Multimodal circulating tumor DNA blood-based colorectal cancer screening test demonstrates clinically meaningful sensitivity across multiple clinical parameters

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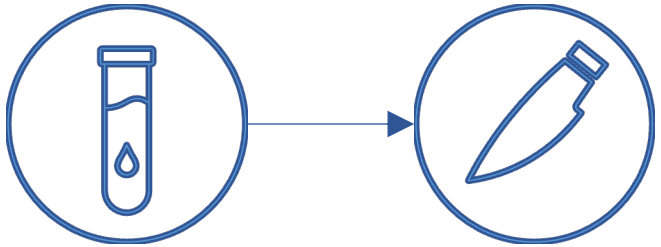
Introduction

- Blood-based colorectal cancer (CRC) screening holds potential to improve screening compliance due to:
  - Ability to seamlessly integrate into standard of care clinical pathways
  - High patient and provider acceptability
- A blood-based screening test must detect CRC across multiple clinical parameters in order to prove clinically meaningful in a screening population
- We aimed to describe the performance of a multimodal ctDNA blood-based CRC screening test in a cohort of patients with newly diagnosed CRC

Cohort Description

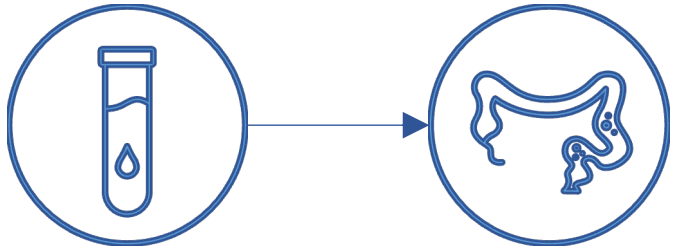
Validation cohort:

Cases: Consented individuals with newly diagnosed CRC (N = 699)



- Whole blood collected prior to surgical resection
- Analysis restricted to Stage I – III CRC diagnoses
- Median age: 63 years (20-89)

Controls: Consented individuals undergoing colonoscopy (N = 297)

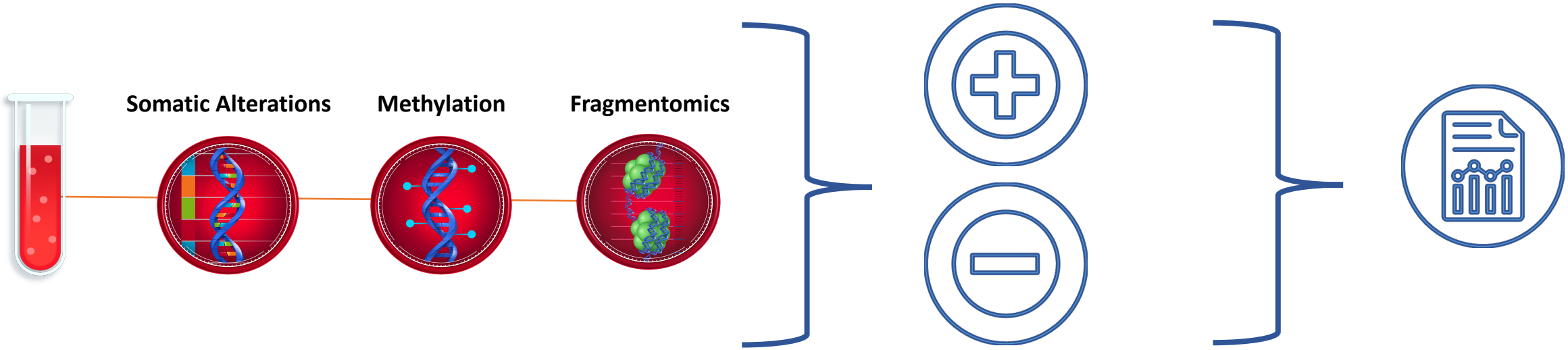


- Whole blood collected prior to colonoscopy procedure
- Analysis restricted to those confirmed negative for advanced colorectal neoplasia
- Median age: 57 years (20 – 91)

Training cohort:

Separate cohort of individuals with CRC (N = 850)
and colonoscopy confirmed negative controls (N = 541)

Blood-based CRC detection cfDNA analysis



Plasma analyzed on a 500kb NGS based panel and bioinformatic platform incorporating cfDNA methylation-based partitioning to identify cancer related genomic alterations and epigenomic modifications

The output is a **“ctDNA detected”** or **“ctDNA not detected”** result

Final results were correlated with key clinical parameters known to influence clinical decision making in CRC

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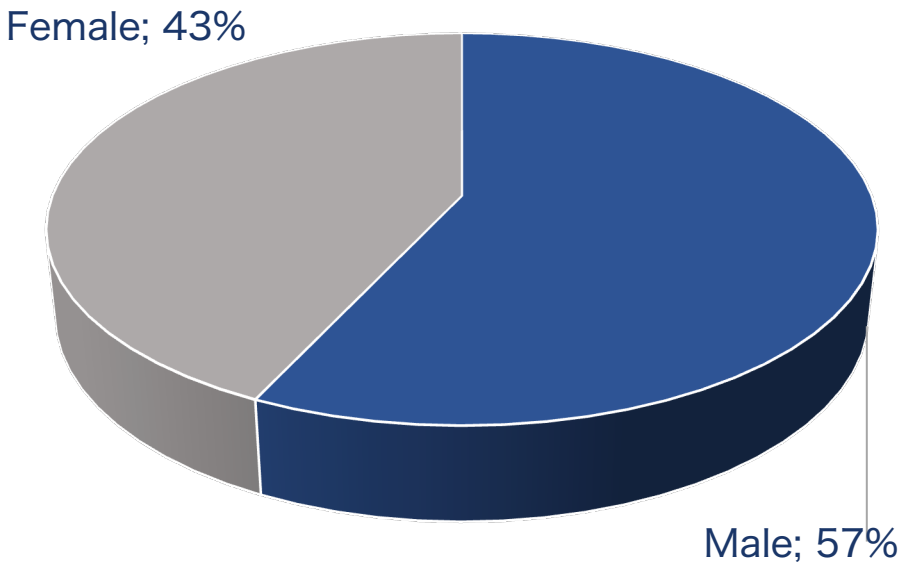
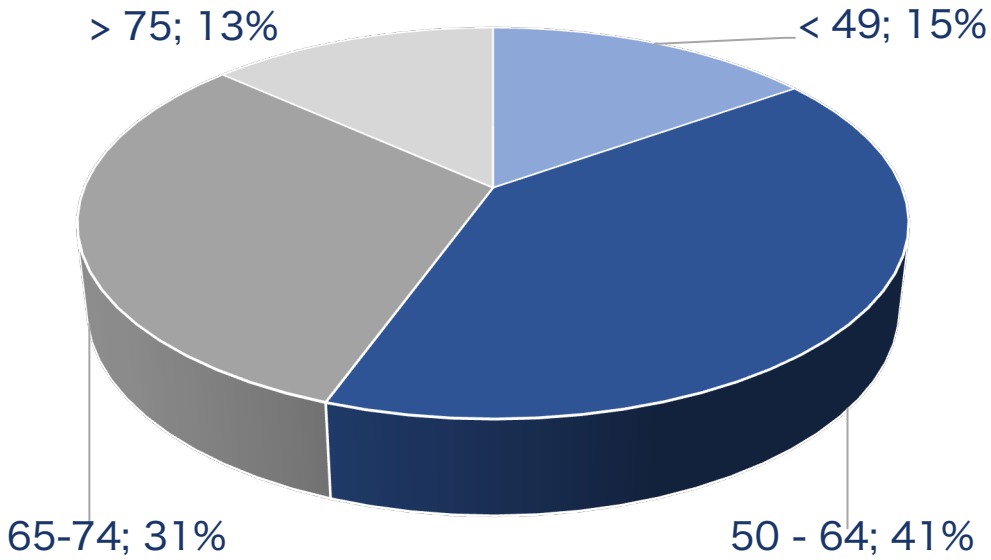
cfDNA: cell-free DNA; ctDNA: circulating tumor DNA; NGS: next-generation sequencing

Case Cohort Demographics

Biological Sex

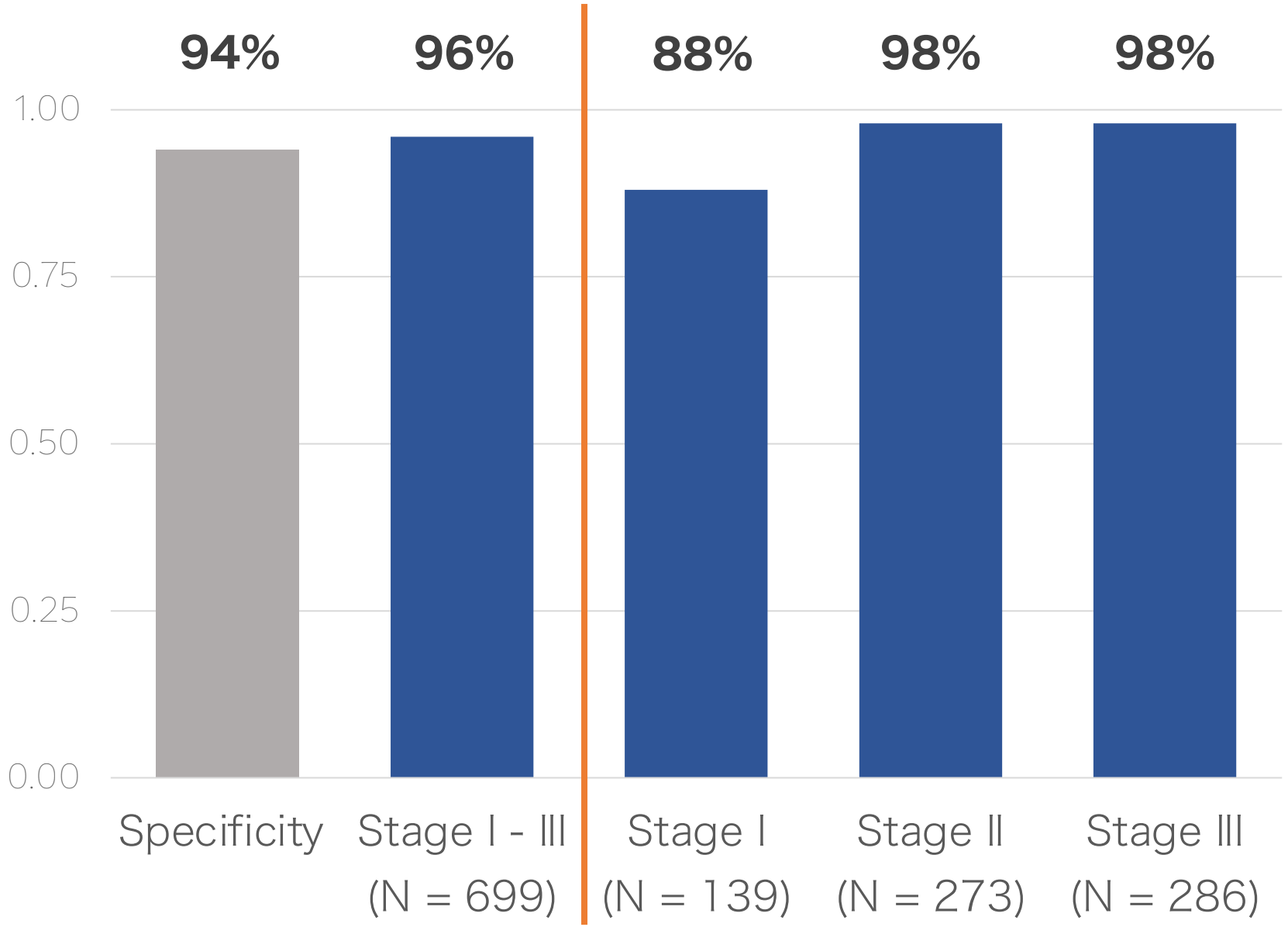


Age at Cancer Diagnosis (in years)



Overall sensitivity for CRC detection: 96%

- In this cohort of individuals with CRC, overall sensitivity was 96% at 94% specificity
- Across stage I, II, and III disease, observed sensitivity was clinically meaningful, on par with currently available non-invasive screening modalities (i.e. stool-based screening)



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Clinically meaningful sensitivity across multiple clinical parameters

- The assay demonstrated clinically meaningful sensitivity across
  - Cancer presentation
  - Primary tumor location
  - Histology
  - MSI status
  - Tumor grade
  - Degree of tumor invasion

- While sensitivity was greater than 90% in each group, significant performance differences were observed in
  - CRC presentation
  - Presence of perineural invasion (prognostic indicator)

Clinical Variable		Number of individuals	% ctDNA detected	
Symptomatic CRC presentation	Asymptomatic	256	93	p< 0.05*
	Symptomatic	350	97	
	Unknown	93	99	
Primary Tumor Location	Right Colon	151	96	ns+
	Left Colon	511	96	
	Transverse Colon	37	95	
Histology	Adenocarcinoma	666	96	ns*
	Mucinous adenocarcinoma	32	100	
	Mucinous adenocarcinoma with signet ring features	1	100	
MSI Status	MSI-High	55	91	ns*
	MSI-Low / MSS	628	97	
	Unknown	16	94	
Tumor Grade	Well-Differentiated (low grade)	175	93	ns+
	Moderately Differentiated (intermediate grade)	462	97	
	Poorly Differentiated (high grade)	32	100	
	Unknown	30	100	
Lymphatic Invasion	Present	67	100	ns*
	Not Identified	632	96	
Venous Invasion	Present	251	97	ns*
	Not identified	448	96	
Perineural invasion	Present	317	98	p < 0.05*
	Not identified	382	94	

*:Fishers exact test; +Chi-squared test; ns: not significant; MSI: microsatellite instability; MSS: microsatellite stable

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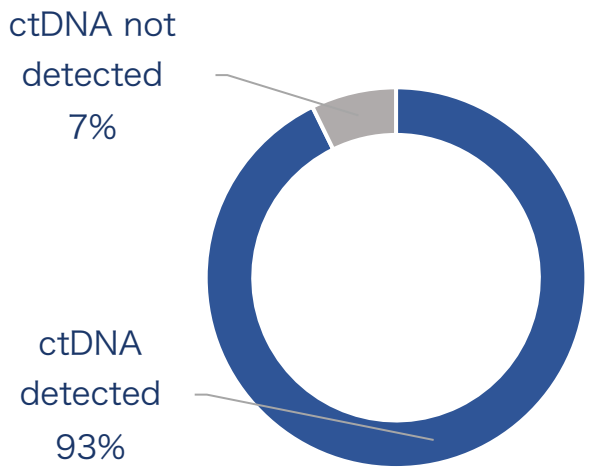
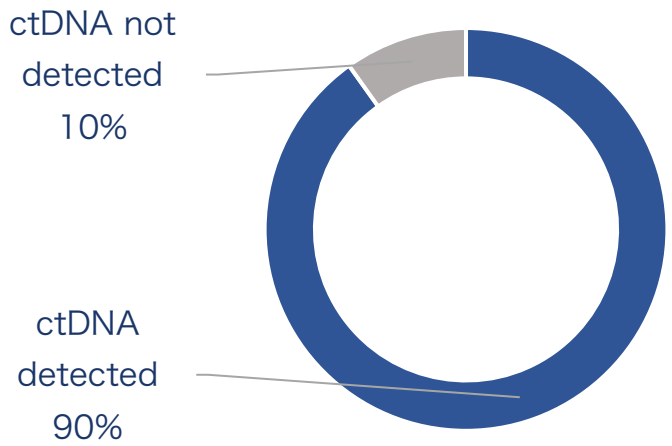
Potential application to CRC screening

Given this is a cohort of individuals with known CRC, completed additional analysis in those with Stage I / II CRC to understand applicability to a screening population

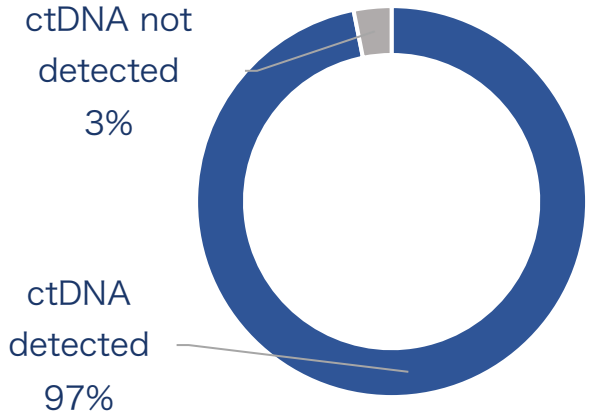
Stage I / II well-differentiated (low grade) tumors (N = 138)



Stage I / II asymptomatic tumors (N = 142)



Stage I / II symptomatic tumors (N = 192)



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ctDNA: circulating tumor DNA

Strengths and Limitations

Strengths:

- Large cohort with extensive clinical data
- Allows for informative sub-analyses across tumor subtypes, especially in early-stage cancers
  - 59% of cohort had Stage I or II disease
  - 37% presented with asymptomatic disease

Limitations:

- Cohorts not reflective of intended use screening population
  - Cohort bias may lead to differential assay performance
  - Ethnicity was not matched for cases and controls in neither training nor testing cohorts which may impact assay results
  - Ongoing studies to evaluate performance in an average risk screening population
- Retrospective analysis of banked plasma samples collected > 5 years ago

Conclusions

- This multimodal ctDNA CRC screening test has **clinically meaningful sensitivity** across multiple clinical parameters, most notably in those with **early-stage asymptomatic disease and early-stage low-grade tumors**
- The data suggest this test may have **clinically meaningful performance** in an **average risk screening population** presenting with varying cancer stages and tumor histologic features
- Future studies aim to **validate this test** in a screen-relevant population
- A **prospective registrational study** to evaluate the test in an average risk, screening cohort is ongoing (NCT04136002)

Thank you

- Patients, Healthy Individuals, and their families who participated in this research
- Clinical and Research Teams at Samsung Medical Center
- Guardant Health Collaborators
- Questions: hckim@skku.edu