

## Supplementary Information

### Details of individual participating IBD cohorts

**REMIND Network** – Prospective cohort of CD patients (NCT03458195) included at time of ileocolonic resection, recruited in 15 centers from the REMIND network. Extensive biobanking at surgery and post-operative endoscopy. The aims are to identify predictors of post-operative endoscopic recurrence, and to better understand the pathophysiology of recurrence.

**CCIM German cohort** – Cohort was recruited through the Comprehensive Center for Inflammation Medicine (CCIM) of the University Hospital. Tertiary referral center with an IBD ambulance.

**SPARC IBD** – Study of a Prospective Adult Research Cohort with IBD – is a multicentered longitudinal study of adult IBD patients. The goal of the study is to find predictors of response to therapy and predictors of relapse that will lead to precision medicine strategies and new therapeutic targets that will improve the quality of life of patients with IBD. Data and biosamples are used for basic, clinical, and translational research.

**Belgium IBD ULG** – IBD clinics, Erasme hospital, Brussels, Belgium (2800 IBD patients, 650 patients on biologics) within the Belgium IBD Consortium together with the IBD clinical and research groups of ULG, ULB and ULiège.

**The Miami cohort** – made up of IBD patients from both an academic Crohn's and colitis referral center (the University of Miami Crohn's and Colitis Center) and a large, community-based practice (GastroHealth) in South Florida.

**The MIRIAD Biorepository** – Cedars-Sinai recruits adult and pediatric IBD patients who attend the IBD Centers at Cedars-Sinai as well as through collaborators across the world (particularly East Asia). Both adult and pediatric subjects are recruited and while the majority of subjects are of Northern European and Ashkenazi Jewish emphasis on African-American and Hispanic recruitment (the latter through a collaboration with the University of Puerto Rico).

**The Nurses' Health Studies** – NHS is among the largest prospective investigations into the risk factors for major chronic diseases in women.

**FINRISK** – The population-based FINRISK study has been followed up for IBD and other disease end-points using annual record linkage with the Finnish National Hospital Discharge Register, the National Causes-of-Death Register and the National Drug Reimbursement Register. Controls were chosen to have a high polygenic risk score for IBD without an IBD diagnosis. A detailed description of the FINRISK cohort can be found at Borodulin et al.

**NIDDK IBD Genetics Consortium** – The NIDDK Inflammatory Bowel Disease Genetics Consortium (IBDGC) was created in 2002 by the National Institute of Diabetes, Digestive and Kidney diseases (NIDDK) to advance knowledge on the inflammatory bowel diseases, specifically Crohn's Disease and Ulcerative Colitis. The Consortium consists of six genetic research centers (GRC) and a data coordinating center (DCC) that prospectively recruits a combination of cases, controls, and trios to gather a large collection of samples and linked phenotype information. DNA samples are used to conduct genetic linkage and association studies. For more information please see <https://ibdgc.org/>

**NIDDK-Quebec** – a cohort of Crohn's disease patients, and healthy controls (spouses and/or "best friend") recruited in the Province of Quebec, Canada as part of the activities of the Montreal-Boston Genetic Research Center (GRC, Rioux is PI), one of six GRCs of the NIDDK-funded IBD Genetics Consortium (<https://ibdgc.uchicago.edu/grc/montreal/>). Patients and controls were recruited at university-based hospitals throughout the province by gastroenterologists specializing in IBD that formed the Quebec IBD Genetics Consortium. For more information please see <https://www.medgeni.org/projects/qibdgc>

**Genome Quebec-GENIZON** – a cohort of Crohn's disease patients, and healthy controls, of French Canadian origin recruited in the Province of Quebec, Canada. Previously collected by Genizon Biosciences Inc. but now part of a public biobank overseen by G enome Qu ebec. For more information please visit: <https://www.genomequebec.com/genizon-biobank/>

**Belgium IBD Leuven center** – a tertiary referral center for IBD. Annually 3.000 patients are followed up in the clinic (2/3 are CD and 1/3 is UC). Patients are recruited via the IBD clinic to participate in the research on IBD by providing biomaterials and clinical data, stored in the electronic clinical records (KWS or Clinical Working Station) to the IBD Biobank (CCare, PI: S everine Vermeire, EC approval). Controls are also recruited into CCare as healthy spouses of the included patients and through advertisements on campus. IBD Leuven is part of the Belgian IBD Genetics Consortium, together with the IBD clinical and research groups of ULG, ULB and ULi ege.

**MGH Pediatric Inflammatory Bowel Disease Center** – a collection that provides care for children and adolescents with inflammatory bowel diseases (ulcerative colitis, indeterminate colitis, and crohn's disease).

**PRISM (Prospective Registry in IBD Study at MGH)** – a registry that includes more than 3,000 enrolled IBD patients and healthy controlled individuals.

**SHARE** – Investigators from seven major IBD centers formed the Sinai Helmsley Alliance for Research Excellence (SHARE) in 2010 to integrate information from basic science, epidemiology and information sciences to advance IBD research across multiple high-volume centers.

**Epi25 Controls** – is a collaboration of more than 200 partners from over 50 research cohorts from around the world to investigate the genetics of epilepsy. Whole exome sequencing data from the following Epi25 cohorts were included in these analyses: Germany: Bonn; Germany: Kiel; Germany: Tuebingen; Germany: Leipzig; Ireland: Dublin; USA: Philadelphia/CHOP; USA: EPGP; USA: Human Epilepsy Project; and USA: Penn/CHOP. Detailed descriptions of the cohorts, study PIs and teams, and local acknowledgements can be found in Epi25 Collaborative, AJHG, 2021. (<https://pubmed.ncbi.nlm.nih.gov/33932343/>)

**UK-IRL-UCL Controls** – samples were extracted from EBV transformed peripheral blood lymphocytes from unscreened healthy British blood donors and from whole blood samples from healthy volunteers of UK or Irish ancestry.

**MIGEN-Leicester Controls** – cases were ascertained from two studies: (i) the British Heart Foundation Family Heart Study and (ii) the BRICCS Study. Control subjects were ascertained from the control subjects being recruited as part of the UK Aneurysm Growth Study (UKAGS). All exome sequencing was performed at the Broad Institute of Harvard and MIT; sample sequence capture was performed using Illumina's ICE Capture reagent and sequencing was performed on an Illumina HiSeq 2000 or 2500.

**MIGEN-Ottawa Controls** – The Ottawa Heart Study is a cross-sectional case-control study designed to identify genes that predispose to angiographically defined coronary artery disease. All exome sequencing was performed at the Broad Institute of Harvard and MIT; sample sequence capture was performed using Agilent SureSelect Human All Exon Kit v2 and sequencing was performed on an Illumina HiSeq 2000 or 2500.

**ASC-NIMH Controls** – The ARRA Autism Sequencing Collaboration was created in 2010 bringing together an expert large-scale sequencing center and a collaborative network of research labs focused on the genetics of autism. These groups worked together to utilize dramatic new advances in DNA sequencing technology to reveal the genetic architecture of autism through comprehensive examination of the exome sequence of all genes. The Autism Sequencing Consortium (ASC) was founded by Joseph D. Buxbaum and colleagues as an international group of scientists who share autism spectrum disorder (ASD) samples and genetic data.

### **Supplemental acknowledgments of participating consortia and programs**

Additional funding sources and acknowledgment of individual cohorts are as follows: We acknowledge the **Crohn's & Colitis Foundation's IBD Plexus Program** — the results published here are in part based on data obtained from the IBD Plexus program of the Crohn's & Colitis Foundation. We acknowledge the contribution of the **Oxford IBD cohort study** and the **Oxford GI biobank**, which are supported by the NIHR Oxford Biomedical Research Centre. **The Belgium Consortium** would like to acknowledge individual study support from FNRS (Fond National de la Recherche Scientifique, Belgium), funding from H2020 (SYSCID), FNRS (EOS N°30770923 / PDRs N° T.0190.19 and T.0096.19 / CDR N°J.0173.18) and Welbio

(COSIBD) and Myriam Mni, Emilie Théâtre, François Crins, Julia Dmitrieva, Valérie Deffontaine, Yukihide Momozawa and GIGA-Genomics core facility for assistance and technical assistance. **The Canadian IMAGINE cohort** acknowledges the Charles Wolfson Charitable Trust and the Canadian Institute for Health Research Grants SPOR-RN279389–358033. **The German CCIM cohort** acknowledges the German Excellence Initiative EXC 2167 and IMI Programm of the EU ("3TR"), and the European Regional Development Fund 01.2.2-LMT-K-718-04-0003. The **German IBD Consortium** would like to acknowledge the CCIM that receives infrastructure support from the DFG Cluster of Excellence "Precision Medicine in Chronic Inflammation" (PMI). **The Cedars-Sinai IBD study** was supported by the Cedars-Sinai MIRIAD IBD Biobank. The MIRIAD IBD Biobank receives funding from the Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute, NIDDK grants P01DK046763 and U01DK062413, and The Leona M. and Harry B. Helmsley Charitable Trust. The **SHARE consortium** would like to acknowledge The Leona M. and Harry B. Helmsley Charitable Trust. The **SPARC IBD Network** acknowledges that the results published here are in part based on data obtained from the IBD Plexus program of the Crohn's & Colitis Foundation. The **Miami cohort** was supported by the National Institute of Diabetes and Digestive and Kidney Disease Grant (R01DK104844). The **FINRISK controls** were part of the FINRISK studies supported by THL (formerly KTL: National Public Health Institute) through budgetary funds from the government, with additional funding from institutions such as the Academy of Finland, the European Union, ministries and national and international foundations and societies to support specific research purposes. The **UK-IRL Controls** were collected and sequenced with support from the Neuroscience Research Charitable Trust, the Central London NHS (National Health Service) Blood Transfusion Service and the National Institute of Health Research (NIHR) funded Mental Health Research Network. Whole exome sequencing of samples in the **Epi25 Collaborative** was done by the Broad Institute Genomics Platform and was supported by the NHGRI Centers for Common Disease Genomics Genomics (CCDG) grant (UM1HG008895) and the Stanley Center for Psychiatric Research. The **ASC-NIMH-Controls** cohort was first supported by a cooperative agreement grant to four lead sites funded by the National Institute of Mental Health (U01MH100233, U01MH100209, U01MH100229, U01MH100239), and renewed NIMH grants (U01MH111661, U01MH111660, U01MH111658 and U01MH111662), with additional support from the National Human Genome Research Institute through the Broad Center for Common Disease Genomics (UM1HG008895, Mark Daly, PI).

This research has been conducted using the UK Biobank Resource under application number 45669.

Participants in the **INTERVAL** randomized controlled trial were recruited with the active collaboration of NHS Blood and Transplant England ([www.nhsbt.nhs.uk](http://www.nhsbt.nhs.uk) [[nhsbt.nhs.uk](http://www.nhsbt.nhs.uk)]), which has supported field work and other elements of the trial. We thank Klaudia Walter and Kousik Kundu for help with INTERVAL WGS quality control. DNA extraction and genotyping were co-funded by the National Institute for Health Research (NIHR), the NIHR BioResource (<http://bioresource.nihr.ac.uk> [[bioresource.nihr.ac.uk](http://bioresource.nihr.ac.uk)]) and the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014) [\*]. This research was supported by the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014) and NIHR Newcastle Biomedical Research

Centre [BRC-1215-20001]. Sequencing was supported by the Wellcome Trust grant number 206194. The academic coordinating centre for INTERVAL was supported by core funding from the: NIHR Blood and Transplant Research Unit in Donor Health and Genomics (NIHR BTRU-2014-10024), UK Medical Research Council (MR/L003120/1), British Heart Foundation (SP/09/002; RG/13/13/30194; RG/18/13/33946) and NIHR Cambridge BRC (BRC-1215-20014) [\*]. A complete list of the investigators and contributors to the INTERVAL trial is provided in reference [\*\*]. The academic coordinating centre would like to thank blood donor centre staff and blood donors for participating in the INTERVAL trial.

This work was supported by Health Data Research UK, which is funded by the UK Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation and Wellcome.

\*The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

\*\*Di Angelantonio E, Thompson SG, Kaptoge SK, Moore C, Walker M, Armitage J, Ouwehand WH, Roberts DJ, Danesh J, INTERVAL Trial Group. Efficiency and safety of varying the frequency of whole blood donation (INTERVAL): a randomized trial of 45 000 donors. *Lancet*. 2017 Nov 25;390(10110):2360-2371.

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