

and breastfeeding seem to differ between carriers of *BRCA1* and *BRCA2* mutations.^{6,7} Unfortunately, the genes studied here do not provide any new clues.

If attention is limited to the gene variants that have come out of the genome-wide association studies so far and to the known risk factors for breast cancer, we are unlikely to make much progress. The challenge of breast cancer prevention remains and new approaches are needed.

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I declare that I have no conflicts of interest.

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Testing autism interventions: trials and tribulations

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In *The Lancet* today, Jonathan Green and colleagues¹ report results from a multisite randomised trial in children with autism. The investigators compared a parent-training technique that targeted enhancement of the child's social-communication skills (two of the three core deficits in autism) with treatment as usual. The primary outcome was the social-communication score from the Autism Diagnostic Observation Schedule (ADOS),² a widely used diagnostic tool. Secondary outcomes included parent-child interaction, child language, social communication, and measures of adaptive functioning.

Today's results showed no effect of the intervention on the primary outcome and positive effects on some but not all secondary measures, including parent report of language and communication and direct observation of parent-child interaction. This study furthers the field by setting a new bar for the minimum standards of rigorous methodology needed in trials that have potentially far-reaching service and policy implications.³ Strengths include a large sample size, multisite randomised design with masked assessors, balance across treatment groups, a manualised treatment approach (including standards for fidelity and inter-rater reliability), and outcome measures that directly relate to treatment focus. Thus, in a field in which minimum study standards have made it difficult to even look for literature to answer what works for autism, this study is an achievement.

At the same time, today's study exemplifies the complexity of attempting to detect change in samples of young children with such a heterogeneous condition. There are very few positive published trials in autism, for behavioural interventions, traditional pharmacotherapy, or complementary/alternative therapies.⁴⁻⁶ Is this due to non-efficacious treatments, lack of sensitive outcome measures, or heterogeneity of autism—or perhaps all three?

The lack of effects on ADOS social-communication scores with this parent-training intervention dampens optimism about its ability to exert clinically significant change in core symptoms of autism. However, Green and colleagues' use



Teacher works with a boy with autism

of a theoretical model that used both proximal and distal effect analyses is especially important. Unlike in many other trials, symptoms of autism were appropriately used in today's study as the distal treatment effect (as regards the primary outcome) with proximal variables theoretically linked to the treatment as secondary outcomes. In this case, parent-training intervention lent itself easily to the use of proximal parent-child interaction variables, to explore the mechanism of the intended treatment.³ Development of appropriate models, starting with direct treatment targets and following downstream effects, might be needed for truly rigorous behavioural trials to eventually detect mechanisms of action. In fact, the effect of attenuation in today's trial (with more effect seen in proximal than distal outcomes) allowed the investigators to begin to distinguish active crucial components of the treatment. Investigation of these components can provide data for the ongoing debate about the importance of the ingredients in a given intervention.⁷ Some of these multiple components include: implementer (parent vs therapist training), setting (individual vs group and home vs clinic), style (discrete trial vs play-based or relationship-based), and dose (total intervention time vs intensity per time period). Head-to-head comparisons, in which all but one of these variables is controlled, might be needed to answer questions about which ingredients are most active and efficacious.

Another issue is the dearth of outcome measures that are sensitive to change in autism symptomatology, which plagues the field. Autism can be truly pervasive, often including substantial cognitive and language impairments. Thus far the field has failed to identify crucial outcome measures that isolate true symptoms of autism, by adjusting for factors such as age and developmental level. Green and colleagues discuss how the use of an outcome measure designed for diagnosis (eg, ADOS) is useful to capture autism-specific symptoms, but might be a problem for sensitivity to change. Recent efforts to increase comparability of ADOS scores by introducing a severity metric that accounts for chronological age and language level might improve its suitability as an outcome measure.⁸ Furthermore, it is notable that some children (in both groups) in today's study showed movement to less severe diagnostic categories. However, caution is warranted in attributing any specific treatment to such changes, because of the lack of stability of autism diagnosis in very young children.⁹

It is not surprising that, for a behaviourally defined disorder with unclear aetiology, the major focus of treatment has been strategies designed to modify behaviour. We still do not know what autism is, or to be more precise what the "autisms" are.¹⁰ The heterogeneity in this disorder, both behaviourally and aetiologically, works against even the most well-designed trials. Green and colleagues strived to reduce heterogeneity by controlling for pretreatment factors such as severity (eg, only including those with autistic disorder) and found no differential treatment response for several subject variables. However, in addition to those examined within this study (eg, variability in diagnoses, baseline language and cognitive levels, socioeconomic status, and parent's education, age, and sex), there remains a long list of issues that are difficult to even measure and certainly to account for in any sample of individuals with autism. These factors include environmental context, other treatments, comorbid conditions, and as yet unknown differences in genetics and neuropathophysiology. Ultimately, the challenge is to define subtypes within this disorder. These definitions might not only have important treatment implications, but also aid in understanding aetiology.

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