Predicting outcomes for Crohn’s disease using a molecular biomarker: profile trial

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Introduction
Crohn’s disease (CD) and ulcerative colitis (UC), the two major forms of inflammatory bowel disease (IBD), collectively affect 0.8% of the population in the UK. IBD can have a profound health and socio-economic impact on patients, typically affecting educational achievement, relationships and employment. However, the course of IBD varies substantially between individuals and accurate prognostic markers have historically not been available to guide clinical practice. It has, therefore, become widely recognised that no single treatment strategy would be optimal for all patients. Accordingly, there has been an aspiration for a more personalised approach in IBD, being named one of the key research priorities by a research priority-setting partnership group, which included patients, clinicians and other key stakeholders. Previously, our group has described a transcriptional signature detectable within peripheral blood CD8 T-cells at diagnosis, identifying two subgroups of patients, correlating with subsequent disease course. We have sought to develop a biomarker that could re-capitulate the previously identified prognostic CD8 subgroups and then assess whether such a biomarker could improve clinical outcomes by appropriately matching therapy to disease course for individual patients.

Methods
From a training cohort of 69 newly diagnosed IBD patients, we simultaneously obtained a whole-blood PAXgene® RNA tube and peripheral-blood CD8 T-cell sample. Gene expression in both samples was measured by microarray. Statistical modelling was used to identify a transcriptional classifier in whole-blood gene expression data re-capitulating the CD8 findings and optimised into a multi-gene qPCR assay with independent validation in a second, independent cohort of 123 newly diagnosed patients. The PROFILE trial has incorporated this classifier to compare treatment escalation (hazard ratio 2.65 (CD) and 3.12 (UC)). A classifier that predicts disease course from diagnosis in patients with newly diagnosed Crohn’s disease has consistently been reported as important to patients: clinical remission and avoidance/reduction of steroids and surgery, as well as quality of life. Alongside the trial, a formal health economic analysis is being conducted, as well as a national evaluation by the National Institute for Health and Care Excellence (NICE). If clinical utility is demonstrated, then it is anticipated that this biomarker-stratified approach could be implemented into routine clinical care.

Results
Following application of statistical learning methods described, a 17-gene qPCR assay was developed and optimised. In the validation cohort, 123 patients could be classified into two distinct subgroups: IBD (high risk) and IBD (lower risk). Irrespective of the underlying diagnosis, IBD patients experienced significantly more aggressive disease than IBD patients, with earlier need for treatment escalation (hazard ratio 2.65 (CD) and 3.12 (UC)). Subsequently, this biomarker has been used to stratify therapy in the PROFILE trial (395 enrolled), where recruitment has completed and follow-up due for completion in December 2022.

Conclusion
We have developed, optimised and validated a whole-blood qPCR classifier that predicts disease course from diagnosis in patients with IBD. This classifier is currently being assessed in the PROFILE trial, the first biomarker-stratified trial in gastroenterology and, if clinical utility of a stratified treatment approach is demonstrated, this would represent a major step towards personalised therapy in IBD.

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References
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