should be required testing if there are no effective disease-modifying treatments available yet.

Population Considerations

Black and Latino people are less likely to be diagnosed with AD, despite a potentially higher risk of developing it.[54] Additionally, Black and Latino people are less likely to participate in clinical studies; therefore, there are less available data on these individuals.[55] Many of the standards of diagnosis are based on older, White adults. For example, cognitive testing thresholds were based on this standard; however, cognitive tests have been found to have different performance characteristics when administered to different populations.[55] There are also differences in diagnosis related to sex and gender, the extent of which is not fully known.[56,57] The lack of robust data makes it difficult to know if new technologies for diagnosis are generalizable for multiple groups of people or if there were biases in the evidence that would lead to a less effective diagnosis for certain groups. If new biomarker technologies used for early diagnosis become the new standard practice but these technologies are not

well studied in different groups of people, it is unclear if this lack of data will affect effective treatment or diagnosis in these other groups.

Final Remarks

There are many new technologies in the research and development phase for early diagnosis of AD that focus on the prevailing amyloid and tau hypothesis. These include blood tests, imaging tests, saliva tests, ocular tests, and integrating AI algorithms into testing. One sole definitive test that can diagnose AD at an early stage is not available; instead, testing is done in different combinations, and all testing begins after a person starts to show symptoms of the disease. Currently, there is only 1 blood-based test available on the market (in the US). Other tests are in research phases, but it is unclear if these tests will be effective, when these tests will be available for the public, or when these tests will be available in Canada. Criticisms of these new tests include an unknown level of accuracy for all population groups, an assumption that the pathology of AD is known, an assumption that AD is a homogenous disease, and the potential for unnecessary anxiety and stigma for people with AD when effective disease-modifying treatments are not available yet. Gaps in the research knowledge for diverse populations also limits the generalizability of new technologies for diagnosis. However, if proven effective, these newer tests have the potential to help diagnose AD in early stages before irreversible damage occurs and be less invasive, quicker, and expose people to less radiation. This can allow people time to plan for care and support needs and make changes in their life if desired and allow for early intervention if effective disease-modifying treatments become available. It is hopeful that more research and larger clinical trials will show benefit of these newly proposed diagnostic tools.

References

1. Dementia In Canada, Including Alzheimer's Disease Highlights From The Canadian Chronic Disease Surveillance System. Ottawa (ON): Public Health Agency of Canada; 2017: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/dementia-highlights-canadian-chronic-disease-surveillance/dementia-highlights-canadian-chronic-disease-surveillance.pdf. Accessed 2022 May 2.
2. Alzheimer's Disease Fact Sheet. Bethesda (MD): National Institute on Aging; 2021: https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet. Accessed 2022 May 2.
3. Inside the Brain: A tour of how the mind works. *Part 2: Alzheimer's Effect*. Chicago (IL): Alzheimer's Association; 2022: https://www.alz.org/alzheimers-dementia/what-is-alzheimers/brain_tour_part_2. Accessed 2022 Feb 10.
4. Liss JL, Seleri Assuncao S, Cummings J, et al. Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: a review and synthesis. *J Intern Med.* 2021;290(2):310-334. PubMed
5. 2018-2019 Impact Report. Toronto (ON): Alzheimer Society of Canada; 2018: https://impactreport.alzheimer.ca/2019/?_ga=2.162922044.1278814557.1644362443-956981805.1644362443. Accessed 2022 May 2.
6. Di Meco A, Vassar R. Early detection and personalized medicine: Future strategies against Alzheimer's disease. *Prog Mol Biol Transl Sci.* 2021;177:157-173. PubMed
7. Graham SA, Lee EE, Jeste DV, et al. Artificial intelligence approaches to predicting and detecting cognitive decline in older adults: A conceptual review. *Psychiatry Res.* 2020;284:112732-112732. PubMed
8. Watt J MR, Hemmelgarn B, Straus SE, Should Canadian patients look forward to aducanumab for Alzheimer disease? *CMAJ.* 2021;193(36):E1430-E1431. PubMed
9. Understanding Aducanumab: An Information Guide for Patients. Chicago (IL): Alzheimer's Association; 2022: https://www.alz.org/media/Documents/aducanumab-patient-treatment-information-guide.pdf. Accessed 2022 May 2.
10. Ismail Z, Black SE, Camicioli R, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. *Alzheimer's dement.* 2020;16(8):1182-1195. PubMed
11. MOCA Cognitive Assessment. 2022; https://www.mocatest.org/. Accessed 2022 Apr 14.
12. Davis DH, Creavin ST, Yip JL, Noel-Storr AH, Brayne C, Cullum S. Montreal Cognitive Assessment for the diagnosis of Alzheimer's disease and other dementias. *Cochrane Database Syst Rev.* 2015;2015(10):Cd010775. PubMed
13. van Oostveen WM, de Lange ECM. Imaging Techniques in Alzheimer's Disease: A Review of Applications in Early Diagnosis and Longitudinal Monitoring. *Int.* 2021;22(4):20. PubMed
14. Tromp K, Smedinga M, Richard E, Perry M, Schermer MHN. Views on Early Diagnosis of Alzheimer's Disease Among Dutch Physicians: A Qualitative Interview Study. *J Alzheimers Dis.* 2021;79(2):917-927. PubMed
15. Fereshetian S, Agranat JS, Siegel N, Ness S, Stein TD, Subramanian ML. Protein and Imaging Biomarkers in the Eye for Early Detection of Alzheimer's Disease. *JAD Rep.* 2021;5(1):375-387. PubMed
16. C2N Diagnostics Statement on FDA Accelerated Approval of Aducanumab for Alzheimer's Treatment. St. Louis (MO): C2N Diagnostics; 2021: https://precivityad.com/news/cn-diagnostics-statement-on-fda-accelerated-approval-of-aducanumab-foralzheimers-treatment. Accessed 2022 Feb 21.
17. What can PET scans tell us about dementia? London (UK): Alzheimer's Society; 2022: https://www.alzheimers.org.uk/blog/pet-scan-dementia-explained. Accessed 2022 May 2.
18. Amyloid PET Scan for Alzheimer's Disease Assessment. San Francisco (CA): University of California San Francisco; 2021: https://radiology.ucsf.edu/patient-care/services/specialty-imaging/alzheimer#:~:text=Amyloid%20PET%20imaging%20represents%20a,killing%20nerve%20cells%20in%20Alzheimer's. Accessed 2022 May 2.
19. Boccardi M, Festari C, Altomare D, et al. Assessing FDG-PET diagnostic accuracy studies to develop recommendations for clinical use in dementia. *Eur J Nucl Med Mol Imaging.* 2018;45(9):1470-1486. PubMed
20. Canadian Medical Imaging Inventory Service Report The Role of Neuroimaging in Drugs Targeting Amyloid-Beta in Alzheimer Disease: Part 1. Ottawa (ON): CADTH; 2021: https://www.cadth.ca/sites/default/files/attachments/2021-11/role_neuroimaging_in_drugs_targeting_amyloid-beta_in_alzheimer_disease.pdf. Accessed 2022 May 2.
21. Isologic. First diagnostic radiotracer for early diagnosis of Alzheimer's disease approved in Canada. *Newswire.* 2017. https://www.newswire.ca/news-releases/first-diagnostic-radiotracer-for-early-diagnosis-of-alzheimers-disease-approved-in-canada-614982573.html. Accessed 2022 May 2.
22. NEURACEQ (florbetaben F 18 injection), for intravenous use SIlver Spring (MD): U.S. Food and Drug Administration; 2014: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204677s000lbl.pdf. Accessed 2022 May 2.
23. Yang L RD, Ganley C, Brain Amyloid Imaging — FDA Approval of Florbetapir F18 Injection. *N Engl J Med.* 2012;367:885-887. PubMed
24. Vizamyl: Flutemetamol F 18 Injection. Silver Spring (MD): U.S. Food and Drug Administration; 2013: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203137s008lbl.pdf. Accessed 2022 May 2.

25. Lilly Receives U.S. FDA Approval of TAUVID™ (flortaucipir F 18 injection) for Use in Patients Being Evaluated for Alzheimer's Disease. Indianapolis (IN): Eli Lilly and Company; 2020: https://www.prnewswire.com/news-releases/lilly-receives-us-fda-approval-of-tauvid-flortaucipir-f-18-injection-for-use-in-patients-being-evaluated-for-alzheimers-disease-301067441.html. Accessed 2022 May 2.
26. Positron Emission Tomography Drug Products; Safety and Effectiveness of Certain PET Drugs for Specific Indications. Silver Spring (MD): U.S. Food and Drug Administration, HHS.; 2000: https://www.federalregister.gov/documents/2000/03/10/00-5865/positron-emission-tomography-drug-products-safety-and-effectiveness-of-certain-pet-drugs-for. Accessed 2022 May 2.
27. Niemantsverdriet E, Valckx S, Bjerke M, Engelborghs S. Alzheimer's disease CSF biomarkers: clinical indications and rational use. *Acta Neurol Belg.* 2017;117(3):591-602. PubMed
28. IMPACT-AD. 2018; https://www.impactad.org/. Accessed May 2, 2022.
29. University of British Columbia. NCT05002699: Investigating the Impact of Alzheimer's Disease Diagnostics in British Columbia (IMPACT-AD BC). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2021: https://clinicaltrials.gov/ct2/show/NCT05002699. Accessed 2022 May 2.
30. E C. Aduhelm approval amplifies amyloid assays. 2021; https://www.evaluate.com/vantage/articles/news/policy-and-regulation/aduhelm-approval-amplifies-amyloid-assays. Accessed May 2, 2022.
31. The PrecivityAD™ Test: Advanced Diagnostics in Alzheimer's Disease. 2020; https://precivityad.com/. Accessed Feb 22, 2022.
32. AltPep's SOBA-AD test for Alzheimer's disease secures FDA breakthrough status. 2022; https://www.nsmedicaldevices.com/news/company-news/fda-grants-breakthrough-status-for-altpeps-soba-ad-test-for-alzheimers-disease/. Accessed Mar 10 2022.
33. Diadem gets FDA breakthrough status for blood test to detect Alzheimer's. 2022; https://www.nsmedicaldevices.com/news/diadem-gets-us-fda-breakthrough-device-designation-for-blood-test-that-predicts-ad/. Accessed Mar 10, 2022.
34. Diadem Receives CE-IVD Certification to Market Its AlzoSure® Predict Prognostic Blood Test for the Early Prediction of Alzheimer's Disease in Europe. 2022; https://www.biospace.com/article/releases/diadem-receives-ce-ivd-certification-to-market-its-alzosure-predict-prognostic-blood-test-for-the-early-prediction-of-alzheimer-s-disease-in-europe/#:~:text=AlzoSure%C2%AE%20Predict%20is%20a,before%20definitive%20symptoms%20are%20apparent. Accessed Mar 10, 2022.
35. Getting A Diagnosis Toolkit. Toronto (ON): Alzheimer Society; 2018: https://alzheimer.ca/sites/default/files/documents/getting-a-diagnosis-toolkit.pdf. Accessed 2022 May 2.
36. Feng L, Li J, Zhang R. Current research status of blood biomarkers in Alzheimer's disease: Diagnosis and prognosis. *Ageing Res Rev.* 2021;72:101492. PubMed
37. The Genetics of Alzheimer's Disease. Toronto (ON): Alzheimer Society; 2022: https://alzheimer.ca/en/about-dementia/what-alzheimers-disease/genetic-testing-alzheimers-disease. Accessed 2022 Apr 14.
38. Agarwal M, Khan S. Plasma Lipids as Biomarkers for Alzheimer's Disease: A Systematic Review. *Cureus.* 2020;12(12):e12008. PubMed
39. Chew H, Solomon VA, Fonteh AN. Involvement of Lipids in Alzheimer's Disease Pathology and Potential Therapies. *Front Physiol.* 2020;11. PubMed
40. Bouftas M. A Systematic Review on the Feasibility of Salivary Biomarkers for Alzheimer's Disease. *Jpad.* 2021;8(1):84-91. PubMed
41. Gleerup HS, Hasselbalch SG, Simonsen AH. Biomarkers for Alzheimer's Disease in Saliva: A Systematic Review. *Dis Markers.* 2019;2019:4761054. PubMed
42. Dan X, Wechter N, Gray S, Mohanty JG, Croteau DL, Bohr VA. Olfactory dysfunction in aging and neurodegenerative diseases. *Ageing Res Rev.* 2021;70:101416. PubMed
43. Chalkias E, Topouzis F, Tegos T, Tsolaki M. The Contribution of Ocular Biomarkers in the Differential Diagnosis of Alzheimer's Disease versus Other Types of Dementia and Future Prospects. *J Alzheimers Dis.* 2021;80(2):493-504. PubMed
44. Optina Diagnostics: What We Do. 2022; https://optinadx.com/what-we-do. Accessed May 2, 2022.
45. RetiSpec. 2021; https://www.retispec.com/technology. Accessed May 2, 2022.
46. Alzheimer's Disease Neuroimaging Initiative (ADNI): ABOUT ADNI. 2017; https://adni.loni.usc.edu/about/. Accessed May 2, 2022.
47. Agarwal D, Marques G, de la Torre-Diez I, Franco Martin MA, Garcia Zapirain B, Martin Rodriguez F. Transfer Learning for Alzheimer's Disease through Neuroimaging Biomarkers: A Systematic Review. *Sensors (Basel).* 2021;21(21):31. PubMed
48. Ursin F, Timmermann C, Steger F. Ethical Implications of Alzheimer's Disease Prediction in Asymptomatic Individuals through Artificial Intelligence. *Diagnostics (Basel).* 2021;11(3):04.
49. Whitehouse PJ. Ethical issues in early diagnosis and prevention of Alzheimer disease. *Dialogues Clin Neurosci.* 2019;21(1):101-108. PubMed
50. Ahmed H, Naik G, Willoughby H, Edwards AGK. Communicating risk. *BMJ: British Medical Journal.* 2012;344:e3996. PubMed
51. ME G. Ethical Issues in the Early Diagnosis of Alzheimer Disease. *Virtual Mentor.* 2011;13(12):868-872. PubMed
52. Swallow J. Expectant futures and an early diagnosis of Alzheimer's disease: Knowing and its consequences. *Soc Sci Med.* 2017;184:57-64. PubMed
53. Carpenter BD, Xiong C, Porensky EK, et al. Reaction to a Dementia Diagnosis in Individuals with Alzheimer's Disease and Mild Cognitive Impairment. *J Am Geriatr Soc.* 2008;56(3):405-412. PubMed

54. Race, Ethnicity, and Alzheimer's. Chicago (IL): Alzheimer's Association; 2020: https://www.alz.org/aaic/downloads2020/2020_Race_and_Ethnicity_Fact_Sheet.pdf. Accessed 2022 May 2.

55. Barnes LL. Alzheimer disease in African American individuals: increased incidence or not enough data? *Nature Reviews Neurology.* 2022;18(1):56-62. PubMed

56. Mielke MM. Sex and Gender Differences in Alzheimer's Disease Dementia. *Psychiatr Times.* 2018;35(11):14-17. PubMed

57. Mielke MM, Aggarwal NT, Vila-Castelar C, et al. Consideration of sex and gender in Alzheimer's disease and related disorders from a global perspective. *Alzheimer's dement.* 2022. PubMed