New prognostic test could enable personalised treatment of inflammatory bowel disease

May 2 2019

Scientists at the University of Cambridge have developed a new test that can reliably predict the future course of inflammatory bowel disease in individuals, transforming treatments for patients and paving the way for a personalised approach.

Ulcerative colitis and Crohn's disease—collectively known as inflammatory bowel disease (IBD) - are chronic conditions that involve inflammation of the gut. Symptoms include abdominal pain, bloody diarrhoea, weight loss and fatigue. There is currently no cure, but there are a growing number of medicines that aim to relieve symptoms and prevent the condition returning; however, the more severe the case of the IBD, the stronger the drugs need to be and the greater the potential side effects.

Researchers at the Department of Medicine, University of Cambridge, and Cambridge University Hospitals NHS Trust previously showed that a genetic signature found in a certain type of immune cell known as a CD8 T-cell could be used to assign patients to one of two groups depending on whether their condition was likely to be mild or severe (requiring repeated treatment). However, isolating CD8 T- cells and obtaining the genetic signature was not straightforward, making the test unlikely to be scaleable and achieve widespread use.

In the latest study, published in the journal *Gut*, the researchers worked with a cohort of 69 patients with Crohn's disease to see whether it was possible to develop a useful, scaleable test by looking at whole blood

samples in conjunction with CD8 T-cells and using widely-available technology.

The team used a combination of machine learning and a whole blood assay known as qPCR—a relatively simple tool used in NHS labs across the country—to identify genetic signatures that re-created the two subgroups from their previous study.

The researchers then validated their findings in 123 IBD patients recruited from clinics in Cambridge, Nottingham, Exeter and London.

"Using simple technology that is available in almost every hospital, our test looks for a biomarker—essentially, a medical signature—to identify which patients are likely to have mild IBD and which ones will have more serious illness," says Dr. James Lee, joint first author of the study.

"This is important as it could enable doctors to personalise the treatment that they give to each patient. If an individual is likely to have only mild disease, they don't want to be taking strong drugs with unpleasant side-effects. But similarly, if someone is likely to have a more aggressive form of the disease, then the evidence suggests that the sooner we can start them on the best available treatments, the better we can manage their condition."

The accuracy of the test is comparable to similar biomarkers used in cancer, which have helped transform treatment, say the researchers. They found the new test was 90-100% accurate in correctly identifying patients who did not require multiple treatments.

"IBD can be a very debilitating disease, but this new test could help us transform treatment options, moving away from a 'one size fits all' approach to a personalised approach to treating patients," says Professor Ken Smith, senior author and Head of the Department of Medicine.

The test is now being developed further by PredictImmune, a spinout company co-founded by Professor Smith with support from Cambridge Enterprise, the University's technology transfer arm. The team is involved in a £4.2 million trial to see whether using the biomarker to guide treatment at the time of diagnosis can lead to better outcomes for patients.

The findings have been welcomed by Helen Terry, Director of Research at Crohn's & Colitis UK, which helps fund the research. "It's really exciting that we are moving away from a 'one size fits all' approach for people with Crohn's or Colitis. Dr. Lee and his team's latest study is the accumulation of 10 years' worth of research and we're now at the stage where this test will be available in the NHS. This could drastically change the lives of people with Crohn's or Colitis as it means they can be started on the best medication for them sooner."

Additional funding for the research came from Wellcome, the Medical Research Council and the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre.

Later this year, Professor Smith and his team are due to move into the new Cambridge Institute of Therapeutic Immunology and Infectious Disease, to be based in the Jeffrey Cheah Biomedical Centre on the Cambridge Biomedical Campus, the centrepiece of the largest biotech cluster outside the United States.

Case study: Kate Gray, aged 31, Amersham, living with Crohn's

Kate was diagnosed with Crohn's Disease when she was 14 years old having been unwell with symptoms for quite some time.

This meant she needed surgery. "I was told by my consultant I would only need a little bit of a resection and that it's unlikely I would be

bothered by symptoms for decades, giving me the impression that was probably the end of it."

Within 9 months of her bowel resection, Kate's symptoms had returned. She tried various medications, including immunosuppressants and steroids but nothing worked, and she kept getting more unwell. She also had some nasty side effects from the drug mercaptopurine, becoming neutropaenic (low on neutrophils), leading to two admissions to hospital.

This pathway continued throughout Kate's secondary education and once on the drug infliximab, it reached the point where Kate couldn't eat solid foods. Her bowel was so strictured and damaged that she was told she needed an ileostomy at the age of 20. In the lead-up to this Kate had a nasal-gastric feeding tube which involved long stints in hospital.

When Kate woke up from her operation, she was told that the damage was much more extensive than thought and she would have a permanent stoma.

Following surgery, Kate was started on the biologic drug, Humira and has been on this weekly ever since. "My stoma's been amazing and bowel wise, my symptoms have been good for the past decade."

Kate could have benefited hugely from a prognostic test, making her more aware of disease course and allowing her to try stronger treatments earlier.

"I do sometimes wonder what would have happened if I knew my disease was going to be more severe and not mild, as I was told. It's likely I would have opted for my ileostomy sooner and would have been keen to try stronger drugs earlier as this might have halted to progression of my Crohn's. It would also have been good to have known what other symptoms I could have expected with more severe Crohn's, including

issues with my joints, uveitis and Crohn's on the skin at the site of my surgery scars."

More information: Daniele Biasci et al, A blood-based prognostic biomarker in IBD, *Gut* (2019). DOI: 10.1136/gutjnl-2019-318343

Provided by University of Cambridge