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Measuring outcomes in MS studies: Tracing the pervasive implications of PIRA

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Introduction

Recent research[1], found notable proportions of people with early relapsing MS (PweRMS) had disability progression independent of relapse activity (PIRA). These findings undermine 3 assumptions: PweRMS are stable between episodes; MS phenotypes (relapsing, secondary and primary progressive) accurately represents the disease; MS is progressive from onset infrequently. These PIRA observations in PweRMS also have considerable measurement implications for clinical trials and practice.

Aim

To identify the implications for MS outcomes measurement by tracing the PIRA findings

Method

An application of measurement theory to clinical trial data.

Results

Kappos 2020 showed:

- A notable proportion of PweRMS had PIRA (≈21%)
- Progression was in ≥1 of three outcomes measured: expanded disability status scale (EDSS), Timed 25-foot walk (T25FW), 9-hole peg test (9-HPT).

Measurement limitations and their implications

- All participants were taking MS disease modifying treatments proven effective in MS. This implies the proportion of PweRMS with PIRA in an untreated sample would be greater.
- Progression was determined using three disparate measures. Given MS has more widespread manifestations, this implies PweRMS can progress in other functional domains. Had these been measured, the proportion with PIRA would likely have been greater.
- All three outcome measures used have limitations that risk type II error. This implies that even the proportion who progressed, on these functional domains, was likely higher than measured.
- Published criteria for clinically significant change thresholds were used. However, binary cut-off criteria are heavily caveated implying accepted methods for determining clinically significant change are conceptually weak. This implies the proportion who progressed on these outcomes may be greater than measured.

Conclusions

These measurement implications, combined with evidence of inflammation throughout the disease, suggest biological progression may be universal and clinical progression, as measured, the tip of the iceberg. To test this hypothesis, we require instruments ensuring measured progression accurately reflects actual progression.

References:

Kappos et al. JAMA Neurol 2020; 77(9):1-9 (doi:10.1001/jamaneurol.2020.1568)