Early Detection for Invisible Patients

With a determination to improve patient recruitment and identify 'invisible' patients in dementia clinical trials, innovative patient registries have become an important focus in the prevention of Alzheimer's disease

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Dementia is a devastating condition that has grown into a major public health issue, particularly due to our increasingly aging populations. Despite the push for new and better treatments, no exciting breakthroughs have emerged so far. However, evidence is building in support of tangible benefits from treatments able to prevent or reduce the risk of dementia before it takes hold. New approaches to improving brain health in mid- and late life offer a real possibility for adults to manage their own risk many years before any symptoms emerge. This new perspective also raises the opportunity to conduct innovative trials of treatments to prevent dementia in people who are known to be at risk.

Opportunities for Dementia Prevention

Where previously there was scepticism about the preventability of dementia, now there are options for improving brain health and reducing risk. Even delaying the onset of dementia by just six months could have an enormous impact on health and costs at both an individual and population level, but current ambitions are far more optimistic. Several preventative strategies carry strong evidence. These include a number of lifestyle approaches known to reduce the risk of dementia, including physical exercise, maintaining a healthy weight, and stopping smoking (1). There is also strong evidence for other lifestyle approaches such as the regular use of cognitive training and games that engage the brain, both of which have been shown to improve brain function (2-3). A recent large-scale study that used data from 200,000 people showed that lifestyle factors could overcome the increased risk conferred by known Alzheimer's disease (AD) genes (4). This represents a tangible 'call to arms' for all older adults to take control of their own risk through changes to lifestyle.

Medical management is also a major aspect in dementia prevention. Early detection and treatment of hypertension is well established as a key aspect of dementia risk. Other conditions also have close links to brain health, including diabetes, cardiovascular disease, and depression. All of these conditions have established treatment paradigms that offer a means of improving brain health and managing risk.

The 'holy grail' for drug development would be to truly prevent dementia through intervention before symptoms emerge. This goal requires a number of critical elements to be in place, including realistic strategies for prevention – most likely a combination of pharmacological and non-pharmacological elements – and a means of identifying people who are at an increased risk of dementia later in

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life. It is of equal importance to have a means of delivering prevention and risk reduction strategies in a cost-effective way to thousands, or even millions, of people across a population. Innovative research now offers solutions to these needs.

A Different Approach to Dementia Prevention

Traditionally, clinical studies take patients who have a positive diagnosis with the condition in question, a treatment is trialled, and its effect on that condition is monitored for efficacy and safety. However, many AD researchers are now taking a markedly different approach, recognising that neurological changes may be taking place decades before the outward manifestation of any Alzheimer's symptoms (5). These clinicians are seeking to halt the condition at its earliest stages, before significant cognitive decline occurs, thereby optimising quality of life in the long term for both patients and caregivers.

Unfortunately, in practice, in the absence of a known family history of dementia or any pre-existing genetic testing, asymptomatic individuals needed for such trials simply do not present themselves to the healthcare system. Moreover, the attrition rate in clinical trial recruitment is high, and very few patients who are put forward will ultimately take part in a clinical study. Therefore, for a reasonable Phase III clinical trial, which may require 1,500 patients depending on inclusion and exclusion criteria, an initial cohort of tens of thousands of potential participants may be needed.

There are few sources of this size, especially for asymptomatic or undiagnosed individuals. This has led clinicians to consider patient registries as a source of individuals for clinical studies. A number of registries of differing sizes exist, but most are small and focused on people who already have AD or dementia.

More recently, larger initiatives have emerged that aim to include much earlier stage patients or identify and pre-screen at-risk and asymptomatic individuals with a view to supporting AD prevention studies. Among these is the new Synexus HealthyMinds Registry, an online registry coordinated by Accelerated Enrollment Solutions (AES) in collaboration with the University of Exeter, UK. The registry not only allows people to be contacted about upcoming trials, but also monitors brain health over time and offers an engaging web-based experience, including access to brain training programmes that are believed to improve brain health. Other registries include the National Institute of Health's National Institute on Aging Alzheimer's Prevention website, run by the Banner Institute in the US, but they are relatively passive, with little ongoing monitoring of the participants' cognitive function over time.

The Importance of Tracking Brain Health

The Synexus HealthyMinds Registry is part of a global family of online cohorts. The original site is based in the UK, called the Platform for Research Online Investigating Cognition and Genetics in Aging (PROTECT) study and led by the University of Exeter. It has recruited more than 25,000 people over the age of 50 and aims to understand how brain functioning changes with age. In particular,

the study is investigating how genes and lifestyle factors (such as exercise and education) affect brain aging, with a view to informing future research to prevent degenerative conditions. In addition to medical and family history and cognitive testing, registered participants are also asked to consent to genetic testing.

Much of the research focus in AD is now taking an approach that involves personalised medicine, and the existence of disease biomarkers may be a key part of identifying susceptible individuals many years before any classic symptoms of dementia are evident. Identifying biomarkers may also eventually form the basis of a simple diagnostic test that would reveal disease onset early enough that future treatments stand a better chance of slowing or even halting further cognitive decline. The PROTECT study will run for 25 years, during which participants are followed up annually to update tests and information.

Aside from being an exciting research study, PROTECT offers a means of identifying people who are more at risk of dementia later in life. The study can track brain health in unprecedented detail, pinpointing individuals who are showing the very earliest cognitive decline. It can combine this with other known risk factors, including genetic, lifestyle, and medical factors. This information is precisely what is needed to recruit the right people to trials of new preventative treatments. PROTECT opens up a whole new opportunity to improve the way trials are designed. The study already has recruited more than 1,500 people with early cognitive impairment and continues to support major collaborations and trials across the world.

The Synexus HealthyMinds Registry is the US-based sister initiative that aims to recruit 30,000 adults aged 50 years and older without pre-existing signs of dementia. This five-year study will look at lifestyle and genetic risk factors and their impact on cognitive function over time, again with a view to identifying potential methods of prevention and possible treatments. Importantly, the registry will also allow people to access groundbreaking new trials on dementia prevention and risk reduction in the same way as PROTECT in the UK.

AES is promoting participation in the Synexus HealthyMinds Registry to its database of more than 100 million US households, providing an enormous pool of potential participants for longitudinal screening and potential trial recruitment. Participation in this registry also brings a high level of engagement with participants, providing information about advancements in dementia research as well as free brain training exercises and games that may help participants retain cognitive function and identify any changes in performance.

In the coming years, an estimated 50,000 participants will be needed for AD clinical trials in the US alone (6). Although patient recruitment remains a challenge, patient registries will undoubtedly be part of the solution, particularly those that include ongoing cognitive assessment and are able to identify individuals who are on the cusp of the subtle cognitive changes that may signal the onset of longer-term decline. Importantly, patient registries can help support AD clinical research, especially in identifying those prodromal patients who may not otherwise present themselves to the healthcare system. The approach is a significant step forward in patient identification and recruitment for clinical trials, and one that may pave the way to a long overdue breakthrough in the treatment of AD.

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