Multimodal circulating tumor DNA (ctDNA) colorectal neoplasia detection assay for asymptomatic and early-stage colorectal cancer

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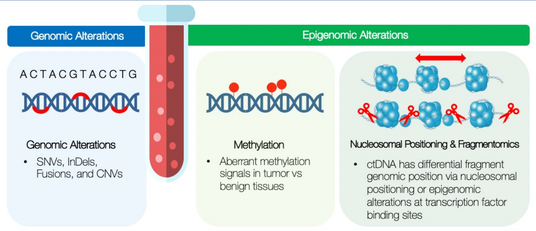
Background

- National colorectal cancer (CRC) screening rates have remained largely unchanged and well below rates recommended by leading public health organizations, despite numerous available screening options.
- CRC screening options that address patient and provider reported compliance barriers (e.g., time and convenience) are needed to improve screening compliance.
- We evaluated the LUNAR-2 blood-based colorectal neoplasia detection test (Figure 1) in a large cohort of patients with newly diagnosed CRC

Figure 1: The LUNAR-2 test is a multimodal blood-based colorectal neoplasia detection assay incorporating ctDNA (circulating tumor DNA) assessment of **somatic mutations** and tumor derived **methylation** and **fragmentomic patterns**, aimed to maximize sensitivity for early-stage CRC detection

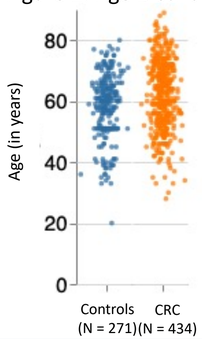


Methods

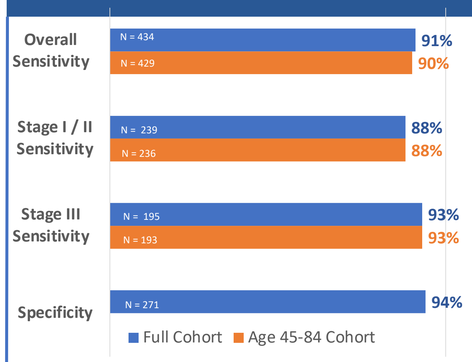
- 434 individuals diagnosed with stage I, II, or III CRC between 2013 and 2016 consented to provide blood samples prior to surgical resection (Table 1)
  - Those treated with neoadjuvant chemotherapy were excluded
  - Blood was collected in EDTA tubes and processed to plasma (median 3mL)
- Control samples were collected from age-matched CRC–free individuals (Figure 2)
- Isolated plasma samples were analyzed with LUNAR-2 (Guardant Health, USA)
- A held-out training set of samples from 614 individuals (CRC or CRC-free) was used to generate a model with calling thresholds targeting 90% specificity
- Final "ctDNA detected" or "ctDNA not detected" results were generated using this separately trained model
- ctDNA results and clinical characteristics were correlated

Table 1: Demographics
Cases N = 434 41% Female Median age : 63 years (range 28-89)
Controls N = 271 51% Female Median age : 60 years (range 20-80)

Figure 2: Age Distribution



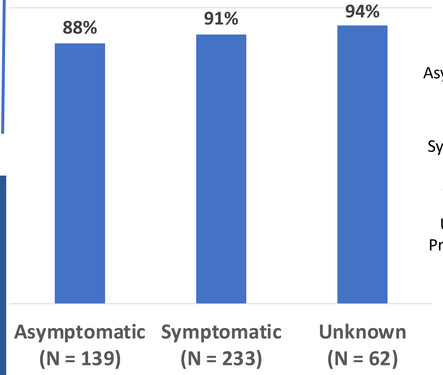
Results



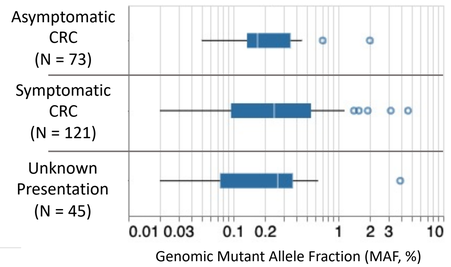
- Overall CRC sensitivity was **91%** with high sensitivity across stages I, II, and III CRC and **94%** specificity (blue bars)
- No difference in sensitivity was observed when excluding those with early (<45 years) or late (>84 years) onset CRC (p=0.95; orange bars)

There was no difference in sensitivity between asymptomatic as compared to symptomatic presentation of CRC (Panel A; p=0.4). However, lower cell-free DNA tumor fractions were observed in the asymptomatic cohort especially in stage I and stage II CRC (Panel B)

A. Sensitivity by CRC Presentation

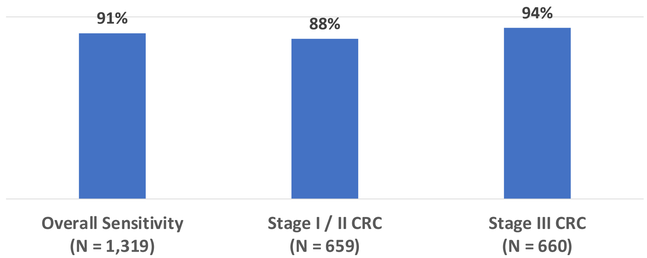


B. Median Genomic Mutant Allele Fraction (MAF, %) of Stage I/II CRC by Presentation



Sensitivity for detection of right-sided and left-sided CRC was similar (p=0.5)

Expanded multi-cohort analysis of CRC cases (N = 1,319)



At 94% specificity, sensitivity was maintained across a multi-cohort analysis

Conclusions

In this large early-stage CRC cohort, multimodal ctDNA assessment has ***high sensitivity for CRC detection with high specificity***.

Equivalent sensitivity in the asymptomatic cohort suggests this test will have ***clinically meaningful performance in an average-risk screening population***.

No difference in CRC sensitivity was observed when focusing on the ***aged 45 – 84 cohort***.

A ***prospective registrational study is ongoing*** to evaluate the test in an average-risk CRC screening cohort.

Additional questions? Please contact Jeeyun Lee, MD at Jyunlee@skku.edu