

Introduction

- Ulcerative Colitis (UC) is an aggressive and incurable inflammatory bowel disease that affects young people typically in their teens and early twenties.
- Patients with chronic UC are at an increased risk of developing colorectal cancer.
- Current surveillance strategies miss up to half of cancers in this young population.²
- Methylation biomarkers may enable early detection of high risk individuals before the onset of cancer (neoplasia).

Rationale for Study

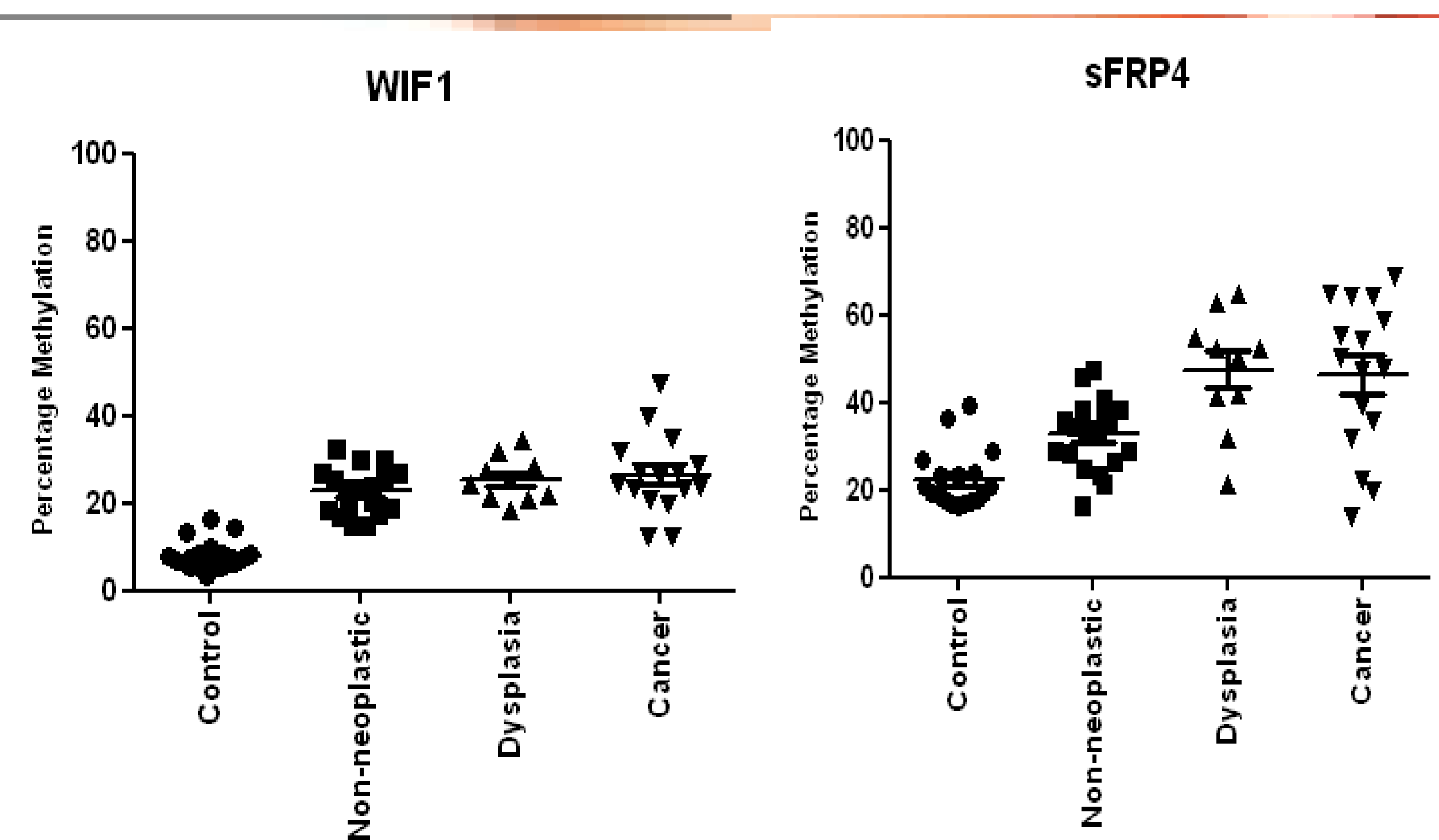
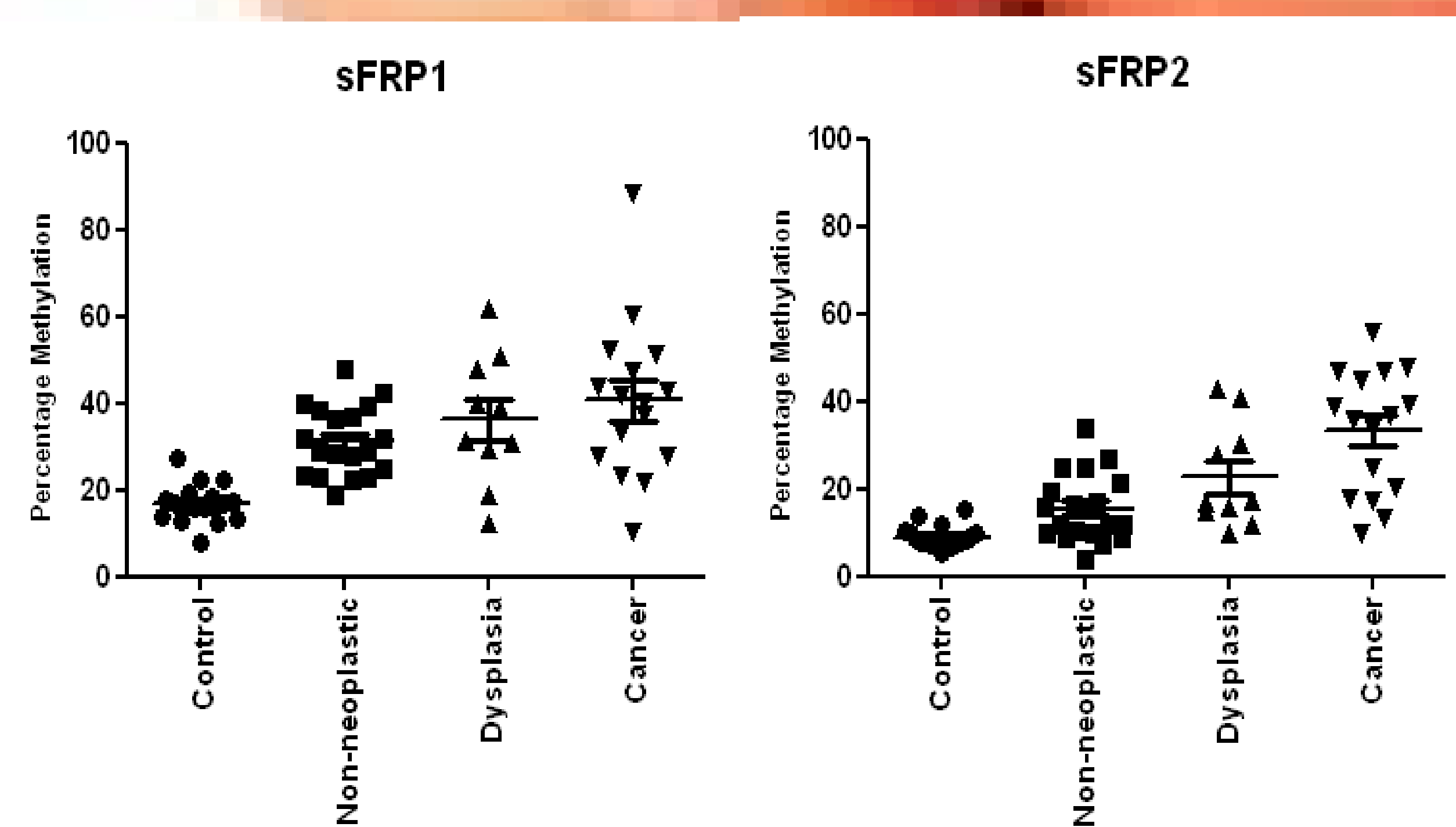
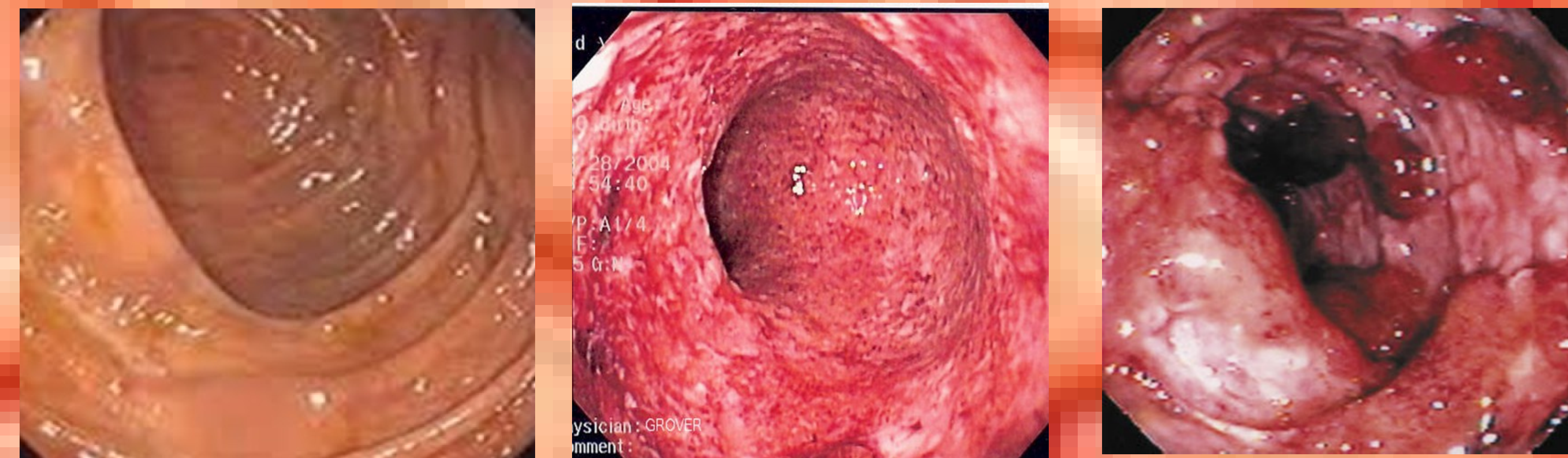


Figure: Pilot data shows increased levels of methylation seen in pre invasive and invasive cancer in chronic UC .

Hypothesis

Aberrant methylation of Wnt genes in chronically inflamed mucosa in UC predates clinically detectable neoplasia and this can be exploited to stratify cancer risk.



Normal healthy colon

Ulcerative Colitis colon

Ulcerative Colitis Colon Cancer

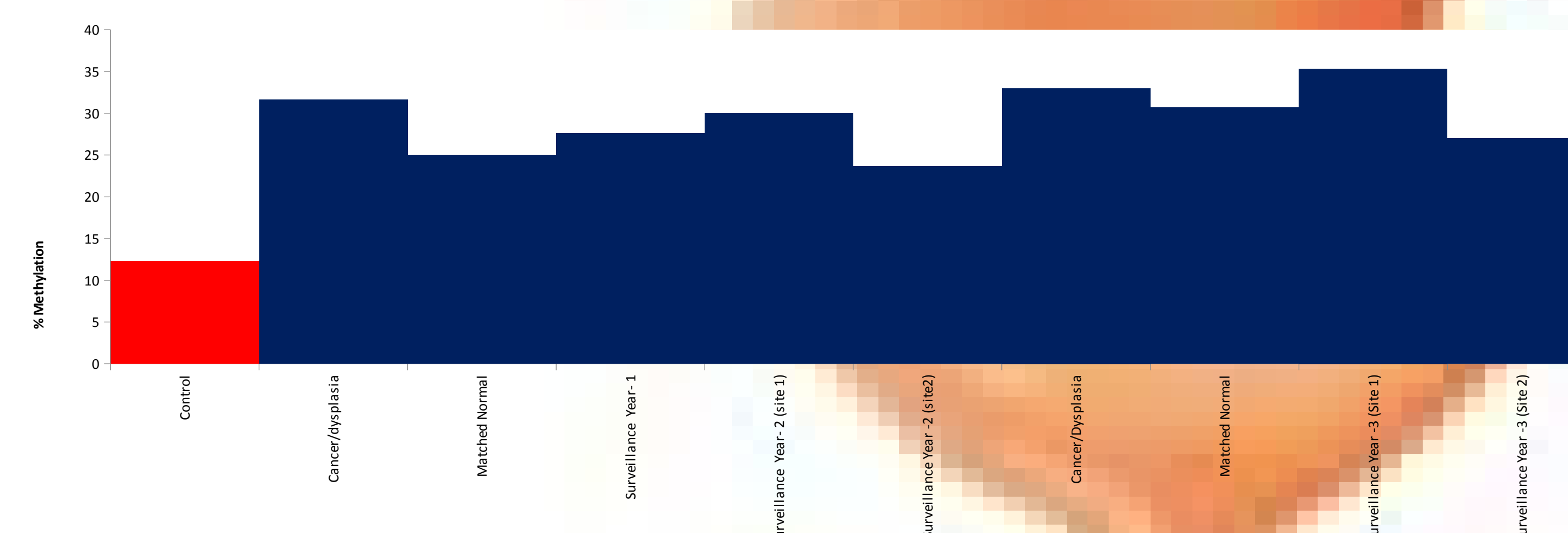
Can methylation markers prevent cancer progression in UC?

Research Aims

To determine the time course of methylation change relative to the clinical detection of neoplasia and investigate whether a supplementary methylation test can contribute to risk stratification in UC surveillance.

Pilot data looks promising!

Methylation analysis of a 73 year old female with chronic colitis



Proposal

A nested matched case-controlled study will be performed using archived FFPE biopsies from a cohort of patients with UC who have been under surveillance for at least three episodes (6 - 8 years).

Cases have been selected where cancer or dysplasia has been identified following two or more negative surveillance episodes.

Controls have been drawn from patients who remained free of disease after a period of follow-up similar to that at which the matched case is diagnosed with cancer or dysplasia. These will be matched for duration of disease, the number of negative surveillance episodes, age and gender. Two controls have been identified for each case.

All tissue extracted from controls and cases will be examined for the presence of methylated markers from our panel of Wnt genes.

55 cases (110) controls having been identified will be analysed in a nested case-control study

For a gene that is hypermethylated in 50% of patients with CAN and 5% of controls, this will have at least 80% power to detect a 10-fold increased risk of progression to neoplasia associated with hypermethylation.

What is the Clinical potential of this research?

The delivery and evaluation of a DNA based test that will enhance the detection of colitis associated neoplasia before invasive malignancy has developed.

The potential, in the future, to target novel chemoprevention agents at an identifiable high risk population.

References

- Eaden JA, Mayberry JF. Colorectal Cancer complicating ulcerative colitis: a review. *Am j Gastroenterology*. 2001 95: 2710-9
- Shu X et al. Survival in cancer patients hospitalised for inflammatory bowel disease in Sweden. *Inflamm Bowel dis*. 2011.17:816-22