Circulating nucleosomes levels improve FIT performance for detecting advanced adenomas in a symptomatic population

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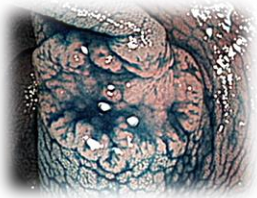
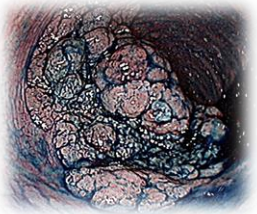
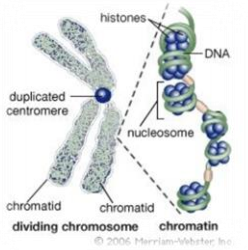
Background and aim

- Colonoscopy is the current standard practice for evaluating symptomatic patients despite its invasive nature but non-compliance to colonoscopy leads to higher CRC mortality.
- There is a need for alternative tests for triaging patients prior colonoscopy to improve diagnostic yield and enhance compliance.
- FIT is a viable approach but its sensitivity for detecting high-risk neoplasms [CRC or advanced adenomas (AA)] is a concern.
- We aimed to evaluate the discriminative power of circulating nucleosome containing specific epigenetic histone modifications in blood to detect high-risk neoplasms in combination with FIT in symptomatic subjects.

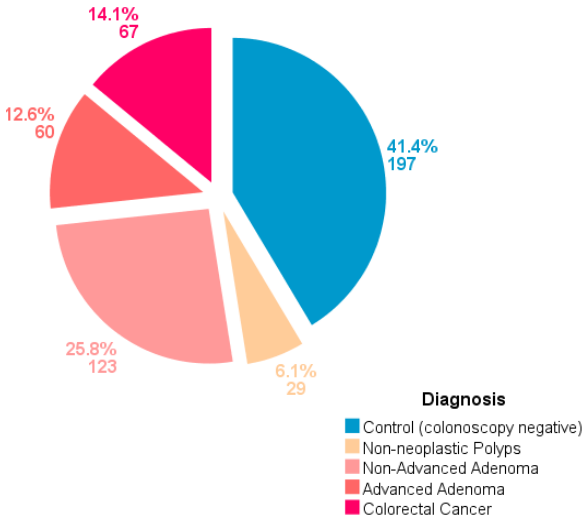






Material and Methods

- 476 patients referred for surveillance colonoscopy or secondary to bowel symptom were enrolled: (i) CRC (n= 67), (ii) advanced adenoma (AA) (n=60), non-AA (n=123); (iv) non-neoplastic polyps (n=29); (vi) colonoscopy negative (controls) (n=197).
- Plasma and stool samples were obtained prior to colonoscopy.
- Circulating Nucleosome levels:
  - ✓ Nu.Q® quantitative immuno-assays: Belgian Volition SRL, Belgium.
  - ✓ 7 different assays measuring: H3.1-, H3K27Me3-, H3K36Me3-, H3K9Me3-, H3K14Ac-, H3K27Ac- and H3R8Cit-nucleosomes.
- FIT: OC-SENSOR (Eiken Chemical Co., Ltd., Tokyo, Japan) using positive cut-off of 20 ug/g of feces.

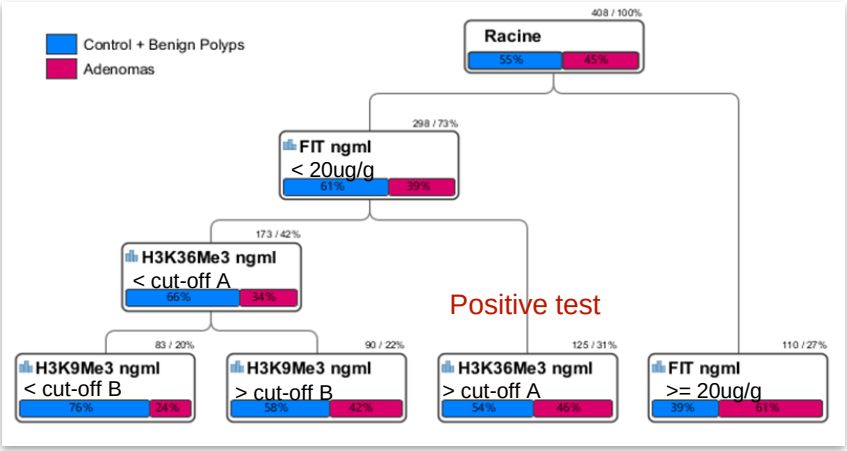


Results

Nu.Q® biomarkers: H3K36Me3 and H3K9Me3 with FIT in a decision tree model improved sensitivity for CRC+AA vs Controls

Combination of two Nu.Q® biomarkers H3K36Me3 and H3K9Me3 with FIT showed:

- An improved sensitivity of 98.4% for CRC + AA vs Controls compared to FIT alone (83.5%).
- A detection of all CRC patients and 97% of the patients with AA including all high-risk adenomas whereas 35% of the AA were missed by FIT alone.



Diagnosis	Positive Triage Test	
	FIT	Nu.Q® + FIT
CRC	67/67	67/67
Advanced Adenoma (AA)	39/60	58/60
<= 1cm	9/15	14/15
1-2 cm	15/23	22/23
> 2 cm (high risk AA)	15/22	22/22
Non-AA	28/123	105/123
Non-neoplastic polyps	6/29	23/29
Control	37/197	139/197

Results

Nu.Q® biomarkers: H3K36Me3 and H3K9Me3 with FIT could reduce unnecessary colonoscopy without missing any CRC or high-risk AA

The same combination could reduce unnecessary colonoscopies by 28%, including 28.9% in the control and 20.7% in the non-neoplastic polyps subgroups.

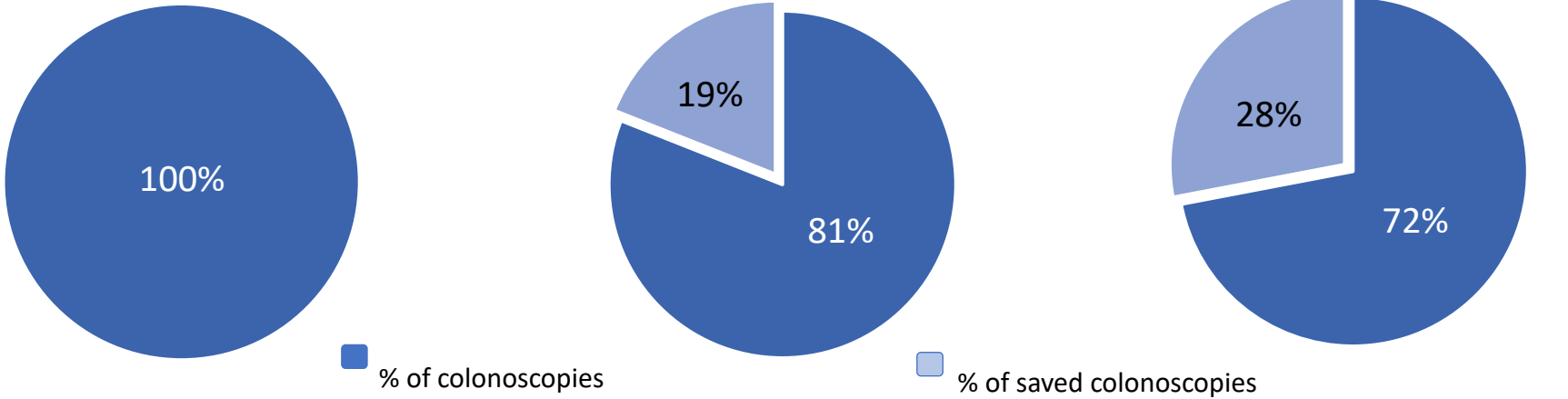
Direct colonoscopy*

Triage test prior to colonoscopy

FIT alone

Nu.Q® biomarkers + FIT

*current practice



Conclusion

- H3K27Me3 and H3K9Me3-nucleosome levels, in combination with FIT in a decision tree model could:
  - ✓Detect all CRC patients and all high-risk adenomas
  - ✓Help to reduce unnecessary colonoscopies
- Further prospective validation is warranted