Background: Barrett’s oesophagus (BE) is the main risk factor for the development of oesophageal adenocarcinoma (OAC), yet few patients ever go on to progress to cancer. The acquisition of events during the metaplasia-dysplasia-cancer sequence is poorly characterised. We present a large, unbiased, multi-omics analysis of a cross-sectional cohort of pre-cancer samples, with the aim of providing a comprehensive insight into the diversity and molecular changes driving the disease to cancer.

Methods: We generated and integrated the genomic (50X), transcriptomic and epigenomic (850K EPIC array) landscapes of snap-frozen endoscopic biopsies from 146 patients with a range of outcomes (27 long-standing non-dysplastic; 12 prior to progression to dysplasia; 14 low-grade; 25 high-grade; 21 intramucosal carcinoma; 47 cases of BE taken adjacent to OAC) and 642 person years of follow-up. All biopsies were reviewed independently by 3 pathologists and had associated annotation with detailed clinical information.

Results: The total number of structural variants (SV) captured the most variance between samples. Complex SVs and LINE-1 retrotransposon activity were observed even before dysplasia had developed and increased with progression. Increasing SV burden was associated with chromothripsis (12%, 18/146) and breakage-fusion bridges (BFBs; 8%, 13/146). In more than 50% of these, the BFBs were in chromosome 17, harbouring the oncogenes ERBB2 and CDK12, for which expression was significantly higher. With progression there was increased expression of genes related to cell-cycle checkpoint, DNA repair and chromosomal instability, and the epigenetic silencing of genes in WNT-signalling and cell-cycle pathways.

Conclusions: Genomic complexity occurs very early in the natural history of BE and increasing genomic instability appears to tip the balance towards cancer. This may inform the potential for progression to cancer beyond the clinically discernible phenotype. Efforts to better understand the triggers for chromosomal breakages and rearrangements that underly progression will aid clinical prediction and prevention strategies.