Test-treatment RCTs are sheep in wolves' clothing
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Letter 689wds:

Test-treatment RCTs – sheep in wolves’ clothing

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We thank Siontis and colleagues for their interesting review of diagnostic RCTs [1]. Assuming that changes to patient health are caused by improvements in test accuracy, the authors expected health effects observed in their cohort of RCTs to be complemented by changes in downstream diagnostic and treatment decision-making. Yet the authors found no overall correlation. We would argue their findings are based on a flawed assumption: that diagnostic accuracy is the only mechanism driving change to health outcomes. Although this reflects previous thought [2], recent research suggests this to be an incomplete model with tests shown to change patient health through 3 other causal chains of effect: by the direct effects of the testing process, by changing timeframes of management, and by altering patient and clinician perceptions [3]. Using this complete model, we offer alternative explanations for the authors’ findings and challenge their call for more diagnostic RCTs.

First, the authors selected two process outcomes (further test use and treatment use) that are not always fair surrogate markers for more appropriate decision-making. More accurate tests improve patient health through their ability to enhance decisions, which does not necessarily alter the frequency of subsequent test or treatment use. Equally, while more accurate tests could increase testing by identifying more patients who need further investigation, less able tests might also increase further testing if they reduce a clinician’s diagnostic confidence. In other words, the meaning of observed changes in further test use or treatment use, and whether one would expect any correlation with health effects, is entirely dependent on the clinical context being evaluated.

By focussing on accuracy-driven change, the authors did not always analyse the processes actually driving changes to patient health in each trial. This is clearly shown in the example of point-of-care ultrasonography (PLUS) for ER trauma cases given by the authors (Box 2). In this add-on comparison, observed improvements to patient health (reduced probability of experiencing serious complications) are largely driven by PLUS’s ability to expedite urgent treatment; this is reflected in the trial’s primary finding that PLUS significantly reduced time-to-operative care (on average 57 minutes vs. 166 minutes) [4]. The reduction in further testing (use of CT) is therefore unrelated to changes in downstream patient health in this trial, and is instead likely to reflect physicians’ confidence in the ability of PLUS. The lack of correlation observed in this study between health effects and markers of accuracy is therefore also explained because health effects are not always driven by improved accuracy in this cohort of 140 trials.
It is highly probably that many of the trials are underpowered to detect differences in patient outcomes, which could in part explain both the rarity of significant health effects and lack of correlation with process outcomes.

In an RCT comparing tests, treatment effects are diluted by the subgroup of patients receiving no change in diagnosis and treatment. Small differences in the sensitivity of comparative tests (say 20%) means the proportion of diseased patients (in a group with 20% prevalence) benefiting from different treatment will also be a small subset of the study population \([3,5]\) \((20\% \times 20\%, \text{or } 4\%)\); thus to detect differences in patient outcomes sample sizes must be inflated to account for this ‘dilution effect’ (by 25 times, or \(1 \times 4\%\)). The 49 RCTs evaluating diagnostic tests (a third of the cohort) had a median size of 372, which is smaller than found in RCTs of treatments \([6]\).

We suggest caution before embarking on a test-treatment RCT. There are major barriers to conducting valid trials that can deliver: competing test–treat pathways must be described, interventions and complex decision–making protocolized, sample sizes must be large enough, and the web of mechanisms driving change to patient health (accuracy and otherwise) must be identified and measured to ensure that diagnostic processes are operating as intended. Often this is not achievable within acceptable budgets and timeframes, and the RCT cannot deliver. We would rather highlight an excellent alternative: using modelling to link evidence for all important mechanisms that are identified, on a case–by–case basis, to cause changes to patient health.

References


