77 new-onset patients, a team led by Benaroya immunologists Alice Long and Peter Linsley probed gene expression profiles in the blood and identified a population of CD8-positive T cells, thought to be the cells that kill beta cells, with traits of exhaustion that increased in number among subjects who responded favorably to the therapy (*Sci. Immunol.* **1**, eaai7793, 2016).

For reasons that are not entirely clear, those T cells are more susceptible to teplizumab-induced activation than other immune subsets, Long explains. "Although [the antibody] hits all CD3 cells," she says, "what it modulates most are exhausted cells." The proliferation of those partially exhausted cells then creates a more tolerogenic immune landscape that safeguards beta cells from further attack.

Long thinks the same mechanism is likely operating in the pre-diagnosis setting as well—which would explain why teplizumab proved so efficacious in the recently published trial, where the median time to type 1 diabetes diagnosis was just over four years in the teplizumab group; in the placebo group, it was half that duration. Side effects were mild, without any EBV-related complications. "But," says Greenbaum, "we don't yet know whether there's something unique about this therapy as compared to other immune therapies."

Greenbaum and her fellow TrialNet investigators previously showed that oral insulin did not delay disease onset among autoantibody-positive relatives of people with type 1 diabetes. The group is now running prevention studies with two other immune-modulating drugs, the anti-malarial hydroxychloroquine and the cytotoxic T lymphocyte antigen 4 (CTLA-4) analog Orencia (abatacept), with plans to start two more trials—one involving anti-thymocyte globulin (a preparation of rabbit-derived anti-human T cell antibodies), the other with the CD20-targeted antibody rituximab and Orencia.

Janssen is also wrapping up a trial of its tumor necrosis factor-α blocker Simponi (golimumab), and several academic studies are looking at other putative beta cell–saving agents in at-risk individuals. These include a decades-old blood pressure medication called methyldopa, a concoction of probiotic bacterial strains, and the glucagon-like peptide-1 receptor agonist Victoza (liraglutide), commonly used to treat type 2 diabetes

Tiziana Life Sciences, headquartered in London, also has a fully human anti-CD3 antibody called foralumab that binds to the T cell receptor complex to modulate regulatory and effector T cells, and could be used in diabetes prevention. But according to CEO Kunwar Shailubhai, the company first plans to evaluate an oral formulation of foralumab in healthy volunteers before advancing the drug for non-alcoholic steatohepatitis, Crohn's disease and, if funding comes through from diabetes-focused non-profits, type 1 diabetes as well.

Any prophylaxis will ultimately only be as good as the screening effort used to find children positive for islet autoantibodies, though, and researchers are still "trying to figure out the best way to reach kids," says Kimber Simmons, a pediatric endocrinologist at the University of Colorado Barbara Davis Center for Diabetes in Aurora, who has helped screen over 20,000 children at doctors' offices, emergency rooms, urgent care centers, pop-up clinics and community health fairs over the past three years. And in Germany, a coalition of some 650 pediatricians from across Bavaria and Lower Saxony—led by Anette-Gabriele Ziegler, an endocrinologist at Helmholtz Zentrum München—have tested for autoantibodies in nearly 100,000 children over a similar time period.

Those kinds of population-wide screening efforts can help reduce life-threatening complications but ultimately falter because "we've never had [a preventative drug therapy] to actually offer kids," Simmons says. Should teplizumab enter the marketplace in 2021, as Provention hopes it will, "then we will be able to discuss screening more population-wide," says Helena Elding Larsson, a pediatric endocrinologist from Lund University in Sweden. ❐

Elie Dolgin
*Somerville, MA, USA*

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## DTC pharmacogenomics testing under scrutiny

Since last October, the FDA has been signaling to patients and healthcare providers to exercise caution when applying the results of direct-to-consumer (DTC) pharmacogenomics testing to prescribing drugs. That signal got stronger in April when the FDA sent a warning letter to the genomics testing lab Inova, instructing it to modify labeling and marketing materials for several pharmacogenomics tests. Now some genomics companies, among them Color, Genomind and OneOme, as well as the NIH-sponsored All of Us Program, report that they are in discussions with the FDA and in some cases have already modified their informational materials. The tests at issue are mostly lab-developed tests, which typically are exempt from regulatory review so long as the testing lab is CLIA certified. However, FDA has the right to revoke that exemption in cases where public safety is at issue. With DTC marketing of pharmacogenomics tests, the fear is that individuals will modify their drug use on their own. Whereas companies profess that the FDA is not clear on which tests it considers dubious, the agency appears to be drawing the line at tests not described in drug labels. So far, 23andme is the only DTC genomics testing company that has an approved pharmacogenomics test: its Personal Genome Service Pharmacogenetic Report tests for multiple variants in eight genes that affect the metabolism of some 50 drugs. Further confusing the issue, United HealthCare in August announced that it will cover panels of genetic test for guiding the use of drugs for major depression and other depressive disorders, although the American Psychiatric Association's research council last year concluded that the evidence for testing in those indications is not conclusive.

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"If I tell you I wasn't disappointed, then I would be lying to you. But I'm also willing to accept that there are certain situations in which there are limitations to the technology." Huang Yu, who paid $35,000 to the Chinese company Sinogene to clone his dead cat Garlic. The cat clone, the first produced in China, was missing a black patch on its chin that Garlic had. (*The New York Times*, 4 September 2019)

"Although none of our companies are working on germline therapy, when I talk to people not involved in the biotechnology business, one of the first questions I get is: 'Aren't you worried about designer babies?' I am spending more time on this kind of question than at any point in my career." Jim Burns, CEO of Casebia and cochair of the Alliance for Regenerative Medicine task force on gene editing. The group put out a statement in August that germline gene editing is currently inappropriate. (*Financial Times*, 26 August 2019)

"In a world without any discrimination, understanding human behavior is a noble goal, but we don't live in that world," said Steven Reilly, researcher and member of the LGBTQ steering group at the Broad Institute. The publication of the largest genetic study of same-sex sexual behavior by the Broad Institute raised the hackles of LGBTQ community, even from within the Broad itself. (*The New York Times*, 29 August 2019)