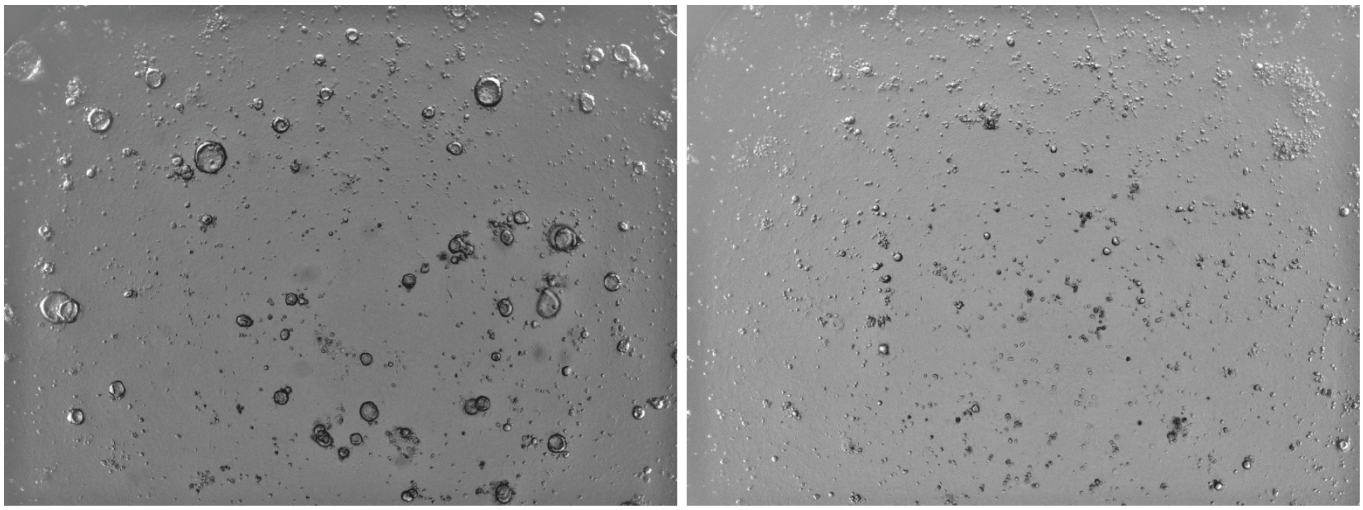

Herve Tiriac, Dannielle Engle, David Tuveson

Telling treatment: Organoids from pancreatic tumors before treatment (right) and after (left), showing tumor shrinkage.

of treatment. But translating these findings from an organoid to a patient in a trial, or making them part of regular practice, is not a current concern, Aguirre says. "We are optimistic that the approach has value, but we're really trying to prove to ourselves that the approach is feasible." Aguirre says that there is a possibility that tumors could evolve in response to first-line treatment; to account for this, his team performs biopsies in some patients after treatment to recreate organoids from these post-treatment tumors. However, he adds that given the rapid progression of pancreatic cancer and the fact that organoids cannot be grown and tested in a rapid enough timeframe to keep up with the cancer's progression, "we would still need to use pre-treatment organoids for pharmacologic testing in preparation for second-line therapy." In the future, however, expediting organoid growth and testing through technology development could enable researchers to interrogate the cultures after every round of treatment, he says.

Culture to clinic

Despite the excitement surrounding the use of organoids in the clinic, some scientists are pondering the potential obstacles of this brave new world of these cell structures. Boehm, who helped to establish the cell lines that Aguirre uses in his work, says that the field is headed toward an interesting regulatory future. "How do you regulate predictions made *ex vivo* to inform *in vivo* treatment?" he asks—especially when the 'diagnostic' is material derived from human tissue? Organizations pursuing this work will have to be certified by Clinical Laboratory Improvement Amendments in much the same way that genetic tests for tumors are currently, but there is little precedent when it comes to the approval of organoid-based tests. "The real challenge is figuring out the circumstances under which a clinician can use information from these tests," Boehm says. "There is a lot of enthusiasm and hope, and often with that hope comes some hype," he adds.

Much as with genetic-sequencing tests, those who are making clinical decisions on the basis of findings in organoids are running into issues with insurance reimbursement. In the Netherlands, where cystic fibrosis patients with rare mutations are responding to drugs that have not been approved for those specific disease-causing mutations, insurance companies have been hesitant to pay for these drugs, some of which cost $300,000 annually. In January this year, HUB and three Dutch insurance companies—CZ, Zilveren Kruis and Menzis—announced that they would be conducting a trial to validate the organoid-based testing that was used successfully to confirm Kalydeco as a potential treatment for van der Ent's 17-year-old patient two years ago. The goal, according to Clevers, is to help health insurers to decide whether to pay for drugs that proved effective for patients through this technique, and to avoid paying for unnecessary treatments. As *Nature Medicine* went to press, the trial had not yet begun. Clevers says that HUB is planning similar validation studies to help insurers determine whether to pay for certain cancer therapies.

Some think that the window during which organoids are tested with potential drugs could still be shortened. Rubin says that a feasible ideal would be 1–2 weeks from when a biopsy is conducted. Otherwise, only those without advanced disease really stand to benefit from organoid-based testing. Additionally, "the growth rates differ widely among patients," Clevers says. He also notes that, whereas some tumors can grow into organoids within a week or two, other slow-growing cancers, such as breast cancer, can take up to six months to become organoids, adding that the patient's genetics, the cancer type and the growth medium could all contribute to the varying speeds.

For those who are already utilizing organoids in the clinic, the benefits seem to far outweigh the challenges. "The process is always too long, but I think it's so innovative and life changing for patients," van der Ent says. He sees organoids as becoming even more important in the clinic as more drugs are developed. "Right now, we are only focused on patients with ultra-rare mutations," he says. "In the future, I think that the model will be much more helpful for a much bigger group of patients."

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Correction

In the June 2017 issue, the story "Biased for benefit: Stimulating the world's most popular drug targets with more nuance" (*Nat. Med.* **23**, 649–651, 2017) misspelled the name of Laura Bohn's postdoctoral advisor as Mark Caron. It should be spelled Marc Caron. The error has been corrected in the HTML and PDF versions of the article.

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