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The government's growing recognition of the importance of clinical trials has led to the establishment of clinical trial offices at universities

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Professor at the Chinese University of Hong Kong since 1993 and pioneer in studying the causes of stroke in China, Lawrence Wong comments on neurology advancements over the past 30 years; the increasing number of Alzheimer's cases amongst Asian populations, and the need to go from a symptomatic approach to earlier diagnosis. He also weighs in on the shift in Hong Kong's clinical trials landscape and the government's growing recognition of clinical research.

As a neurologist, how have you seen the perception of and advancements in neurology-related conditions evolve in recent years, especially in terms of scientific, business, and public perspectives?

I still remember, more than 30 years ago when I started in neurology, people would say that neurology is a specialty where you know a lot of things but can do very little to help patients. At that time, many neurological diseases had no treatments—conditions like stroke, Alzheimer's, or even migraines lacked specific treatments.

However, over the last 30 years, this has changed dramatically. We had the first treatment for stroke about 30 years ago with clot-busting drugs, which transformed stroke care into a medical

emergency similar to a heart attack, necessitating quick action within the golden window of 4.5 hours.

Since then, we have seen numerous breakthroughs. For instance, in migraine treatment, the identification of the CGRP receptor led to the development of molecules that can block it, resulting in an explosion of effective drugs in the last five years. This has significantly transformed patients' lives. I had a patient who suffered from daily migraines and could not function normally, but after the new treatment, he experienced full recovery and could work without issues. He told me he did not realize he had been operating at only 70 percent capacity before the treatment.

Alzheimer's disease is another area where we have made substantial progress. Last year, we had the first FDA-approved disease-modifying treatment, which targets the disease itself rather than just offering palliative care. A second drug was recently approved by the FDA, and we hope to see more in the future. Alzheimer's is one of the most devastating diseases in neurology, progressively affecting patients' lives and placing a significant burden on their relatives, especially in places like Hong Kong or Asia where many elderly people live with their families.

Apart from drugs, there are advancements in technology such as robotics, exoskeletons, brain-computer interfaces, and virtual reality that are aiding in the rehabilitation of patients with conditions like stroke, Parkinson's, or dementia. This multidisciplinary approach is truly revolutionizing our field.

Given the historical challenges for undefined endpoints and a lack of biomarkers in the field, what has been your experience as a clinician in clinical trials? Are the frames of the protocols improving?

I have been deeply involved in numerous clinical trials, and one of the recurring jokes in our field is that the success of a clinical trial often depends on how well you choose your primary endpoint. Selecting the right primary endpoint is crucial. If it is not chosen correctly, you might end up with a negative primary endpoint, but have positive secondary endpoints, which can complicate the interpretation of the results.

There are countless scales and angles to consider when determining endpoints. For example, in stroke trials, we used to focus solely on whether a patient could live an independent life or not, a very black-and-white measure. Now, we have shifted towards using more sensitive scales that measure the degree of improvement, allowing us to capture subtle but meaningful changes in

patient outcomes. The FDA now acknowledges these more nuanced scales as valid and important.

In addition to clinical outcomes, there is a growing emphasis on objective measures such as CT scans, blood markers, and PET scans. For dementia, for instance, we now look at PET scans before and after treatment to assess how well the drug clears amyloid plaques, alongside cognitive tests conducted through interviews.

There is much more agreement now on what constitutes meaningful endpoints, both scientifically and in terms of regulatory acceptance. This progress has significantly advanced the field of clinical trials in neurology, making them more robust and reflective of real-world patient experiences.

Have we reached this point of more scientific validation in neurology because there are more companies conducting more trials, or because of other factors?

It is a combination of factors. The drugs themselves have improved significantly, but the methods of diagnosis have also become much more accurate. For example, in Alzheimer's, we now use PET scans to detect amyloid plaques. In stroke cases, we can examine blood vessels to see if they are open or occluded.

This technological advancement has played a crucial role in validating treatments. Collaboration between clinical scientists and regulatory authorities has also been essential. Ultimately, both sides aim to ensure that a drug or treatment genuinely benefits patients.

The process involves continuous dialogue with regulatory bodies to determine acceptable outcomes and adjust clinical trials accordingly. Over the last 30 years, the gap in understanding between scientists and regulatory authorities has narrowed significantly. This convergence is largely due to advancements in tools such as blood biomarkers, imaging biomarkers, and even genetic biomarkers, all of which have improved our ability to validate and measure treatment efficacy.

What do we know about Alzheimer's today that is different from what we knew 10 or 20 years ago?

Our understanding of Alzheimer's has evolved significantly over the past two decades, particularly with the development of amyloid tests. These tests have become the clinical gold standard for diagnosing Alzheimer's. Previously, diagnosis was more challenging and less definitive. Today,

amyloid PET scans allow us to detect amyloid plaques in the brain, providing a clear and reliable diagnosis.

In some cases, clinicians might use lumbar punctures to test for amyloid in the cerebrospinal fluid (CSF), but this method is less popular in Asia due to its invasiveness, although it is more commonly accepted in Europe.

In addition to amyloid PET scans, there has been substantial investment in developing imaging and blood biomarkers over the last decade. These biomarkers are less invasive, more cost-effective, and more accessible. For instance, researchers at the University of Science and Technology (UST) have developed highly accurate blood tests for Alzheimer's diagnosis, which are now used routinely in clinical practice.

Amyloid accumulation starts many years before symptoms appear. It begins with amyloid build-up, followed by neuronal dysfunction and brain shrinkage, leading eventually to memory problems and dementia. Advances in biomarkers, such as the tau protein 217, aim to detect Alzheimer's at an even earlier stage, before significant brain shrinkage and symptoms occur. AI technology is also being used to analyse MRI scans to identify Alzheimer's earlier and more accurately, but the blood biomarkers seem to be a significant advancement in diagnosing Alzheimer's disease

Are there any notable differences in risk factors of Alzheimer's in Asian populations compared to Western populations? Given the rapidly aging populations in places like Hong Kong and Japan, how does this affect clinical trials and treatment approaches?

In Asian populations, there are some distinct features related to Alzheimer's disease. For example, the prevalence of the ApoE4 allele, a key genetic risk factor for Alzheimer's, tends to be lower in Asians compared to Western populations. Additionally, lifestyle factors such as diet and exercise contribute to a potentially lower risk of Alzheimer's. In many Asian cultures, diets are often more plant-based, and there is generally a higher level of physical activity and social interaction, which are protective factors against cognitive decline.

However, despite these potentially protective factors, the rapidly aging populations in countries like Japan, Korea, and China mean that we are facing an increasing number of Alzheimer's cases. The prevalence of the disease is expected to rise significantly in the coming decades due to this demographic shift.

In terms of clinical trials, Asia is becoming a crucial region due to its large, aging population and increasing investment in neuroscience. The lower genetic risk might influence some aspects of trial results, but overall, the region provides valuable insights and a diverse population for studying Alzheimer’s.

Looking ahead, the aim is to shift Alzheimer’s diagnosis and treatment from a symptomatic approach to an early detection and prevention model, similar to how diabetes management has evolved. The goal is to screen individuals for biomarkers like amyloid and tau proteins before symptoms appear, allowing for earlier intervention and potentially better outcomes. This transition to a more proactive approach in Alzheimer’s care will likely depend on advancements in screening technology and reducing treatment costs, making widespread screening more feasible. Testing typically should begin around age 50, but it may start earlier, such as 40, for those with a family history, or later, like 60, for others, depending on their risk profile.

Should we be rethinking the patient diagnosis cycle to improve early detection and treatment?

The progress in diagnostic tools, including blood biomarkers, has indeed been crucial in understanding and managing Alzheimer’s. Currently, these tests are used primarily for patients who are already symptomatic, but the goal is to catch the disease even earlier.

Similar to national screening programs for colorectal cancer, where tests are mailed to individuals at certain ages, we could benefit from implementing early screening for Alzheimer’s. However, there are challenges to overcome.

For instance, the cost of these blood tests is currently around USD 800 to 1,000, which makes widespread screening impractical. To integrate such tests into routine screening, their cost would need to decrease significantly. Additionally, the cost of treatments would also need to be reduced to make early intervention more feasible.

In summary, while diagnostic advancements are promising, making these tools more affordable and accessible is essential for shifting towards earlier detection and prevention of Alzheimer’s disease.

The approval and commercialization of Biogen/Eisai's Alzheimer's medicine sparked debate but marked a significant step after 17 years without new treatments. What has been your experience with such treatments here in Hong Kong, and how do they impact patients in the real world?

Aducanumab, as the first new drug in 17 years for Alzheimer's, albeit only with restricted approval from the FDA, has been a significant milestone despite initial controversies over its endpoints and results. The second amyloid-targeting drug coming into clinical practice is lacanemab, which got full approval from the FDA in 2023. In clinical trials, it effectively clears amyloid from the brain—about 70 percent—which is crucial because amyloid plaques are associated with Alzheimer's. Although it does not reverse cognitive decline, it slows its progression, with a 27 percent reduction in the rate of cognitive decline in chronic sufferers. After approximately 18 months of treatment, there is a delay in disease progression by about 6 months. This treatment is approved for patients with mild to early-stage Alzheimer's, not for advanced cases, due to the severity of cognitive damage in more advanced stages. Side effects include brain swelling in about 20 percent of patients, but this is usually asymptomatic, affecting only 1-2 percent with noticeable symptoms. Importantly, this treatment does not cause additional psychiatric issues or dependencies, focusing solely on clearing amyloid plaques rather than affecting neurotransmitters.

What are your hopes for the future direction of Alzheimer's treatments?

The future of Alzheimer's treatments will likely involve the refinement in how these drugs are administered and a reduction in side effects. For example, current intravenous treatments are administered every two weeks, but there is progress towards subcutaneous and potentially oral formulations, which would simplify the treatment regimen. Additionally, as more options become available, the cost of treatment is expected to decrease, making it more accessible to a broader patient population.

How do you see the role of Hong Kong and its robust key opinion leader (KOL) community in defining local and regional clinical trials?

Over the past 30 years, I have observed a significant shift. Initially, teaching hospitals were managed by academic staff, which facilitated easier execution of clinical trials. However, as clinical practices have become busier, there has been a division between academic and service roles. This

split has made conducting clinical trials more challenging because the service side focuses on patient care, while the academic side is dedicated to research.

On the positive side, the Hospital Authority in Hong Kong has an excellent IT system and extensive data, which is now becoming more accessible to researchers. The government's growing recognition of the importance of clinical trials has led to the establishment of clinical trial offices at universities. This development is promising and could help build a more sophisticated infrastructure to support clinical research in the future.

Is there anything else you would like to add to our discussion?

Beyond pharmaceuticals, there is a wealth of advanced technology emerging in neuroscience. This includes innovations like robotic exoskeletons, brain stimulation or neuromodulation, virtual reality, and brain-computer interfaces. These technologies offer new ways to support neurological patients. Additionally, recent developments even allow for implants in the brain. While these technologies are promising, there is a need for better integration between these various tools to maximize their effectiveness.

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