## **Title:** Correlation between patient-derived intestinal organoids and clinical responses to CFTR modulators in people with cystic fibrosis homozygous for F508del

**Lay Title:** Mini-guts help test responses to CFTR modulators in people with cystic fibrosis carrying F508del

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**What was your research question?**

We asked whether lab-grown “mini-guts” (patient-derived intestinal organoids) from people with cystic fibrosis carrying two F508del mutations could predict how well they would respond to CFTR modulator treatments.

**Why is this important?**

Cystic fibrosis treatments called modulators have greatly improved health and quality of life. But even patients with the same genetic mutation can respond differently. Finding ways to predict who benefits most is vital for tailoring treatments and avoiding unnecessary therapies. Mini-guts, which carry a patient’s own genetic code, are a promising tool to test drug responses outside the body. If they can reliably reflect real-life improvements, they could help guide treatment choices and make personalized medicine a reality for people with cystic fibrosis.

**What did you do?**

We studied 60 people with cystic fibrosis who had two copies of the F508del mutation. From rectal biopsies, we grew mini-guts in the lab and measured how much they swelled when exposed to modulator drugs (a sign of drug effectiveness). We compared the 15 highest and 15 lowest lab responders with patients’ real-world health outcomes after treatment, including lung function, sweat salt levels, weight, and number of lung infections. We also checked whether tiny genetic differences or patterns in gene activity explained differences in drug response.

**What did you find?**

Patients’ mini-guts responded more strongly to the triple drug combination (elexacaftor/tezacaftor/ivacaftor) than to the dual combination (tezacaftor/ivacaftor). When looking at all patients together, the size of the mini-gut response matched improvements in sweat salt levels and lung function. However, when comparing only the highest and lowest responders, differences in actual patient outcomes were not clear. Genetic variations and gene activity did not explain why some mini-guts responded more than others.

**What does this mean and reasons for caution?**

Mini-guts can reliably show whether a person with cystic fibrosis is likely to respond to CFTR modulators. However, the size of the response in the lab does not always match the size of the clinical improvements seen in all measures, such as lung function, weight, or infection rates. This suggests that while organoids are strong tools for identifying responders, other factors; like age, drug handling in the body, or pre-existing lung damage, may influence how much benefit each person experiences. More research is needed to understand these differences and improve how lab results translate into real-world outcomes.

**What’s next?**

Future studies will test larger patient groups, use improved lab methods, and combine mini-gut results with other patient data to better predict individual treatment benefits.

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