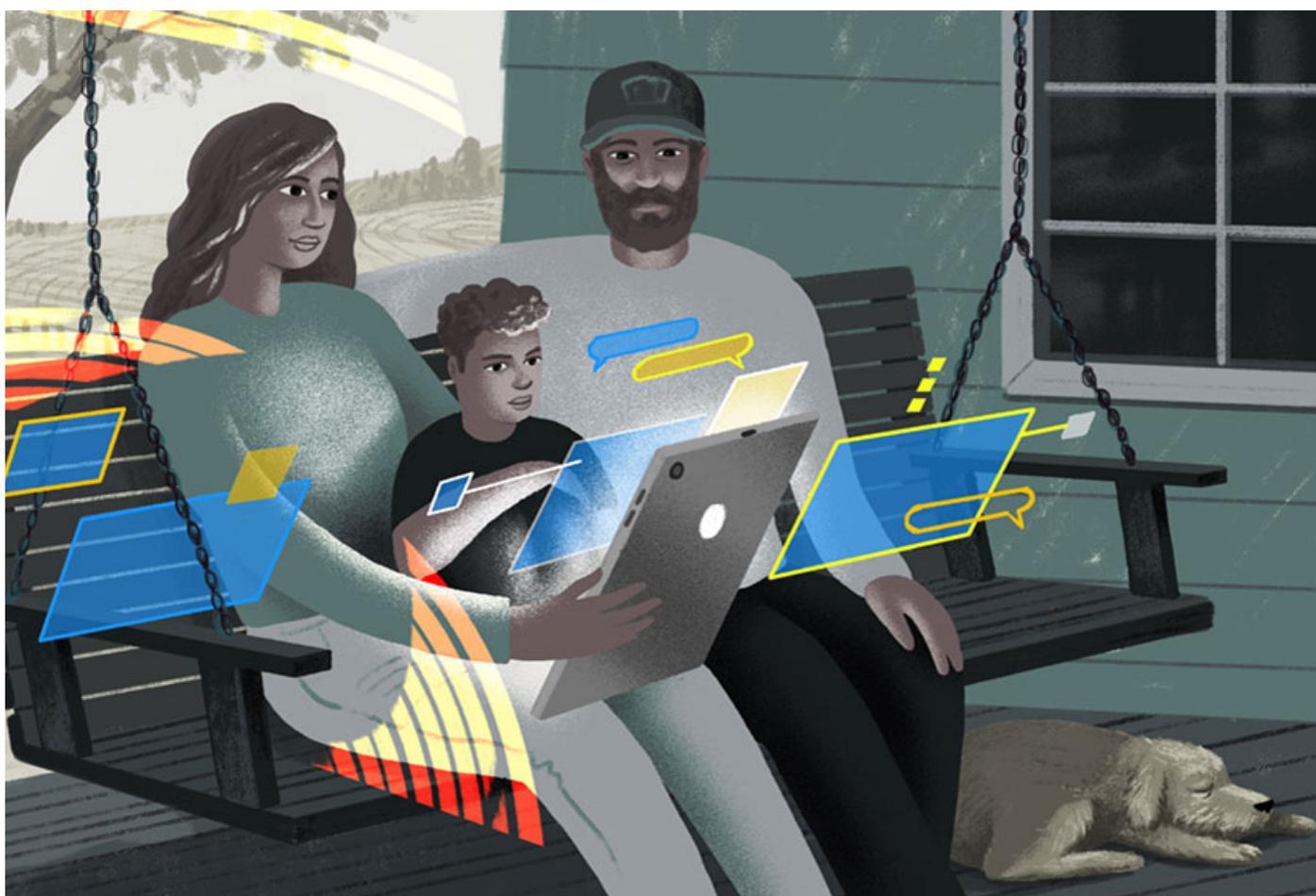


VIEWPOINT

Telehealth may enable remote participation in autism trials

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For many years, my colleagues and I have been studying a single-gene condition called **tuberous sclerosis complex** (TSC) that is strongly associated with autism and developmental challenges. We found in earlier studies that we could identify predictors of autism in the first year of life,

motivating the first randomized **clinical trial of early intervention** for these infants. However, we quickly realized that there were major barriers to the success of this trial.

Clinical trial readiness for neurodevelopmental conditions has largely been focused on defining meaningful endpoints, identifying **biomarkers** and developing strategies to mitigate the placebo response. However, these efforts prove futile if families cannot enroll in trials.

As we discovered with our TSC study, many families struggle to enroll in research studies and clinical trials because they do not have the time or the resources to participate, which in turn leads to underpowered studies with skewed samples. More importantly, it causes families to miss out on opportunities that could significantly benefit their child.

Telehealth has become much more integrated into standard medical care across various disciplines, and physicians are becoming more comfortable caring for people remotely. Some models, such as **Project ECHO**, are being designed to provide expert consultation to other clinicians.

I believe that with the right approach, telehealth technologies can also help families participate in research studies right from their homes.

Our experience with the TSC early-intervention trial is a good example of telehealth technologies' potential.

TSC is often diagnosed before or shortly after birth due to the presence of benign tumors in the brain and heart. More than half of people with TSC also have autism, and an even higher proportion have developmental delays.

Several years ago, my colleague **Charles Nelson** and I set out to identify the earliest signs of autism in infants with TSC, with the goal of improving early monitoring and detection. We found that by 12 months of age, infants later diagnosed with autism are already exhibiting delays in their nonverbal communication and cognitive skills. They also show differences in electroencephalography markers of brain function^{1,2,3}.

These early predictors necessitated a clinical trial of early behavioral intervention for these infants, and in 2017 we received funding from the U.S. National Institutes of Health to conduct our trial.

Unexpected burden:

The study involved weekly visits to either the University of California, Los Angeles or Boston Children's Hospital in Massachusetts for a parent-intervention training called Joint Attention Symbolic Play Engagement Regulation (**JASPER**), developed by my colleague **Connie Kasari**.

The trial received tremendous attention in the TSC community, and parents nationwide indicated their excitement about enrolling. For many of them, the trial represented the first access to a therapy designed specifically for autism, and often the first opportunity to access early behavioral intervention of any kind. We expected rapid enrollment and engagement.

Much to our surprise, after one full year of funding, we had enrolled only one family in Boston and two in Los Angeles. Another 20 families had contacted our team to indicate interest but ultimately did not enroll. We interviewed caregivers regarding barriers to enrollment and found that the major deterrent was access: They were unable to spend the time or financial resources to travel to the study sites for weekly sessions.

For many families, just the stress of taking an infant with developmental delay, **epilepsy** and other medical needs to a center for weekly intervention sessions was not only impractical but overly burdensome. One parent told us, “We are already traveling one to two times per month for his doctors’ appointments. If virtual ever becomes an option, we would be interested.”

That suggestion catalyzed a redesign of the study. We went back to the drawing board and sought guidance from experts in informatics and technology, and we transformed the study into a remote delivery design.

Parents visited the core site at entry for assessments and an in-person JASPER training. We then provided them with an iPad and instructions on its use for recording JASPER sessions. We sent a daily text message to encourage the parents to practice JASPER, even if only for five minutes, and we also collected data on study participation.

Once per week, we asked parents to record and upload a video of a JASPER session to a central server, and the therapists reviewed the session. The therapist and the caregiver then discussed the session and the following week’s module via video conference. Parents also completed weekly online questionnaires that tracked their child’s progress and their own experience with the intervention.

These modifications still seemed a bit antiquated, but given our limited resources and need for rapid modifications, this was the best that we could do.

And it worked. Within eight months of this redesign, our enrollment surged from 3 to 30 children, and it has continued to grow rapidly⁴.

Realistic solutions:

To consider this experience in a broader context, we know that more than 10 percent of autistic people have an identified genetic cause. As the clinical availability of genetic testing improves, we have opportunities to diagnose these genetic conditions much earlier in development, thus opening

the door for early monitoring and therapy well before clinical diagnoses are made.

I like to consider this early detection a key aspect of the ‘precision health’ movement, with precision referring not simply to targeted treatments, but also to more accurate and effective timing of diagnoses. This improved timing, in turn, can inform more developmentally appropriate, timely interventions.

However, as we learned from our TSC study, two key challenges may dampen our chances of fulfilling this goal.

First, each of these genetic conditions is individually rare, accounting for less than 1 percent of people with autism. And these families are spread across the world, not necessarily near tertiary medical centers or research facilities.

Second, these syndromes are often associated with more severe conditions, such as global developmental delay and epilepsy. These challenges fundamentally compromise families’ abilities to access research and treatment.

Telehealth can help with both challenges.

We must consider the need to maintain standardization when delivering interventions remotely and in working with families without access to, or comfort with, technology. Remote delivery also seems much more feasible with behavioral interventions, but what about with pharmacological treatments?

Ultimately, telehealth can help families get the support and care they need. As articulated by one of the families participating in our TSC trial: “We said when he got the diagnosis that we would go wherever and do whatever to give him the best chance, but the remote intervention was a life-changer for us.”

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