# Circulating nucleosomes for Detection of Colorectal Cancer and High-risk Advanced Adenomas

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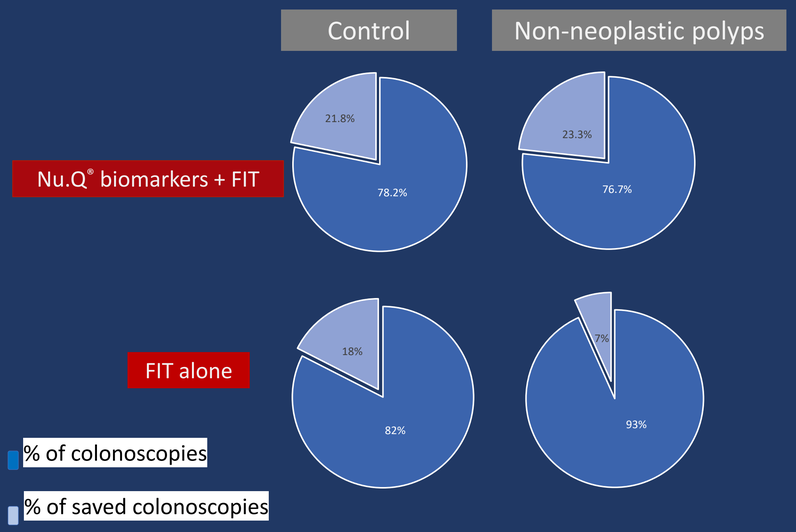
## Background:

- Approximately **60%** of Fecal immunochemical tests (FITs) are **false-positive** and result in a lot of unnecessary colonoscopies.
- There is an unmet need for a simple test to supplement FIT to triage individuals at high risk who require colonoscopy referral.
- FIT is less effective in detecting **proximal** lesions even advanced neoplasms.
- We investigated the levels of circulating free nucleosomes containing different epigenetic modifications in patients referred for colonoscopy and the detection rate of proximal neoplasms.

## Methods:

- 520 Patients enrolled including (i) CRC (n= 33), (ii) advanced adenoma (AA) (n=123, including 18 with AA>2cm); (iii) non-AA (n=168); (iv) non-neoplastic polyps (n=30); (vi) colonoscopy negative controls (n=166).
- Plasma and stool samples were obtained prior to colonoscopy.
- Nucleosome levels were tested by using 7 different quantitative immunoassays (Nu.Q® assays; Belgian Volition SRL, Belgium) targeting H3.1-nucleosomes and different histone modifications.
- FIT was performed by using OC-SENSOR (Eiken Chemical Co., Ltd., Tokyo, Japan)

## Circulating Nucleosome Levels in Combination with FIT Improves Detection of High-risk Advanced and Proximal Adenoma and Provides a Method to Reduce Unnecessary Colonoscopy

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## Results:

- At a cut-off of 20µg/g, FIT had a sensitivity of 92.9% at 17.5% specificity for CRC. All the CRC patients and 83.3% of the high-risk AA (>2cm) patients were FIT positive.
- Combination of 2 Nu.Q® biomarkers: H3K27Me3 and H3R8Cit plus FIT in a logistic regression model showed improved sensitivity of 95% at 20.6% specificity, allowing the detection of all CRC patients and 94.3% of AA patients including all high-risk adenomas.

| Diagnosis | Positive Test | |
|---|---|---|
| | FIT | Nu.Q® + FIT |
| CRC | 33/33 | 33/33 |
| Advanced Adenoma (AA) | 112/123 | 116/123 |
| <= 1cm | 45/48 | 43/48 |
| 1-2 cm | 52/57 | 55/57 |
| > 2 cm (high risk AA) | 15/18 | 18/18 |
| Non-AA | 141/168 | 149/167 |
| Non-neoplastic polyps | 28/30 | 25/30 |
| Control | 137/166 | 131/165 |

- FIT detected 46 out of 55 proximal adenomas whereas the combined model could detect 50 proximal adenomas including 3 proximal AA >2cm not being detected by FIT ($p<0.05$).
- Unnecessary colonoscopies are potentially reduced by 21.8% of the control and 23.3% of the non-neoplastic polyp subgroups compared to 17.5% and 6.7%, respectively with the FIT.