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Dementia: a roadmap for the next decade

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The last decade has seen extraordinary advances in our understanding of dementia. Unfortunately, much of this hard won science points to dementia being a complex problem. For example, genetic studies tell us that dementia is a heterogeneous group of diseases rather than a single clinical entity as we had previously thought. Epidemiological studies report a surprising decline in the occurrence of dementia, most likely due to improved lifestyle and cardiac health among the general population.¹ This decline illustrates the multi-factorial nature of dementia, and importantly, shows that at least a portion of it is amenable to intervention and preventative measures.

Improved management of cardiac risk factors has perhaps carried us as far as it can go, and the dementia burden that remains likely represents intrinsic neuronal problems and true neurodegeneration. This is not just of academic interest. Aging of the global population, combined with improved life expectancy and the increasing cost of healthcare means that there is an economic tsunami heading our way. This is certainly not news to neurologists, but it does mean that we have to consider how to lead the fight against dementia. To prompt us to address this issue, Roger Rosenberg posed two questions to us: where do we see dementia research in ten years' time, and how do we get there?

The first question may have a relatively straightforward answer: we need a clearer understanding of the genetic, lifestyle and environmental causes of dementia; we want to understand the role that aging plays in its pathogenesis; we want the ability to identify people at risk of disease decades before they become sick, as well as a safe and affordable intervention to prevent them from manifesting disease; and, above all, we want to be able to reverse the dementing process in those suffering symptoms.

The second question is more challenging, though the last decade of progress in the dementia field does hint at possible solutions. In general terms, we believe that large-scale, data-driven, collaborative efforts are a promising way forward and likely to yield robust knowledge. The specific areas where this approach will bear fruit, and so should be prioritized, are genetic screening, biomarker discovery, and the collection of clinical phenotype data and biospecimens. Focusing on these key areas is expected to provide a solid

foundation for drug discovery and therapeutic development down the road. Before we discuss each of these areas in detail, it is important to consider however that bigger will not always be better. Research on rare families with unique mutations has unequivocally shaped our current understanding of Alzheimer's disease and other forms of dementia. Therefore, focused research studies on patients with high familial aggregation, unusual phenotypic features or small subject cohorts with the availability of exclusive datasets should continue to be pursued.

First, we believe large-scale genetic studies will be important to discover the genetic factors responsible for all dementia cases. This applies not just to Alzheimer's disease, but also to less well studied forms of neurodegeneration, such as frontotemporal dementia, dementia with Lewy bodies and corticobasal degeneration. The identification of genetic factors that modify the phenotype, either in terms of age at onset, rate of progression and severity, are also particularly exciting. There is little doubt that a complete catalog of the genetic factors underlying neurodegeneration would paint a coherent picture of the cellular processes that lead to neurodegeneration, identify common pathways, and provide targets for *in vitro* and *in vivo* modeling and ultimately for therapeutic development. The maturation of gene therapy that can target any part of the human genome would shorten the time from gene discovery to first-in-human clinical trials.

Biomarker discovery and development should also be prioritized, first as a means to facilitate clinic trials and therapeutic development, and ultimately as a potential population-screening resource. Such a tool would allow us to identify individuals at risk of dementia long before symptoms arise and to potentially intervene. Tau imaging and exosome-associated tau levels in cerebrospinal fluid show early promise^{2,3}, but would be difficult to implement widely in the community. Again, we believe that unbiased -omics approaches that facilitate hypothesis-free data mining offer a robust solution for making these advances. Such data driven analyses have already shown great promise in predicting Parkinson's disease onset in an individual up to 5 years prior to symptom onset.⁴ Of particular note, this study analyzed myriad demographic, clinical and genomic datasets to distill a useful model. This hints at another reality faced by the dementia field, namely that unraveling of complex diseases will require equally complex, multi-dimensional approaches involving many data types.

Genetic and biomarker discovery efforts do not occur in a vacuum. Their success will rely heavily on the availability of large cohorts, numbering in the tens of thousands, or even more. For this reason, greater emphasis must be placed on deep phenotyping of patients diagnosed with mild cognitive impairment and dementia. This will provide the necessary data to subtype patients based on their clinical presentation, to understand the role played by lifestyle and environmental factors in neurodegeneration, and to provide access to biospecimens. Early efforts, such as the Alzheimer's Disease Neuroimaging Initiative, have been successful, but future efforts should focus on expanding this and other programs to all corners of the nation and to the entire dementia spectrum. This industrialization of data collection will require the establishment of many more dementia centers, and is ambitious and expensive. Consideration will also have to be given to how the numerous collaborators, who dedicate significant time and effort to these mega-projects, will be appropriately

recognized for their efforts and how individual contributions would be translated in terms of scientific merit and academic promotions. Nevertheless, such a network would benefit those facing the burden of dementia now, and may also help to minimize clinical costs through economies of scale. In particular, the broader use of electronic health record systems may harmonize data collection. Continuous measurement of activity, sleep and other cognitive performance using smartphone technology and wearable devices offers obvious advantages over discrete collection of data in the doctor's office.

The true power of our proposed genomic, biomarker and phenotyping efforts will come from combining them into multi-dimensional databases and analyzing the aggregate dataset to identify subpopulations of patients (and pre-symptomatic individuals) suitable for targeted therapeutic interventions. This type of precision medicine applies not just to treatment, but also to diagnosis and prognosis. Indeed, selection of patients for clinical trials based on their *APOE* genetic profile is already taking center stage, and we expect tailored healthcare to play an increasingly important part of clinical practice in the future.

Achieving this utopian vision of the future will require a fundamental shift in our mindset at all levels of society. Patients and their families must continue to be educated to recognize the central importance of research in conquering dementia and should be encouraged to enroll in national and international studies. Physicians and researchers should view massive collaborations as the norm, with standardized phenotype data, biospecimens and assay results being made publicly available, quickly and freely. Geriatricians, psychiatrists, neurologists and neuropsychologists will each play an important role in these efforts. There needs to be greater cooperation between academia and the pharmaceutical industry, particularly when it comes to the mountains of non-proprietary phenotype data and biospecimens collected during industry-sponsored clinical trials. The US Congress recently provided an additional \$300 million in funding over the next five years. While this is a good start, larger investments are needed. This makes fiscal sense, as dementia costs the US economy \$215 billion annually, a figure that is growing at an alarming rate.⁵ There also needs to be an emphasis on collaboration between countries, a grand coalition of nations coming together to share resources and expertise.

Finally, all of us are responsible for conveying a sense of the urgency to the populace. Dementia is the scourge of our modern times. It has already taken too many of us, our parents and our friends, and we share a common mission to defeat our adversary.

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