Prognostic biomarkers to identify patients likely to develop severe Crohn’s disease: a systematic review

Steve Halligan,1* Darren Boone,1 Lucinda Archer,2 Tariq Ahmad,3 Stuart Bloom,4 Manuel Rodriguez-Justo,5 Stuart A Taylor1 and Sue Mallett1

1Centre for Medical Imaging, University College London, London, UK
2Centre for Prognosis Research, School of Primary, Community and Social Care, Keele University, Keele, UK
3Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
4Department of Gastroenterology, University College Hospital, London, UK
5Department of Histopathology, University College Hospital, London, UK

*Corresponding author s.halligan@ucl.ac.uk

Declared competing interests of authors: Sue Mallett reports grants from the University of Birmingham during the conduct of the study and a National Institute for Health Research (NIHR)-funded grant, METRIC EF (NIHR Award ID 15/59/17; https://fundingawards.nihr.ac.uk/award/15/59/17), outside the submitted work. Sue Mallett was also funded by the NIHR Birmingham Biomedical Research Centre. Tariq Ahmad reports grants and personal fees from AbbVie, Inc. (North Chicago, IL, USA), Celltrion (Incheon, Republic of Korea) and Celgene Corporation (Summit, NJ, USA), and personal fees from Takeda Pharmaceutical Company (Tokyo, Japan) and Pfizer, Inc. (New York, NY, USA) outside the submitted work. Stuart A Taylor reports personal fees from Alimentiv Inc. (London, ON, Canada) outside the submitted work. Steve Halligan reports grants from the NIHR Health Technology Assessment programme outside the submitted work during the conduct of the study. Stuart A Taylor, Manuel Rodriguez-Justo and Steve Halligan were also supported by the NIHR University College London Hospitals Biomedical Research Centre. Lucinda Archer was funded by the UK NIHR Research Methods Fellowship.

Published July 2021
DOI: 10.3310/hta25450

Plain English summary

Prognostic biomarkers to identify severe Crohn’s disease

Health Technology Assessment 2021; Vol. 25: No. 45
DOI: 10.3310/hta25450

NIHR Journals Library www.journalslibrary.nihr.ac.uk
Crohn’s disease causes inflammation of the intestines. Traditional treatment uses drugs, such as steroids, at a gradually increasing dose as symptoms worsen. Newer ‘biological’ drugs may stop disease, but are not used as an early treatment because they are expensive and have serious side effects. Using biologics early means knowing which patients will develop severe disease in the future.

A ‘prognostic biomarker’ is a measurement made on a patient that predicts a future outcome. A lot of research has attempted to identify biomarkers that predict severe Crohn’s disease, but research is haphazard and of variable quality. We therefore carried out a ‘systematic review’, which identifies research in a comprehensive and unbiased fashion. We found nearly 30,000 research papers, 71 of which were acceptable quality and described 56 groups of Crohn’s disease patients. We then used a statistical method called ‘meta-analysis’ to combine results from multiple studies. This allowed us to identify the most promising biomarkers to predict future severe disease. We found five clinical biomarkers (e.g. age and smoking), two blood biomarkers and one genetic biomarker that seemed reasonably able to predict future severe Crohn’s disease.

However, we also found that most research was poorly performed and frequently confused diagnosis (current disease) with prognosis (future disease). Some commonly used biomarkers were not sufficiently investigated. We were surprised to identify so few prognostic biomarkers in the face of a seemingly vast amount of research.

Future research should be better conducted and not confuse diagnosis with prognosis. We will use statistical methods to combine the promising biomarkers that we identified into a ‘prognostic model’, which is a mathematical formula that provides the likelihood of developing severe disease in the future. We will then test how well this works by using patient data from existing Crohn’s disease databases.
Criteria for inclusion in the Health Technology Assessment journal

Reports are published in Health Technology Assessment (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 14/210/07. The contractual start date was in April 2016. The draft report began editorial review in October 2019 and was accepted for publication in October 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

© Queen’s Printer and Controller of HMSO 2021. This work was produced by Halligan et al. under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
NIHR Journals Library Editor-in-Chief

**Professor Ken Stein**  Professor of Public Health, University of Exeter Medical School, UK

NIHR Journals Library Editors

**Professor John Powell**  Chair of HTA and EME Editorial Board and Editor-in-Chief of HTA and EME journals. Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK, and Professor of Digital Health Care, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

**Professor Andréé Le May**  Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals) and Editor-in-Chief of HS&DR, PGfAR, PHR journals

**Professor Matthias Beck**  Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

**Dr Tessa Crilly**  Director, Crystal Blue Consulting Ltd, UK

**Dr Eugenia Cronin**  Senior Scientific Advisor, Wessex Institute, UK

**Dr Peter Davidson**  Consultant Advisor, Wessex Institute, University of Southampton, UK

**Ms Tara Lamont**  Senior Scientific Adviser (Evidence Use), Wessex Institute, University of Southampton, UK

**Dr Catriona McDaid**  Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

**Professor William McGuire**  Professor of Child Health, Hull York Medical School, University of York, UK

**Professor Geoffrey Meads**  Emeritus Professor of Wellbeing Research, University of Winchester, UK

**Professor James Raftery**  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

**Dr Rob Riemsma**  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

**Professor Helen Roberts**  Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

**Professor Jonathan Ross**  Professor of Sexual Health and HIV, University Hospital Birmingham, UK

**Professor Helen Snooks**  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

**Professor Ken Stein**  Professor of Public Health, University of Exeter Medical School, UK

**Professor Jim Thornton**  Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

**Editorial contact:** journals.library@nihr.ac.uk