FDA clearance paves way for computerized ADHD monitoring

Last month, a mother came into the Focus-MD clinic in Mobile, Alabama, with a concern about her eight-year-old son. A year and a half earlier, the boy had been diagnosed with attention deficit hyperactivity disorder (ADHD), but he was not responding well to stimulant medications. She wondered: could the drugs be failing simply because the original diagnosis was wrong?

After interviewing the boy, James Wiley sat him in front of a computer and strapped a motion-tracking sensor to the child's forehead. For 15 minutes, the boy then completed a neuropsychological 'game': if a gray circle appeared on the screen he was supposed to press a button with his finger; if the circle contained a black X he was instructed to do nothing. All the while, an infrared camera captured all of the boy's movements. "No other [motion analysis] platform for making a diagnosis of ADHD has the scientific evidence base that this platform has," says Wiley, a pediatrician and founder of Focus-MD.

This task is called QbTest, short for quantified behavior test. It's a derivative of a motion-tracking system first developed more than 20 years ago by Martin Teicher and his colleagues at McLean Hospital, a psychiatric affiliate of Harvard Medical School in the suburbs of Boston (*J. Am. Acad. Child Adolesc. Psychiatry* **35**, 334–342, 1996). By gauging people's impulsivity and engagement during the circle-identification task in addition to how much they fidget in their seats, QbTest is meant to provide a more objective measure of attention and hyperactivity problems than the clinical questionnaires and rating scales used routinely for ADHD diagnosis and monitoring.

On 24 March, QbTest became the first such commercial platform to win clearance from the US Food and Drug Administration (FDA) as an aid in the evaluation of treatment interventions in people with ADHD. A competing platform called the Quotient ADHD System has also been cleared by the FDA, but only for diagnostic assessment.

With a global rise in ADHD diagnoses in recent years and the subsequent surge in prescriptions for Ritalin, Adderall and other stimulants, some mental health professionals have begun to question whether many children are being mislabeled with ADHD. In response, some in the medical community have begun to embrace QbTest and Quotient for their ability to diagnose individuals with ADHD more objectively and then monitor treatment responses in an unbiased fashion. Clinical researchers and healthcare providers are taking notice, too.

Qbtech

Bobbling heads: The QbTest uses a motion-tracking device to measure behavior.

"It's good to see ADHD care moving more toward a medical and neurological model," says Wiley, whose own son was diagnosed with ADHD in 2007 with the aid of the QbTest. (He does not have any financial relationship with Qbtech, the Stockholm-based company behind the tool.) "This is not a standalone test, but it's a very helpful, objective test," Wiley continues, "and to have an objective measure in our tool kit, I think, is a game changer."

Attention grabber

In Sweden, where QbTest was first introduced more than a decade ago, about 25–30% of all clinical evaluations for ADHD now involve QbTest. According to Carl Reuterskiöld, chief executive of Qbtech, other countries—most notably, Germany and the US—are beginning to catch up. "We see significant growth in all our markets," Reuterskiöld says.

Still, no organization, such as the American Academy of Pediatrics or the American Psychiatric Association (APA), has yet included motion tracking into its clinical best practice guidelines. For neuropsychiatrist F. Xavier Castellanos, director of research at the New York University Child Study Center and a member of the ADHD subcommittee behind the 2013 update of the APA's Diagnostic and Statistical Manual (DSM), the evidence base is simply too weak for these types of motion analysis systems to be included yet in any psychiatric handbooks.

"With enough validation it might be possible for this type of approach to be incorporated into future versions of the DSM," Castellanos says. "The real question over the next few years will be whether it assists the clinical process in meaningful ways."

Dozens of clinical trials are now ongoing to address that question. For example, Kaiser Permanente, the US's largest nonprofit health plan, launched a 500-person trial earlier this year at three of its California hospitals to evaluate whether children newly diagnosed with ADHD reach a stable drug dose more quickly when their treatment response is measured

using Quotient testing. Researchers at the King's College London Institute of Psychiatry, led by molecular psychiatrist Philip Asherson, are now running a trial in a UK prison population with ADHD; their goal is to determine whether early changes seen in the QbTest after the first one or two doses of medication correlate with long-term clinical outcomes more strongly than clinical interviews do. Meanwhile, psychologist Hanna Christiansen and her colleagues at the Philipp University of Marburg in Germany are now assessing the usefulness of the QbTest in people newly diagnosed with ADHD over the age of 50.

Both QbTest and Quotient still rely on some aspect of behavior, though, and many researchers would like to see ADHD diagnoses made with a more rigorous biomarker, either on a brain scan or by a blood test. That could provide the ultimate objective assessment of neurobiological pathology.

A vast amount of research is ongoing into biomarkers for ADHD. In the meantime, Teicher notes that the available computerized attention tasks might be reflecting deeper-seated biology in the brain. In a 2000 report in *Nature Medicine* (*Nat. Med.* **6**, 470–473, 2000), he and his colleagues showed that blood volume in the striatum, as measured by magnetic resonance imaging, strongly correlated with young boys' scores on motion analysis tests. "It gives you a window into brain function," says Teicher, who maintains a financial stake in Quotient (which is marketed by the global learning company Pearson).

As for the young patient at the Focus-MD clinic, QbTest indicated that the boy was "absolutely rock-solid normal" in terms of attentiveness and hyperactivity, Wiley says. He didn't need stimulant medications. He didn't have ADHD. What he did have was dyslexia, a disorder that can resemble ADHD when clinicians rely only on verbal and written clinical measurements. Thus, for Wiley, QbTest "gave me the confidence to tell this mother, 'I think we're barking up the wrong tree.'"

Elie Dolgin

Mystery around drug adherence still plagues medical literature

The randomized controlled trial, or RCT, represents the gold standard of interventional studies of new drugs. But how reliable are the results when it remains unknown whether subjects in the trial actually took their medicines at all? A 2007 analysis found that only 33% of 192 papers describing RCTs of oral therapies for six chronic diseases disclosed adherence results (*Am. J. Med. Sci.* **334**, 248–254, 2007). Now, in light of new data suggesting a continued lack of information about drug adherence in the medical literature, some researchers are calling for a reform of reporting guidelines.

"Failure to find significant results when they actually exist between treatment arms, underestimation of a drug's efficacy or side effects and overestimation of the effective dose are all potential undesirable consequences of inadequate adherence in drug trials," says William Robiner, a clinical health psychologist who studies drug adherence at the University of Minnesota Medical School in Minneapolis. "The truth is we don't know enough about patient adherence in RCTs—adherence is a weak link in clinical research."

In a study that appears in the April issue of the journal *Clinical Trials* (**11**, 195–204, 2014), Walter Kernan and his colleagues at the Yale School of Medicine in New Haven, Connecticut, report that only 46% of 111 oral therapy RCTs published in ten high-impact medical journals in 2010 reported patient drug adherence. Notably, studies that reported adherence were more likely to also report negative findings.

Given the low rates of adherence reporting, some researchers see the US Food and Drug Administration (FDA) as the solution. Currently, the FDA provides soft guidelines on clinical trial conduct, but it only encourages, not requires, accurate adherence monitoring. "The FDA should have explicit requirements on this," says Terrence Blaschke, emeritus professor of medicine at Stanford University who has studied drug adherence and served as a chair and member of drug advisory committees for the FDA.

In the papers

Others say that the onus should fall on the medical journals that report RCTs. Yet Jeffrey Drazen, editor-in-chief of the *New England Journal of Medicine*, is more equivocal about whether publications should include adherence data. "All the randomized clinical trials [we] published for the past two years have their protocols on [our] website," says Drazen, who adds he does not have a strong opinion on whether patient drug adherence should be reported in medical journal's papers reporting clinical trial results.

Kernan believes that drug adherence reporting in publications will not improve until it is required as part of the standards set by the CONSORT (Consolidated Standards of Reporting Trials) group, which has been publishing and updating a guideline on trial data disclosure since 1993. "This guideline is policy setting," says Kernan, "For publication in top medical journals, [investigators] adhere to these guidelines." At present, CONSORT does not provide a firm stance on whether investigators should report patient adherence. (*Nature Medicine* and other *Nature* journals ask that authors follow the CONSORT guidelines.)

According to Kenneth Schulz, lead author of the most recent CONSORT guidelines, excluding nonadherent patients can actually lead to biased results—ones that do not reflect how patients take their oral medications in the real world. This is also the FDA's rationale for using intent-to-treat analysis (ITT) to evaluate most RCTs. ITT incorporates all randomized patients regardless of whether they adhered to the study protocol, and the analysis is thought to mimic real-world effectiveness. This helps avoid reliance on self-reported adherence information from patients, which is usually "terrible," says Schulz, and never used. "Too many trial resources are devoted to monitoring adherence," he adds. However, his detractors point out that although ITT is the standard, if too many patients in the treatment arm are nonadherent, this can bias the results towards a negative outcome.

Ultimately, Kernan holds out hope that the scientific community—including researchers, funding and regulatory agencies and medical journal editors—will one day reach a consensus on both terminologies and standards for detailing drug adherence in RCTs. "Improved reporting of adherence will enhance the value of clinical trial research," he says, "and everyone would benefit from this development."

Anna Azvolinsky