Predictive models comprising combinations of clinical parameters, blood results, and endoscopy findings were ranked by AIC with a final model selected with an emphasis on simplicity and ease of implementation. This model was validated in 110 patients admitted to GCUH, Australia between 2015-20 and 62 patients admitted to AIIMS, India between 2015-8. The Oxford cohort were compared with data from the same unit in 1992-3 (Travis et al, Gut 1996; 38: 905-10).

Results Admission CRP, albumin, and UCEIS scores predicted steroid non-response at day 3 (FDR $p=0.00066$, 0.0066 , and 0.015). A 4-point model was developed involving CRP $\geq 100\text{mg/L}$, albumin $\leq 25\text{g/L}$, UCEIS ≥ 4 , or ≥ 7 . Scoring 0 or 4 was 100% accurate in all cohorts. 19.5% of patients scored 3 or 4 of whom 83% in Oxford, 85% in GCUH and 80% in AIIMS failed steroid treatment. In the combined validation cohorts the PPV for steroid failure was 0.84 (0.70-0.98), OR 11.9 (10.8-13), with the number needed to screen 8.2 (5.8-13.7).

In the current Oxford cohort 54% of patients received rescue therapy (27% ciclosporin, 27% anti-TNF), increased from 27% ciclosporin in 1992-3, $p=0.0015$. Colectomy during admission halved (15% vs 29%, $p=0.033$), but an eight-fold increased risk of colectomy in the following year is still seen after a partial steroid response.

Conclusions Our model identifies on admission a subset of patients very unlikely to respond to steroid treatment and allows stratification for early intensification of management. In 25 years colectomy rates for ASC have halved while second-line therapy use has doubled. Long-term outcomes remain poorer in patients who do not clearly respond to steroids.

OMO-1 EPIGENETIC ALTERATIONS IN IBD: DEFINING GEOGRAPHICAL, GENETIC, AND IMMUNE-INFLAMMATORY INFLUENCES ON THE CIRCULATING METHYLOME

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Introduction DNA methylation may provide critical insights into gene-environment interactions in inflammatory bowel disease (IBD).

Methods Using the multi-centre IBD Character inception cohort (295 controls, 154 CD, 161 UC, 28 IBD-U), epigenome-wide methylation was profiled using Illumina Human-Methylation450 platform. Differentially methylated position analysis was performed using age, sex and cell proportions as covariates. Integration of paired genomic and transcriptomic layers was done with Multi-Omics Factor Analysis v2 (MOFA). Unsupervised principal component analyses were performed to examine correlates of treatment escalation and clinical predictors of disease severity.

Results We report 137 differentially methylated positions (DMP) in whole blood in IBD, including *VMP1/MIR21* ($p=9.11\times 10^{-15}$) and *RPS6KA2* (6.43×10^{-13}); with consistency seen across Scandinavia and UK. Cell of origin analysis preferentially implicated the monocyte lineage. Dysregulated loci demonstrate strong genetic influence, notably *VMP1* ($p=1.53\times 10^{-15}$). Age acceleration is seen in IBD (coefficient 0.94, $p<2.2\times 10^{-16}$). Several immuno-active genes demonstrated highly significant correlations between methylation and gene expression in IBD, in particular *OSM*: IBD $r=-0.32$, $p=3.64\times 10^{-7}$ vs. non-IBD $r=-0.14$, $p=0.77$). Multi-omic integration of methylome, genome and transcriptome also identified specific pathways that associate with immune activation, response and regulation at disease inception. At follow up, a signature of 3 DMPs (*TAP1*, *TESPA1*, *RPTOR*) associated with treatment escalation to biological agents or surgery (hazard ratio of 5.19 (CI:2.14-12.56, logrank $p=9.70\times 10^{-4}$)).

Conclusion This study highlights the stability of the IBD-specific circulating methylome across regions with shared ancestry. Through integrative multi-omic analyses we identify key pro-inflammatory genes that are upregulated in IBD at inception. Furthermore, differential methylation within certain genes such as *TAP1* associate with disease course over time.

OMO-2 FILGOTINIB EFFICACY IN PATIENTS WITH ULCERATIVE COLITIS BY LINE OF THERAPY: PHASE 2B/3 SELECTION RESULTS

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Introduction Filgotinib (FIL) is a once-daily, oral, Janus kinase 1 preferential inhibitor. We assessed the efficacy of FIL in biologic (bio)-naïve and bio-experienced patients with UC, and in bio-experienced patients with failure of 1 or ≥ 2 biologics or 1 or 2 mechanisms of action (MoAs).

Methods SELECTION (NCT02914522) was a phase 2b/3 double-blind, randomised, placebo-controlled trial comprising two induction studies and a maintenance study. Adults (18-75 years) with moderately to severely active UC were randomised 2:2:1 to FIL 200 mg, FIL 100 mg or placebo (PBO) once daily for 11 weeks in Induction Study A (bio-naïve) and B (bio-experienced). Patients in either clinical remission or Mayo Clinic Score (MCS) response at week 10 (responders) could enter the Maintenance Study. Responders who received induction FIL were re-randomised 2:1 to continue their induction regimen or PBO through week 58. Responders who received induction PBO continued PBO. We assessed clinical remission and MCS response at weeks 10 and 58 in bio-naïve patients and bio-experienced patients with failure of 1 or ≥ 2 biologics and 1 or 2 MoAs (TNF antagonists and vedolizumab). All p values for subgroup analyses are nominal.

Results Week 10 clinical remission was achieved by a significantly higher proportion of bio-naïve and -experienced patients treated with FIL 200 mg than PBO. A higher proportion of bio-experienced patients with 1 biologic or MoA failure treated with FIL 200 mg than PBO achieved clinical

remission at week 10 ($p < 0.05$). Higher proportions of patients treated with either dose of FIL than PBO achieved MCS response at week 10. At week 58, higher proportions of bio-naïve and experienced responders, and bio-experienced responders with ≥ 2 biologic or 2 MoA failures treated with maintenance FIL 200 mg than PBO achieved clinical remission ($p < 0.05$). Higher proportions of responders treated with maintenance FIL 200 mg than PBO achieved MCS response at week 58.

Conclusion FIL 200 mg was effective in inducing and maintaining clinical remission in bio-naïve and -experienced patients. Induction results suggest FIL 200 mg is most effective in bio-naïve patients, and those who switch after failure of 1 biologic or MoA.

OMO-3 SAFETY ANALYSIS OF FILGOTINIB FOR ULCERATIVE COLITIS: PHASE 2B/3 SELECTION STUDY AND LONG-TERM EXTENSION RESULTS

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Introduction Filgotinib (FIL) is an oral preferential Janus kinase (JAK) 1 inhibitor. FIL for the treatment of moderately to severely active ulcerative colitis (UC) was evaluated in the phase 2b/3, double-blind, placebo (PBO)-controlled SELECTION study (NCT02914522) and its long-term extension (LTE) study (NCT02914535). Here we report safety results.

Methods Patients received FIL 100 mg, FIL 200 mg or PBO (2:2:1) once daily orally for up to 11 weeks for induction (cohort 1). At week 11, FIL induction responders were rerandomised 2:1 to continue FIL or receive PBO maintenance for 47 weeks (cohort 2). Week 10 non-responders and patients with worsening disease during the maintenance study were eligible for open-label FIL in the LTE. Patients completing the maintenance study could continue blinded dosing in the LTE. Cohort 3 comprised cohorts 1 and 2 and the LTE. Exposure-adjusted incidence rates (EAIRs) and exposure-adjusted event rates (EAERs) per 100 patient-years (PYs) were calculated for treatment-emergent adverse events (AEs).

Results In cohort 1, 1069 patients received FIL and 279 patients received PBO; baseline characteristics were generally similar across treatment groups. EAIRs for AEs of interest were similar across treatment groups in cohorts 1 and 2. Treatment exposure for PBO, FIL 100 mg or FIL 200 mg in cohort 3 (i.e. cohorts 1 + 2 + the LTE) was 318, 360 and 1207 PYs, and median treatment duration was 12, 11 and 67 weeks, respectively. One case of pulmonary embolism occurred with FIL 200 mg induction and three venous thrombosis cases occurred with PBO maintenance/LTE (cohort 3). EAERs for all infections were similar across treatment groups. Opportunistic infections were rare. EAERs for serious infections were low across treatment groups (2.2 [PBO], 3.5 [FIL 100 mg], 2.2 [FIL 200 mg]). EAERs for herpes zoster (HZ) were low in all treatment groups (0.3 [PBO], 0.3 [FIL 100 mg], 1.8 [FIL 200 mg]). HZ infections were cutaneous only and only one was serious. EAIRs for all infections in cohorts 1 and 2 were generally numerically higher for both PBO and FIL in

patients over (vs under) 65 years old and in those with (vs without) biologic treatment failure.

Conclusions FIL was well tolerated in patients with UC. Aggregation of AEs typical for pan-JAK inhibition was not observed, consistent with preferential JAK-1 inhibition with FIL.

OMO-4 DEVELOPING A GENOMIC BIOMARKER OF CANCER RISK IN PATIENTS WITH UC USING UNSELECTED ENDOSCOPIC BIOPSIES

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Introduction Patients with ulcerative colitis (UC) are enrolled into surveillance programs for the early detection of colorectal cancer (CRC). However, most patients under surveillance are low-risk and never progress to CRC, while a significant proportion of CRCs in UC form without a preceding confirmed diagnosis of dysplasia. High resolution chromosomal copy-number alteration (CNA) analysis of unselected formalin-fixed paraffin embedded biopsies taken at surveillance colonoscopies using low pass whole genome sequencing (lpWGS) offers an appealing approach to CRC stratification.

Methods We conducted a retrospective case-control study to compare the CNA burden in four unselected non-neoplastic left-sided colorectal biopsies from patients with E2/E3 UC derived 1-5 years prior to HGD/CRC detection (cases), with that of biopsies from patients who subsequently remained HGD/CRC-free for at least 5 years (controls). The two patient groups were matched by age, gender, duration of IBD and PSC status. lpWGS was performed using a standardised pipeline for epithelial enrichment, DNA extraction, library preparation, next generation sequencing and bioinformatic analysis.

Results 476 biopsies, derived from 42 cases and 77 controls, were analysed. Nearly 80% of patients had a detectable CNA in at least one of their biopsies, with the maximal CNA

Abstract OMO-4 Figure 1