Digitized Health Opens RWE Floodgates. Can Artificial Intelligence Harness the Power?

Apps and other digital health products could produce a massive amount of real-world evidence. But it may also take an abundance of AI to make sense of it all.

By **Thomas Reinke,** *Contributing Editor*

AI can help tackle the tough task of detecting disease progression in cancer, says John Doyle of IQVIA.

Digital health devices and artificial intelligence are creating new opportunities but also new challenges for real-world evidence. There's no question that health care is being increasingly digitized and that apps are now doing things people never imagined. In many cases interactions with smart devices are replacing face-to-face interactions with doctors. Artificial intelligence—which the FDA is regulating as a medical device—is making decisions formerly reserved for doctors. As these electronic devices take over many tasks and create new modes of health care, they are also sponging up vast amounts of patient information that can be rendered into real-world data.

Two years ago the FDA launched its Digital Health Innovation Action Plan to develop approaches for approving digital technologies. That program included partnering with nine leading companies working on digital health devices, including Pear Therapeutics, a company working on a digital addiction treatment. The FDA approved its Reset-O technology late last year. Billed as the first prescription digital therapeutic for patients with opioid use disorder, Pear says Reset-O applies the principles of the community reinforcement approach to deliver cognitive–behavioral therapy to opioid users.

Each therapy session comprises a CBT educational component and personal skill-building exercises. Therapy lessons are delivered primarily through text or audio and may include videos, animations, and graphics. The device provides a means for patients to self-report cravings and other events and the use or nonuse of buprenorphine. In its clinical trial, it significantly extended treatment and recovery from opioid use disorder.

One of the supposed virtues of digital health is that it will capture all kinds of patient-reported outcomes, more or less seamlessly, as part of its functionality. Reset-O fits this bill: It captures and reports specific patient responses or behaviors regarding drug cravings, addiction-related behaviors, and progress in day-to-day addiction self-management. These data far exceed the details of data gathered during therapy visits and recorded in medical records.

Artificial intelligence is creating another new frontier in real-world evidence gathering and analysis. AI's algorithms can approximate—and maybe even surpass—human cognition and judgment in the analysis of complex medical data. With all the tests that can be done and all the clinical variables that may come into play, a single patient can easily generate multiple gigabytes of data. The growing number of AI boosters say that we're not far away from AI rummaging through it all, arriving at diagnosis, and setting out a treatment strategy. Sure, humans will sign off, but AI software will do the heavy lifting. AI has great potential in diagnostic imaging, in particular, because of the high resolution of today's imaging tests.

Last year, the FDA approved an AI device to diagnose diabetic retinopathy. The technology, called IDx-DR, is software that analyzes images of the eye taken with a retinal camera. The images are uploaded to a cloud server and the AI algorithm compares the characteristics of the subject images with similar characteristics in a large reference database. It then provides a positive or negative determination about whether the patient has diabetic retinopathy. The FDA gave IDx-DR a breakthrough device designation that hastened its approval. It is the first autonomous AI system to provide a diagnostic decision without the need for a clinician to also interpret the results. The company says the device is usable by health care providers who may

not normally be involved in eye care. Human ophthalmologists would likely take exception to this simile, but IDx-DR is like a cloud-based ophthalmologist who comes to physician offices on demand.

Reset-O and IDx-DR were reviewed under the FDA's "de novo" premarket review pathway, which is part of a pilot program, the Digital Health Precertification (Pre-Cert) program, that streamlines the digital health device review process. The simplified review covers novel digital health technologies that the FDA has determined to be low to moderate risk as far as safety and effectiveness are concerned. However, to qualify for this pathway, companies must first submit to a thorough assessment by the FDA that they have the expertise and capability to develop safe and effective products. In January, the FDA announced plans to expand the Pre-Cert program to accommodate bringing more digital health products to market.

In yet another step to fuel digital health and real-world evidence, the FDA funded and worked with private industry to create the MyStudies App, an open-source code product designed to facilitate the input of real-world data directly by patients. The code is being released in two versions, one for Apple IOS devices and the other for Android devices. It can also be linked to other software packages that support traditional clinical trials, pragmatic trials, observational studies, and registries.

AI suited to oncology

Visions of how AI might transform health care aren't limited to new apps. By racing through detailed patient-specific information for large patient populations, AI could streamline identification of patients who are candidates for clinical trials. AI might also identify early risk factors for serious diseases by rapidly profiling detailed patient data for large populations.

Much of the early work with AI is in oncology. John Doyle, senior vice president at IQVIA, a contract research organization and the company created from the merger of Quintiles and IMS, says AI can help to tackle the tough task of detecting disease progression in cancer. Statistical regression techniques are often used. A potentially better approach, he says, is to use AI as an early identification tool to pinpoint risk factors associated with progression.

Nancy Dreyer, MD, the chief scientific officer for IQVIA's real-world and analytic solutions efforts, says AI may be used to tailor clinical guidelines. "Guidelines are often one size fits all; they fail to tailor their recommendations to specific subpopulations," she says. "AI has the potential to identify patient characteristics that call for variations in diagnosis and treatment recommendations."

Data quality issues

Despite all the enthusiasm about digital health and AI and the troves of real-world data they might produce, experts are still grappling with the fundamental question of how to ensure that real-world evidence is quality evidence. Insurance claim databases and EHRs remain the primary sources, and their limitations are well documented. Data from digital health devices are likely to present new and unique quality issues.

Experts are working through the issues. "In the last year there has been real progress in building consensus in three aspects of real-world data," says Jennifer Graff, vice president of comparative effectiveness research with the National Pharmaceutical Council. "The first is a basic definition of what RWE is and what it can and should do. The second is agreement that real-world data must be curated and collated to be transformed into evidence, and the third is agreement on standards for real-world evidence itself." There's been headway, but a lot more work needs to be done on standards for data and evidence, says Graff. She also sees considerable progress in the development of study designs for generating data and in the methods for analyzing it.

Dreyer agrees that one of the priorities with real-world data is promoting curation, but she but also mentions "data provenance," which includes considerations of how data elements were defined, where exactly the data came from, how they were collected, and how they are reported. One goal is to improve the consistency and reliability of databases. Dreyer says another is to develop a scalable database platform that can replicate the results of random controlled trials. This crosscheck would, in her view, result in a real step forward in evaluating the generalizability of RCTs and how products perform differently depending on the circumstance and patient population. **MC**

The consistency and reliability of databases must be improved for real-world and analytic solutions efforts, says Nancy Dreyer, MD, IQVIA's chief scientific officer.