Screening for mild cognitive impairment: If not now, when?

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Health care professionals, patients and families often identify Alzheimer disease by short-term memory impairment, which is its most recognizable clinical feature. Research involving genetically at-risk individuals has shown that the pathobiological process of Alzheimer disease begins in the brain decades before the onset of overt clinical symptoms.[1] In this light, it seems only logical to suggest that strategies to combat dementia should be focused on preclinical detection to prevent progression of neurodegeneration. However, the Canadian Task Force on Preventive Health Care, in developing its new guideline on screening for cognitive impairment, found that we are still lacking the reliable tools both to identify and then to intervene at the preclinical stage of dementia.[2] Hence, population-based screening for cognitive impairment in people 65 years of age and older is currently not justifiable. The guideline serves as an important indicator that advancements in the area of Alzheimer disease research are lagging, even in the face of the rapidly increasing prevalence of dementia that is leading to an escalating public health crisis in Canada and worldwide.

The number of Canadians living with dementia is expected to more than double from 2008 to 2038, with a total economic burden of more than $872 billion to Canadian society.[3] Unlike the other leading causes of death in Canada, such as cancer and heart disease, there are currently no population-level screening or prevention strategies for Alzheimer disease, despite many international calls to action. Here, we set out what might be required to justify screening for cognitive impairment in asymptomatic individuals.

First, for screening efforts to be justified, a suitable population must be identified. Even though screening older adults for cognitive impairment may not yet be appropriate, one asymptomatic group that may benefit is first-degree relatives of patients with dementia. This group is well known to be at increased risk of cognitive decline, especially if there is an identified autosomal dominant genetic mutation that confers a 50% chance of inheriting a mutation causing presenile onset.[4] Even in sporadic Alzheimer disease, having one first-degree relative with dementia increases the lifetime risk for the disease as much as 2.5-fold.[5] Moreover, relatives of patients with dementia may be more inclined than the general population to undergo screening, with as many as 50% showing willingness.[2] If screening strategies prove fruitful in a smaller subset of the population, it might serve as an important stepping stone for larger-scale screening programs.

Second, once an appropriate screening sample is identified, the next step is to hone in on more sensitive screening tools for an asymptomatic cohort. Many concerned Canadians have already taken cognitive screening into their own hands, using new self-administered cognitive batteries such as the Cogniciti Brain Health Assessment (www.cogniciti.com) and Cogstate tests (http://cogstate.com) to screen themselves outside of the clinical setting. Concerns raised in the task force guideline[2] over current office-based paper-and-pencil cognitive testing lie in the false-positive rates for mild cognitive impairment with the Mini-Mental Status Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Moreover, the MMSE and MoCA are tools used to assess symptoms, not biomarkers of disease activity in the asymptomatic phase.

Identifying abnormal protein accumulation in the brain used to be confined to autopsy; however, research efforts to identify abnormal pro-

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Key points

- The new Canadian Task Force on Preventive Health Care guideline recommends against population screening for cognitive impairment in adults 65 years of age and older.
- The guideline serves as an important reminder that we are lagging in our response to an imminent dementia epidemic.
- Asymptomatic first-degree relatives of patients with dementia may be an appropriate starting sample for eventual larger-scale screening programs.
- A robust, affordable biomarker needs to be identified for use as a presymptomatic population screening tool.
- Results of ongoing clinical trials in the asymptomatic stage of Alzheimer disease in at-risk people will help determine the direction of future efforts to prevent and treat the disease.

teins in vivo have been increasingly successful. A handful of biomarkers have been validated for use in current diagnostic criteria and in clinical trial settings: amyloid-β42 protein in cerebrospinal fluid (CSF), CSF total tau and phosphorylated tau protein, amyloid imaging with positron emission tomography (PET), atrophy on structural magnetic resonance imaging, hypometabolism on fluorodeoxyglucose-PET and hypoperfusion on single-photon emission computed tomography.[6] Several more exciting biomarkers are on the horizon, including tau-specific PET radioligands,[7] serum markers such as plasma phospholipids[8] and retinal amyloid imaging techniques.[9] A crucial challenge in identifying a robust, affordable biomarker for Alzheimer disease is distinguishing the presence and activity of biomarkers in the normal aging brain compared with the diseased brain. Large-scale natural history studies that observe these biomarkers in healthy individuals and those with the disease are under way.[10]

The final step is to find more effective preventive strategies and interventions for the preclinical phase. The real thrust behind the guideline recommendation against population screening is the seeming futility of screening. Even if a population is identified and a strong biomarker emerges, there is a paucity of effective preventive strategies and disease-modifying interventions for the preclinical phase. The mainstays of pharmacologic treatment of dementia with cholinesterase inhibitors and memantine have insufficient evidence for use in the preclinical or mild stages.[2] Modification of diet and exercise, along with vigorous management of other vascular risk factors, may be preventive in the early stages of both Alzheimer disease and vascular dementia, as may be treatment of comorbid sleep and mood disorders.[2] A plethora of potentially disease-modifying interventions have yielded disappointing results in clinical trials in the dementia stage, but researchers are moving quickly to study their effects in the asymptomatic stage in at-risk people (e.g., the A4 Study, http://a4study.org).

Collaborative provincial and national efforts to support neurodegenerative research are under way, including the Canadian Longitudinal Study on Aging (www.clsa-elcv.ca), the Canadian Consortium for Neurodegeneration in Aging (www.cihr-irsc.gc.ca/e/46475.html), the Ontario Neurodegenerative Disease Research Initiative (ondri.ca) and the Consortium pour l'Identification précoce de la Maladie d'Alzheimer — Québec (www.cima-q.ca), among others. Family physicians, geriatricians and other specialists play a key role in Canada's collective efforts to battle dementia by helping to identify appropriate asymptomatic or early symptomatic individuals willing to participate in critical research trials investigating biomarkers for Alzheimer disease and early interventions. If these trials yield promising results, preclinical screening for cognitive impairment will take on a new lens and purpose. For now, the recent Canadian Task Force on Preventive Health Care guideline serves as an unsettling reminder that we are far from having an effective response to an impending epidemic.

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