

Toward Precision Medicine, December, 2016

Dr. Paul Crane, Professor of Medicine, UW Medicine. *Cognitive testing data to sub-group people with Alzheimer's disease*

Dr. Paul Crane presented general comments about the concept of using cognitive testing data to sub-group people with Alzheimer's disease. He discussed his efforts to develop and implement an approach to categorize people with Alzheimer's disease on the basis of patterns of cognitive functioning in four cognitive domains: memory, visuospatial functioning, language, and executive functioning. His initial findings provide some support for the notion that these subgroups may be biologically distinct, with different neuropathological findings and different genetic architectures. He also discussed data from the Adult Changes in Thought (ACT) study that suggests this approach may be a reasonable one with biological plausibility.

In this recent collaborative work using modern psychometric methods, Crane found that about half of all the study participants with incident Alzheimer's disease had a single domain with a substantial relative deficit. For example, the person with posterior cortical atrophy had an intact memory score and a substantial relative deficit in visuospatial functioning, while the person with primary progressive aphasia had an intact memory score and a substantial relative deficit in language. Further work will be needed to replicate these findings in additional study settings.

Considering only cognitive testing data for the group assignments, Crane and colleagues found that the group with isolated substantial memory impairment had a much higher proportion with APOE ϵ 4 alleles (45% compared with 34% for everyone with Alzheimer's disease), a higher proportion with Braak stage ≥ 4 (97% of this group had Braak stage ≥ 4), and a higher proportion with amyloid angiopathy. This group appears to represent "super Alzheimer's disease" – higher proportions with APOE ϵ 4, with almost everyone having a Braak stage ≥ 4 , and 7 SNVs with extreme ORs all in the risk direction.

In the visuospatial group with isolated substantial visuospatial functioning impairment, APOE ϵ 4 was less common than in the isolated memory group (29%). In contrast, each of the other three groups with a single domain with relative deficits had a lower proportion of people with any APOE ϵ 4 alleles (20% to 29%), and had similar Alzheimer's neuropathology findings to the other groups. Vascular brain injury appeared to be somewhat more common among people with substantial relative impairments in language.

Crane noted that if these findings are replicated in other settings, these findings suggest that a non-invasive, widely available technology – cognitive testing – can differentiate people with incident Alzheimer’s disease into biologically relevant and distinct subgroups. As data accumulate in the future, combinations of cognitive testing along with other modalities such as CSF bio fluids or amyloid or tau scanning may be used to isolate subgroups of people with similar biological processes that are distinct from those of people in other subgroups.

Group Discussion

The group discussion explored the possibility that these observations do not actually reflect biologically distinct groups and instead represent the play of chance. Replication in other settings will be very important to resolve this uncertainty. Along those lines, the group suggested that it would make sense to re-analyze clinical trial results across different subgroups to determine whether each group responded the same way to therapies, or whether some sub-group responded while others did not, which may be lost in the noise of non-response. Crane expressed interest in collecting additional data, such as autopsy analyses, from people with AD to compare across subgroups