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OPEN PEER COMMENTARY

Open peer review commentary on building clinically relevant outcomes across the Alzheimer's disease spectrum

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1 | INTRODUCTION

This commentary addresses the impressive paper by Dorene M. Rentz et al.[1] that reports an Alzheimer's Association Research Roundtable on clinical meaningfulness. We begin with a summary, followed by a major comment and then several specific points. I signed my review, having indicated to the Editor before accepting the invitation that I am a "biomarker = disease" skeptic. My view is that biomarkers, including those used in neuropathology, are better understood as risk factors.[2] This obliges nuance in their interpretation.[2–4] Further, I was happily a conferee, and believe that I learned much there. I found the treatment of individualized outcome measurement—the topic about which I had been invited—to be fair. I will not consider it further.[5]

2 | SUMMARY OF THE PAPER

The Roundtables combine leaders from several sectors, spanning patients, carers, academia, and industry. The latter's many companies manufacture and evaluate candidate pharmaceuticals and biomarkers. Agreement is imaginable across such a diverse group, but only should something exist that we do not have now. The paper opens by setting the stage "Undoubtedly, all stakeholders agreed that a therapeutic response which produced a clear and sustainable benefit, while altering the disease trajectory, constitutes a clinically meaningful outcome."[1] As the authors note, though, we are far from such an indubitable consensus.

Bridging the ideal then and the messy now necessitates some tough slogging. To measure meaningfulness "across all stages of the disease" is non-trivial. The authors elaborate a triple trinitarian framework. First, three stages: asymptomatic, prodromal, and dementia. Second, three questions: (1) To whom is the outcome relevant? (2) How is clinical meaningfulness demonstrated? (3) When is it achieved? Third, three perspectives: "the patient, care partner, and clinician," "regulators," and "payers and health economists."[1]

These nine categories are each detailed. The authors underscore that "determining whether an AD intervention is clinically meaningful remains a challenge."[1] Only in the conclusion, however, is a central challenge spelled out: "How cognitive and functional change should be measured is complicated by a syndrome that has considerable heterogeneity in pathologies, phenotype, and rates of progression."[1]

3 | MAJOR COMMENT

In accepting the invitation my purpose was not to persuade the authors to a different point of view, but to suggest viewing the challenge from other perspectives. Too late for that, the result is this commentary. What is true in the budgetary process is true generally: "where you stand depends on where you sit."[6] For readers whose seated posture allows that as a field we got out ahead of ourselves in seeing neuropathology (or its many antecedent biomarkers) as disease-defining, what follows mostly will be self-evident. For those who do not, it will seem nonsensical. Still, let's see where we might find agreement. The

analogy between dementia biomarkers and cancer biomarkers persuades many; that is, real progress must be mechanism-based, which obliges moving from solely clinical descriptions. This I do not dispute; on the contrary, we can benefit from that experience, including its hard lessons.

I find myself unable to see the possibility of an Alzheimer's disease (AD) treatment that would stave off what is now called AD dementia. That undercuts any urgency to change how success is defined. I am glad yet with measuring average improvement on two co-primaries. I understand that were treatment initiated prior to any decline, and were it to prevent decline, then in some far-distant future in which change in biomarker values alone attenuated risk, there would be no improvement to measure. Instead, change in a biomarker would suffice. To get there, however, we would still need some considerable period in which we could know that disease had been prevented by seeing it emerge in people whose trajectory to dementia had not been fundamentally altered.

Might we still find agreement in this proposition: it is risky to largely conflate late-life dementia and AD dementia as one, and to then invest crucial decades on a particular understanding of AD. We were told at the meeting that "the amyloid hypothesis is looking very strong." I see it being asked to bear a weight for which it is unsuited. In consequence, it seemed odd to me to work through such a complex set of considerations only to conclude by acknowledging heterogeneity of syndrome and pathology. The heterogeneity is a place where many might have started. Two points—consider aging and its inherent heterogeneity, including variable disease courses, and address pricing with a more realistic understanding of the costs raises from heterogeneity—form the basis of the further comments.

4 | SOME SPECIFIC POINTS

1. Inevitably, some will see comprehensiveness in the triple trinitarian structure. Others will suspect contingency, and its dark companions, arbitrariness and special pleading.[7] The paper fits well in the decade-ago consensus that led from an understanding of dementia as the heart of the matter to it being seen as a too-late concern.[8–10] Indeed, I heard dementia seen as almost irrelevant to the cutting-edge work of treating, really treating, "AD" as a biomarker-defined single protein abnormality. For many conferees, the main biomarker dispute was whether to stay with the comfortable cover of amyloid, or to seek even more secure shelter under the tarpaulin of tau. Although the paper is agnostic as to which protein is the better target, it does not doubt that for most so afflicted dementia will follow. The counter critique is that the paper fails to consider that "the problems of old age come as a package."[11] This is curious, especially as we see emerging approaches that can embrace aging and its heterogeneity.[12,13]
2. Heterogeneity is inherent in late-life dementia. The Religious Orders Study/Rush Memory and Aging Project shows us the gap between the neuropathology and its clinical expression. It shows us, too, how rare is pure AD, and how commonly other factors are relevant.[14,15] If even the once gold standard of autopsy confirmation is instead an important risk factor, then where stands syndromic heterogeneity? That is why for many, syndromic heterogeneity will be less the after-thought it appears to be here.
3. One aspect of heterogeneity that is likely to be crucial to clinical meaningfulness is the variability of disease courses. Much of what we know about AD and biomarkers comes of course from clinics that commonly treat people who have had more than mild symptoms with more than very slow disease progression. The paper makes little note of variable trajectories, save that we know little about widespread amyloid testing as disease-defining, especially without the Insights to Model Alzheimer's Progression in Real Life study.[16]
4. Considering variable trajectories, if we are to accept the persuasiveness of the analogy with cancer, we should consider lessons might come from cancers that for many do not progress, such as thyroid cancer. In the setting of more and better-imaged thyroid nodules incidence rose dramatically, even as age-adjusted mortality stayed about the same.[17,18] Against the early, costly, and often harmful approach of total thyroidectomy, the current standard is largely active surveillance. Controversies persist, but the practice rests on an understanding that a positive scan is not itself a feared disease. Future treatment considerations expect to focus on advances in ultrasound, cytological assessment of thyroid markers, more specific molecular testing, the benefits of which may allow better individualized assessments of risk and benefit.[17,18]
5. The paper also holds to the conventional wisdom that societal costs can be approximated from clinical trials, and that disease without dementia is simply a "pre-symptomatic" state. This seems self-defeating. Ultimately, it might be best not to divorce the "clinical" from clinically meaningful.[19] To go from the scan to the disease, and the better scan to the lesser disease will need empirical demonstration. Just what will the models assume? From which set of scans? Do we put ourselves at risk of rediscovering that even people with neuropathologically defined AD did not have dementia before they died? Or is the postive amyloid (or tau) scan without dementia to be mired in disputes about whether people were thoroughly enough tested, or lived long enough to express their risk?
6. Further in the analogy with cancer, many advances now come from multi-drug combinations, but often at a price of more side effects.20 I read the blandishments of the health economics "societal perspective" as maximizing price—by ensuring that treatment costs are at least as expensive with any single therapy as they would have been had dementia unfolded according to its natural history. If success in treating dementia requires multi-drug combinations—to me, a not unreasonable prospect—then a slightly less bloodless account of pricing will be needed. However that plays out, a little skepticism about pricing of tests and treatments is warranted from the start.

As we grapple with what clinical meaningfulness might mean, we must not avoid the political nature of the task. Included in this will be understanding how a well-meaning disease-modifying strategy to

prevent late-life dementia will play out, should there be widespread testing for the biomarker-defined diseases that are held to make it up.

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CONFLICTS OF INTEREST

In addition to academic and hospital appointments, Kenneth Rockwood is president of Ardea Outcomes, which in the last 3 years (2 as Ardea Outcomes) has contracts with pharma and device manufacturers (Hollister, Novartis, Nutricia, Shire, Roche, Takeda) on individualized outcome measurement. In 2020 he chaired a Scientific Workshop & Technical Review Panel on frailty for the Singapore National Research Foundation. Otherwise any personal fees are for invited guest lectures, rounds, and academic symposia, received directly from event organizers, for presentations on frailty.

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