Circulating nucleosomes levels improve FIT performance for detecting high-risk colorectal neoplasms in a symptomatic population

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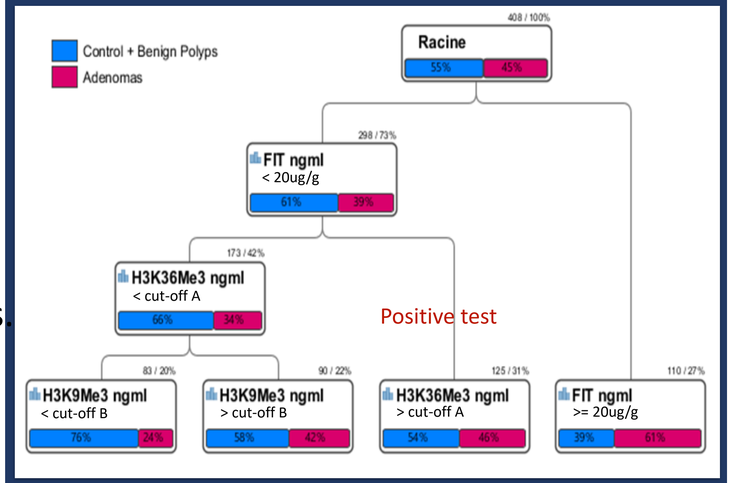
Background:

- 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.

Methods:

- 476 patients referred for surveillance colonoscopy or secondary to bowel symptom were enrolled: (i) CRC (n= 67), (ii) 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.
- 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)

H3K36Me3- and H3K9Me3-nucleosome levels in combination with FIT in a decision tree model could detect all CRC patients and all high-risk adenomas and help reduce unnecessary colonoscopies.



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Results:

- At a cut-off of 20µg/g feces, FIT showed a sensitivity of 83.5% at 82.1% specificity for CRC + AA
- All CRCs were detected but 35% of AA were missed, including 7 high-risk adenomas (AA≥2cm).
- A combination of 2 Nu.Q® biomarkers (H3K36Me3 and H3K9Me3) with FIT in a decision tree model showed:
  - An improved sensitivity of 98.4%
  - Detecting all CRC patients and 97% of the patients with AA including **all** high-risk adenomas.

Diagnosis	Positive 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

- Unnecessary colonoscopy could potentially be reduced by 28%, including 28.9% in control and 20.7% in the non-neoplastic polyps subgroups