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Turning the tide on dementia: prevention, diagnosis, treatment and quality of care

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Thank you, Glenda, for the setting the scene on dementia. I will fan out from here and want to bring to your attention some key issues and opportunities we have in the field at the moment. It's an exciting time to be working in this field, but we do have many challenges ahead of us in terms of how to deal with the increasing number of dementia cases that are set for us.

Globally, there's about 50 million people with dementia. There's 400 to 450 thousand in Australia, but there's an extra 1 million people who have what we call mild cognitive impairment (MCI). This is what could be deemed to be a prodromal stage for dementia. If you have mild cognitive impairment, you show cognitive deficits on the awful tests that we neuropsychologists give you, and about 45% will progress to dementia within 5 years. This is an important period because this is an opportunity for us to think about prevention strategies.

Dementia now overtakes heart disease as a leading cause of disease burden in those over 65. Interestingly, a third of the dementia population live in regional and rural areas of Australia, the prevalence of dementia is three to five times higher among Indigenous Australians, and they also get dementia earlier. $3 billion of Australia's health and aged care expenditure is spent directly on dementia, and there are lots of other indirect costs.

Dementia prevention

First, I want to talk about prevention. Glenda told you about the different types of dementia pathologies, so this is the umbrella term that we use for all the different types of dementia. There are a couple in particular that I'll focus on in this talk — Alzheimer's disease and vascular dementia — these are the ones where there are some risk factors that can be modified. There are two key things to consider when thinking about dementia prevention — again, everyone in this room should be thinking about dementia prevention from midlife, actually even earlier. Certainly we know that the pathological changes that occur in the brain prior to dementia are building up 10 to 20 years before someone ever attends a memory clinic or presents to their doctor with symptoms.

There are many changes in amyloid — the sticky kind of plaque substance that builds up in the brain with Alzheimer's disease. We have changes in the synapses of the brain. We have Tau accumulating. And then we get changes in the structure of the function, and then eventually changes in cognition.

What we know about this is that about 40% of the risk for these types of dementias is due to things that are modifiable and can be mapped across the life course. There was a great paper in 2020 in *The Lancet*, com-

1 This is an edited transcript of the address [Ed.]

missioned by G. Livingston,[2] that identified all of these risk factors and that built on prior epidemiological work looking at the population-attributable risk of these risk factors. The big ones we need to consider are: depression; many different types of diseases linked to cardiovascular disease; hypertension in midlife; cholesterol in midlife; and alcohol.

Regarding alcohol, the epidemiological data suggest more than 21 drinks a week — that's a lot: many people are relieved by that in relation to dementia, but some of the imaging data suggests that perhaps it's a little bit more nuanced than this — may affect the white matter and we should really be thinking about much lower levels of alcohol than that. So the jury's out on that.

Other factors we need to consider are obesity, smoking, social connectedness and social network working in urban planning — these are all important. New factors that have emerged are air pollution which accounts for about 2% of dementia risk, as well as hearing loss. A recent trial showed that if people have cognitive impairment and hearing loss then the cognitive impairment could actually be slowed. It's important to think about all of these risks if we want to take a public health perspective for dementia.

Dementia prevention is everyone's business so we should be thinking about how to create guidelines for dementia prevention. We know a lot about heart disease and what we should do to prevent it. In dementia, the best thing we can do is say, "Follow what the Heart Foundation says because everybody knows that." But no one knows that dementia is actually a multifactorial disease and we really need to be educating the public about what we could be doing. We need to be able to implement, in a memory-clinic setting, what people could do to slow their disease and to build a better evidence base around that and to involve consumers in that: people with diverse cultural backgrounds, Aboriginal Torres Strait Islanders. We have a lot to do at the systems level to improve the services that we provide.

You may or may not have had experience of someone with dementia going to a memory clinic, but typically they're told to go away and get their affairs in order, and not much is provided to them after that. We need to improve what we're doing for health advocacy, also work closely with governments and with policy advisors generally, and have greater connections with the non-government organisations such as Dementia Australia, to get this message out.

Australian Dementia NeTwork (ADNeT)

We also have some new challenges and opportunities in the diagnosis, treatment, and care for people who have established dementia. Once you already have symptoms of cognitive decline, you might typically go to a GP or, if you're lucky, you'll get to go to a memory clinic and have a much more detailed assessment. We've realised that in order to tackle this on a national level we need to unite what we're doing across the fields of diagnosis and treatment. We're very fortunate to receive a grant by the NHMRC for $18 million to bring together many researchers working in this field across Australia, and we established a clinical quality registry, also a screening and trials

2 Livingston G et al. (2020) Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet* 396: 413–446. https://doi.org/10.1016/S0140-6736(20)30367-6

program, working closely with pharma, and also a memory clinic setting which is more health-system-service focused.

The clinical quality registry

The clinical quality registry has been running now for about 3 years and it received continued funding from the government to essentially create a register of people presenting to memory clinics with mild cognitive impairment or dementia. We have 77 sites across Australia that are participating in this, so that we can track the quality of care provision to people presenting with cognitive decline, and so we can create a loop of feedback to continuously improve services for people who are going to a memory clinic or indeed experiencing any type of diagnostic services. This is really to benchmark the clinical practice — it includes people living with dementia and also their care partners. We have a component where we get feedback about the service that they've had. Data from other initiatives internationally have shown that this drives improvements in care. Data are provided to each clinic that participates and, in turn, goes back to their service providers, to change staffing levels, change the way things are done, or change the systems, and also to measure the impact of new treatments on progression. So far we've managed to look at the waiting times across the clinics in Australia in terms of how many clinics are able to offer appointments within 90 days, which is a long time internationally: in the UK, Canada, and other parts of Europe, people get appointments within six weeks and that's considered their gold standard. We got a lot of push-back from the clinicians in Australia around this because they know it's just not feasible. Our memory clinics run like half a day to a day a week. But in Europe they run every single day of the week. I would advocate that that's the scale that we need to go to in order to reduce our waiting times, and certainly increase our capacity.

Memory clinics

We achieve a number of markers and look at the composition of who's actually attending the memory clinic. About 30% of people have mild cognitive impairment. Moreover, the cases that are seen in the memory clinics are typically more complex cases: they might have non-Alzheimer's forms of dementia or might have a much more complicated history. Many people here are used to running memory clinics and so are very familiar with these kinds of presentations, but it's certainly expected that the bulk of dementia presentations will still occur in primary care.

The memory clinics initiative works closely with the clinical quality registry team. And I guess the role that we have is to work closely with government to try to increase services for people attending memory clinics.

To date we've had no national guidelines of how memory clinics should run. We've had many consultations, stakeholder meetings with clinicians, service providers, policy makers on how a memory clinic should run: what should the waiting times be, what should be provided — you'd be surprised to know that no follow-up was mandated or provided for a person diagnosed with dementia — so now we have guidelines for that. Moreover, looking into how we can actually improve post-diagnostic care, we've looked at what kind of care is provided when someone attends the memory clinic; despite spending hours with a neuropsychologist doing assessments, no

interventions were ever provided. So there has been some work — over a decade ago at the Brain and Mind Centre, we looked at cognitive interventions, and asked do they actually help older people who are experiencing cognitive decline? There's now a massive evidence base. Meta-analyses around the world show that you get about a 0.4 effect size improvement in memory with a cognitive intervention, yet people in memory clinics cannot access these. We have a massive evidence-to-practice gap in these areas. For the first time we've mapped all the memory clinic services across Australia. These are available on the Australia Dementia network (ADNeT) website so that GPs, and people experiencing cognitive decline, know where to go if there are any out-of-pocket costs, and also what kinds of services they can expect, and what kind of languages services are available.

Interestingly, for our field we've had some advances in diagnostics, so the typical way to get a definitive, gold-standard diagnosis for Alzheimer's disease is to have not only all of these clinical assessments but also a PET scan looking at the amount of myeloid that you have in your brain. As Glenda said, you'll have it but there certainly needs to be a threshold that you would reach that would give you a diagnosis of Alzheimer's disease. A clinical diagnosis would be the clinical symptoms plus evidence of the disease on PET scans. These have been largely inaccessible — in Melbourne, for example, you can get PET scans, but you can't get them in Sydney, and there is one centre that will do them clinically. It costs about $1,500 so it's certainly out of reach of many older Australians.

Advances in diagnostics: Blood-based biomarkers

There have been advances in detecting Alzheimer's disease by looking at blood samples. Glenda told you about Tau, a very important protein associated with transport in the microtubules. In Alzheimer's disease the Tau is hypophosphorylated, and it's aggregated and mislocalised, and you can find fragments of Tau in the blood. Even though we're looking for Alzheimer's disease, and the earlier signs of that are amyloid, it actually correlates very well with the amount of amyloid that you'll see on a PET scan. These levels are quite specific for Alzheimer's disease but we can use these levels to determine if someone does indeed have Alzheimer's disease, and therefore have greater diagnostic accuracy. This is important because there are new treatments that are coming along that target amyloid specifically. It's really important that we get the diagnosis right. Typically about 40 to 60% of clinical diagnosis in memory clinics can be wrong because we don't really know the underlying pathology. As Glenda said, often cerebrovascular pathology underlines someone's dementia — it's not necessarily always Alzheimer's disease. At the Brain and Mind Centre we're leading a trial where we'll be looking at implementing these blood-based biomarkers into the memory clinic. We want to have a look at what the impact is on clinicians' diagnoses and management of the disease. That's important for trying to advocate for reimbursement of these kinds of tests for Medicare etc., and to be able to roll them out across Australia and importantly into regions where they don't have good services.

New horizons for MCI and AD: Monoclonal antibodies

The other big development in the field is that we now have drugs for Alzheimer's disease. The results of the trial with Lecanemab were released last year at a conference in San Francisco. It was a very exciting time for the field because for the first time one of these anti-amyloid drugs was given and shown to clear the amyloid from the brain, as observed from the PET scan, but also to slow the rate of cognitive decline by 27% and slow the changes in quality of life by 35%. There were lots of other biologic markers of changes in the disease course. The big concern with these drugs is that there are side effects. You can get bleeding in the brain, which is a big concern for us at the moment. Nonetheless, Lecanemab has now got FDA approval in the US and is being rolled out in the US across many centres. There is also approval in Japan and I believe one place in China has approval as well. It has been submitted to the TGA in Australia and in 2024 will undergo evaluation for PBS reimbursement.

Later the results of the Donanemab trial, the Trailblazer 2 study, were released. This had 1,700 people across eight centres. On the same measure that was used in the Lecanemab trial, it actually slowed cognitive decline by 55%, but they used a different outcome measure. They also showed that it if you equate it to kind of a delay in clinical presentation, about 4.4 months delay in disease course was achieved by the drug and 47% of people remained stable on the drug, whereas in the placebo group it was about 29%. Regardless of that, there has been some question about how clinically meaningful this change is in the disease course: there is a risk of the bleeding in the brain; it has to be monitored very, very closely; you need to have an MRI scan at the outset, and a PET scan or a lumbar puncture — which people in Australia don't really like to do. It's done very commonly in Europe and in the US, but you need to have infusions every fortnight and you need to have about five MRI scans over the course of the treatment. The treatment without PBS approval will be about $30,000 a year, so it's quite a significant investment, and certainly the cost to the health services — administering and coordinating these — is significant. We don't really know yet in Australia what our capabilities are to be able to deliver these drugs. We think there are probably very few centres in Australia that have the combination of PET scans, CSF scans, clinical trials, suites with infusion capabilities, expertise in neuroradiology, as well as the patients coming through, so I think we have some time to get used to this but we will need to think seriously about if this does get approved by the TGA. How do we actually roll it out to Australians? And even more so if it gets listed on the PBS.

Delays in diagnosis

A bigger problem is that we have massive delays in dementia in Australia, so it takes someone about 3 to 4 years from the time they first present to primary care or tell a doctor about their symptoms to get a diagnosis. Some people might say, "Well, why would you want to get an early diagnosis of dementia?" But the data actually show that it is important. People do want to know — it informs their choices about their future, including financial and legal matters and other things they may want to achieve

in their life. Moreover, data show that if you get an early diagnosis — particularly if it's a multidisciplinary diagnosis, such as you get in a memory clinic — you'll have a longer duration of independent functioning at home, and so delay admission into aged care facilities. There are many contributors to poor diagnoses, including poor awareness of symptoms, the stigma associated with dementia, reluctance to seek help, therapeutic nihilism, difficulty recognising dementia, and limited access to specialist expertise from GPs as well.

Bottlenecks in primary care

About 50% of cases in primary care go undetected. As you might imagine, GPs are very time-pressured, they don't have very good tools for detecting dementia, there's a lack of specialist support. We've done a bit of a deep dive into the Medicare items for dementia, and it's quite impossible for GPs to make any money out of diagnosing someone with dementia, in terms of what their reimbursements are, in terms of needing to talk to family members, knowing what test to get, and the time taken. So there's not really many incentives for GPs to do this. The memory clinics of course are better set up for this.

Bottlenecks in memory clinics

It is expected that we will start to see an unprecedented demand, not only because we have a better ability to detect Alzheimer's disease using the blood test, but also because of the drugs that are coming along. We have mapped in Australia what our capabilities are in terms of memory clinics: there are only 54 publicly funded clinics across Australia. We estimate that this probably serves only about 4.8% of the population with mild cognitive impairment, and that is health-seeking people with mild cognitive impairment. These are not the community-based prevalence studies. If you add in the private clinics, then we still have an unmet need of about 87%, not including people in the 50- to 65-year-old age range, who also have the earlier onset dementias and may also have a pre-clinical Alzheimer's disease emerging in the brain. Certainly the drug studies, the anti-amyloid drugs are beginning to target people earlier and earlier, so the clinical trial data show that the earlier you give these drugs, the better the treatment response is, so it may well be the fact that we are targeting people in the future, before they even get any symptoms and even come to the doctor, but they have amyloid in their brain.

Bottlenecks by region

A third of the dementia cases are in regional areas, but only 10% of our memory clinics are in regional areas. Hardly any clinics have access to neuropsychology, so certainly no capacity to detect people with mild cognitive impairment, and many of our colleagues say that it may only be about 0 to 5% of their cases, as compared to the 32% that you'll see in the metropolitan areas. As you might expect, the presentations occur very late — often the doctors in regional areas receive referrals very late when the patients have behavioural symptoms of dementia — and there's little that can be done for someone at that stage. It's a very reactive kind of service that they're getting.

New virtual memory clinics

We are working with the Department of Health on developing some new virtual memory clinics so that we can conduct

hybrid models of virtual assessments combined with face-to-face assessments. We'll be starting our first trial in Echuca in Victoria, and then expanding into three areas of New South Wales as well as South Australia. The last part of ADNeT is the screening and trials initiative — this is working closely with pharma to recruit people from the community who are concerned about their memory. We've now characterised about 1600 people who have had in-depth phenotypic assessments using MRI and PET scans etc, and also detailed cognitive tests. This is because we're usually not well placed for conducting clinical trials in Australia in terms of recruiting people, so it is a database of people that then can be offered the opportunity to participate in clinical trials very quickly. We also have a volunteer portal — people can sign up to engage in research. We're doing a lot of work in trying to better understand these new plasma biomarkers and how they could be applied at the community level, and ultimately if they could be applied in primary care. That would be perfect and certainly help the roles of GPs much more.

So lots of considerations for health services and policy planning. We need to think about our workforce, we need to think about dementia prevention and earlier screening, we need to think about how we give people better diagnostic support, offer cognitive interventions and other interventions in the memory clinic setting, we need to think about greater diversity of the people that we service, and how to reduce stigma in the community so that more people do come forward when they have early signs, and working closely across primary care and all health as well.

In summary, we have many challenges and also some great opportunities. We're at the beginning of some exciting developments in the dementia field. It's very early days, but I think within a decade or so we should have developed some of these things much further and be ready to better treat people earlier and also save the government lots of money, which of course they always like to hear about. I'd like to thank the team at ADNeT and also the team at the Brain and Mind Centre and Charles Perkins Centre for their support.