Enhanced neoplasia detection in chronic ulcerative colitis: the ENDCaP-C diagnostic accuracy study

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Scientific summary

The ENDCaP-C diagnostic accuracy study

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Scientific summary

Clinical rationale

Over 30,000 patients in the UK are affected by chronic ulcerative colitis, which is an inflammatory condition associated with a pro-neoplastic drive. The longer and more extensive the inflammation, the higher the risk of colorectal cancer for individuals with ulcerative colitis. The risk of cancer is greatest in those diagnosed young and those having extensive colonic inflammation, reaching 18% after 30 years. Over 1000 colectomies are performed each year in the UK for colorectal cancer or for cancer prevention in those where (precancerous) dysplastic lesions have been identified. Despite intensive colonoscopic surveillance, as many as 50% of cases progress to invasive cancer before neoplasia is detected. The presence of advanced malignancy can prevent safe restoration of bowel continuity, require adjuvant chemotherapy and result in incurable disease and death, which occurs in > 40% of patients with colitis-associated colorectal cancer.

There is a real and urgent need for improved selection of ulcerative colitis patients for surveillance colonoscopy. The use of molecular markers derived from bowel mucosa biopsies have been proposed as a potential method for achieving this.

Methylation changes in gene promoter regions modulate their expression. Such changes are frequently seen in early stages of cancer and pre-cancer disease, and provide a potential diagnostic tool.

Because ulcerative colitis is a diffuse disease of the large bowel mucosa, patients are predisposed to develop multifocal tumours. Consequently, molecular changes are seen at multiple sites and have been reported to occur in the background mucosa, away from the site of a tumour. Therefore, they have the potential to both aid the identification of early neoplastic change and better stratify patients as to their risk of harbouring precancerous changes in the mucosa.

Emerging knowledge about DNA methylation modifications in epithelial neoplastic pathways opens the possibility of a diagnostic test to supplement colonoscopic surveillance for inflammatory bowel disease patients at high risk for development of colon cancer.

Project overview

The ENDCaP-C (Enhanced Neoplasia Detection and Cancer Prevention in Chronic Colitis) collaborative group undertook a three-stage process.

- Module 1: development of a molecular signature to detect bowel neoplasia. Stored biopsy samples were analysed for evidence of methylation changes in the bowel mucosa that were specific to the development of neoplasia.
- Module 2: development and assessment of a high-throughput analysis within an NHS laboratory, attempting to develop a testing platform that would be cost-effectively and reproducibly translated into clinical practice.
- Module 3: prospective evaluation of the methylation signature within a diagnostic accuracy study of over 800 patients, recruited across 31 hospitals over 30 months, from within the NHS surveillance programme.

The overarching ambition was to enhance colon cancer surveillance for ulcerative colitis patients using novel biomarkers to better stratify patients, improve early cancer detection and rationalise colonoscopic programmes.

Module 1

Objective

Module 1 aimed to validate previously identified biomarkers of neoplasia in a retrospective multicentre sample cohort and thereby create predictive models for later validation in a prospective cohort.

Design

A retrospective analysis using bisulphite pyrosequencing of an 11-marker panel (i.e. *SFRP1*, *SFRP2*, *SFRP4*, *SFRP5*, *WIF1*, *TUBB6*, *SOX7*, *APC1A*, *APC2*, *MINT1*, *RUNX3*) in samples from 35 patients with cancer, 78 with dysplasia and 343 without neoplasia all undergoing surveillance for ulcerative colitis-associated neoplasia across six hospitals. Predictive models for ulcerative colitis-associated cancer/dysplasia were created in the setting of neoplastic and non-neoplastic mucosa.

Results

For neoplastic mucosa, a five-marker panel (i.e. *SFRP2*, *SFRP4*, *WIF1*, *APC1A*, *APC2*) was accurate in detecting pre-cancerous and invasive neoplasia (area under the receiver operating characteristic curve = 0.83; 95% confidence interval 0.79 to 0.88). For non-neoplastic mucosa a four-marker panel (i.e. *APC1A*, *SFRP4*, *SFRP5*, *SOX7*) had modest accuracy (area under the receiver operating characteristic curve = 0.68, 95% confidence interval 0.62 to 0.73) in predicting associated bowel neoplasia through the methylation signature of distant non-neoplastic colonic mucosa.

Module 2

Objective

Module 2 aimed to evaluate the utility of next-generation sequencing as an alternative to pyrosequencing, the technology routinely used to determine the methylation status of specific targets in formalin-fixed, paraffin-embedded extracted DNA. Pyrosequencing was not considered an ideal platform (because of cost and efficiency) to deliver a high-throughput strategy for introduction into routine clinical practice.

An amplicon-based target enrichment strategy was selected, using the Fluidigm 48.48 Access Array (Fluidigm Corporation; San Francisco, CA, USA) system with subsequent sequencing analysis performed on the Illumina MiSeq platform (Illumina Incorporated; San Diego, CA, USA). Advantages of this system include speed, single nucleotide resolution, high coverage of each locus, low cost of simultaneously assaying multiple CpG loci and high-throughput capability.

Methods

Bisulphite DNA conversions were performed using the EZ-96 DNA Methylation Gold MagPrep Kit (Zymo Research; Irvine, CA, USA). The amount of input DNA varied, dependent on the sample source (range 1–30 ng), which is a recognised challenge in assessing formalin-fixed, paraffin-embedded tissue samples. Multiplex polymerase chain reaction amplification was performed to enrich the samples for the target biomarkers, using a 48.48 Fluidigm Access Array and the Roche High Fidelity Fast Start Kit (Roche Holding AG; Basel, Switzerland). A bidirectional sequencing protocol was adopted to facilitate simultaneous sequencing in the forward and reverse directions, which was important to provide sufficient base diversity content during subsequent MiSeq Illumina sequencing. The bioinformatics pipeline utilised the 'Bismark' software (Babraham Bioinformatics; Cambridge, UK). Amplification success and predictive ability were assessed by fitting to the statistical models used in module 1.

Results

Amplification performance (range 3–34%) for the 11 targets was, marker for marker, lower than the performance observed in module 1 using pyrosequencing. Overall, the next-generation sequencing assay success rate was 35% lower for each target, so the number of failed results (no interpretable outcome) was too high for this assay to be taken forward. The reasons for poor (failed) amplification performance

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are multifactorial: low concentration of DNA integrity, low concentration (below the minimum threshold required for the Fluidigm Access Array workflow) and longer amplicon lengths.

Where module 2 methylation results were available, predictive models of neoplasia/control status had high discriminatory performance (area under the receiver operating characteristic curve = 0.94), suggesting that despite poor amplification, next-generation sequencing-based assessments are as predictive as in module 1.

Further work is needed to optimise the next-generation sequencing workflow for its use on formalin-fixed paraffin-embedded-derived DNA.

Conclusion

Results show that the Fluidigm approach is less robust, producing a relatively poor amplification performance compared with pyrosequencing, with the low DNA concentrations and DNA degradation leading to higher failure rates. In addition, the intrinsic lack of sequence complexity as a consequence of bisulphite treatment creates several challenges to the sequencing platform, from library generation to data interpretation. There is no doubt that DNA quality would have been improved by the use of fresh tissue, but this is not yet standard NHS practice.

The study has shown however that development of a high-throughput strategy has potential. Advances in sequencing technology since the inception of ENDCaP-C could now produce improved amplification performance.

Module 3

Objectives

Module 3 had a primary aim to prospectively evaluate the ability of the methylation assay identified in module 1 to detect pre-cancerous lesions (dysplasia) missed by histology within a surveillance programme for colitis-associated neoplasia. The secondary aim was to estimate the incremental accuracy of methylation testing over histology within a colitis-associated neoplasia surveillance programme and gain experience of its applicability in the clinical setting.

Methods

A multicentre test accuracy study was designed to generate a comparison of measurements obtained by the index test (methylation test) with those obtained by the reference standard (histology assessment from colonoscopy). In this way, the accuracy of the index test was estimated.

It was estimated that 1000 patients with chronic colitis needed to be recruited to obtain 66 index test positives. Computation of the sample size was based on (1) records indicating that 4% are detected with dysplasia by histology from a high-risk cohort and (2) an assumption that a further 4% are missed (assuming a detection rate of 50% for routine colonoscopy) of which (3) 50% will be detected by methylation testing (i.e. sensitivity = 50%), which will (4) give false-positive results in 5% free of dysplasia (i.e. specificity = 95%).

Index test: adjunctive methylation

The index test was the DNA methylation panel of markers, defined in module 1. After local histological analysis, formalin-fixed, paraffin-embedded blocks were transferred to University Hospitals Birmingham NHS Trust for central review and DNA extraction. Only DNA from blocks without (histological) dysplasia was extracted and forwarded to the West Midlands Regional Genetic Laboratory for analysis. To ensure that the reference standard was undertaken blinded to the methylation result, the methylation results were not released to participants, clinicians or other members of the ENDCaP-C study team during the study period.

Reference standard (repeat colonoscopy)

A sample of histologically negative patients were identified and invited to undergo early repeat colonoscopy. All patients with positive methylation status (test positives) were invited, along with a random sample of negative methylation (test negatives) patients in a 1 : 2 ratio.

The reference standard colonoscopy was to be undertaken 4–12 months after the standard colonoscopy. This reference assessment was to be standardised using dye spray and targeted biopsy to maximise dysplasia detection, and performed by nominated, experienced colonoscopists at each site.

Results

The inclusion criteria defined a group at higher risk of developing colorectal dysplasia: 4827 patients were assessed for eligibility, of whom 3433 did not meet the eligibility criteria, 522 were eligible but were not recruited and 53 had been identified as potential participants but their eligibility was not established.

Among the 818 patients enrolled in the study, the prevalence of dysplasia (11.2%) at the index colonoscopy was almost three times that predicted from published data. This high pick-up rate would suggest that the colonoscopy examinations were of a suitably high standard and this was indeed a high-risk population.

Both models 1 and 2 (derived in module 1) for the methylation signature were assessed in this prospective study.

Accuracy of methylation index test at baseline compared with baseline histology

This comparison provided a 'proof of principle' assessment of whether or not methylation tests identify neoplasia evident at the baseline colonoscopy from biopsies taken at a site distant from any neoplastic change.

There was a statistically significant association between methylation test results and histology results (diagnostic odds ratio = 2.4, 95% confidence interval 1.5 to 3.8; a *p*-value of < 0.001 for model 1, and 2.1, 95% confidence interval 1.3 to 3.3; a *p*-value of 0.001 for model 2). This indicates that the test has a relationship with observed neoplasia. With both models 1 and 2, approximately 50% (model 1, 47%; model 2, 52%) of dysplastic lesions were correctly identified.

Assessment of additional value of methylation testing: reference examination

A sensitivity analysis (for use of dye spray at colonoscopy and correct standard endoscopic technique) and per-protocol analyses (for use of dye spray at colonoscopy, correct standard endoscopic technique and for completion of reference colonoscopy within 12 months) were performed as well as an intention-to-treat analysis for all patients undergoing a reference standard colonoscopy.

Sensitivity analysis ($n = 172$): excluding no dye spray and non-standard endoscopic technique

This analysis standardised the colonoscopy procedure across the participating centres. This was an attempt to quality assure the procedure. In this analysis, the association between methylation status (for both models 1 and 2) and histology findings was in the direction of positive methylation indicating an increased risk of neoplasia but did not reach conventional levels of statistical significance (a *p*-value of 0.27 and a *p*-value of 0.18 for models 1 and 2, respectively). The diagnostic odds ratio measuring the ability of the methylation panels to discriminate was of low magnitude (model 1 diagnostic odds ratio 2.01, 95% confidence interval 0.60 to 6.84; model 2 diagnostic odds ratio 2.12, 95% confidence interval 0.64 to 7.59).

Per-protocol analysis ($n = 104$): additionally excluding follow-up > 12 months Per-protocol analysis excluded a further 68 patients who did not receive their reference colonoscopy within 12 months of the baseline colonoscopy, and reported increases in sensitivity and diagnostic odds ratio. This reduces the potential for de novo dysplasia being identified at the reference examination (stringency test). The diagnostic odds ratio increased to nearly 4 (model 1 diagnostic odds ratio 3.93, 95% confidence interval 0.82 to 24.8; model 2 diagnostic odds ratio 3.59, 95% confidence interval 0.75 to 22.6), but still did not reach levels of conventional statistical significance (a *p*-value of 0.09 for both models 1 and 2).

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Intention-to-treat analysis ($n = 193$): including all patients The intention-to-treat analysis including all patients found a weaker discrimination with diagnostic odds ratios of around 1.5 (model 1 diagnostic odds ratio 1.50, 95% confidence interval 0.48 to 4.45; model 2 diagnostic odds ratio 1.46, 95% confidence interval 0.49 to 4.38) with p-values of 0.45 and 0.46 for models 1 and 2, respectively.

A positive methylation test result slightly increased the probability of being histology positive from the prevalence of 9% to 12%; being methylation negative decreased the probability from 9% to 8%. Changes for model 2 were very similar. These estimates had high uncertainty.

Additional comparisons

Because we were able to repeat the methylation test at the time of the reference colonoscopy, we were able to explore the value of repeated methylation testing over sequential colonoscopy procedures. Methylation results from biopsy samples taken at baseline and reference colonoscopies were compared. Sequential repeated positive testing increased the chance of underlying neoplasia (from 11% to 22%) and sequential repeated negative testing reduced this risk (from 11% to 7%). However, both of these estimates have high uncertainty.

Conclusions

The ENDCaP-C study successfully identified a set of markers that can identify a subpopulation of ulcerative colitis patients with methylation changes in the background mucosa that are associated with neoplasia elsewhere in the colon. This was seen in both our retrospective and our prospective studies with high levels of statistical confidence. This molecular signature was seen in about 50% of patients with colitis-associated neoplasia.

The pyrosequencing methylation assay was successfully translated into routine NHS processes and samples were analysed and reported with a success rate of $> 95\%$ (773/805 colonoscopies from which biopsies were taken). Attempts at developing a high-throughput next-generation sequencing platform were not successful.

Key findings from the prospective study are:

1. It is feasible to successfully deliver a cohort study of 800 participants in this clinical setting with acceptable recruitment and follow-up rates, with over half (56%) of those asked willing to undergo a repeat reference colonoscopy.
2. The methylation markers at baseline showed a significant relationship with baseline histology ($p < 0.0001$).
3. Relationships of the methylation markers with neoplasia detected at the reference colonoscopy were in the same direction, but weaker and statistically non-significant.
4. Repeated methylation positives at baseline and reference colonoscopies identified a high-risk stratum (predicted risk of 22%); a single positive methylation result identified an intermediate risk stratum. The numbers in these subgroup strata were low and the uncertainty in this estimate was high. The findings suggest that (repeated) methylation testing could provide additional risk stratification (above colonoscopy alone) within an existing surveillance programmes.

This study has demonstrated a proof of principle that methylation in the background mucosa is associated with neoplasia in chronic ulcerative colitis. The test showed an increased number of patients with neoplasia associated with primary methylation changes, but this failed to reach statistical significance. So the methylation test, as done, would not yet be recommended for clinical practice.

Trial registration

This trial is registered as ISRCTN81826545.

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