Development of a Highly-Sensitive Targeted Cell-Free DNA Epigenomic Assay for Early-Stage Multi-Cancer Screening

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Disclosure Information

Employee and Shareholder of Guardant Health, Inc

Background

- A blood-based cancer screening test should exhibit performance metrics optimized for the cancer of interest:
  - Clinical diagnostic pathways must be considered.
  - Required to detect early-stage disease to yield a meaningful impact on individual and net population health outcomes.
- For cancers with established paradigms and proven diagnostic pathways:
  - Aim to improve compliance rates with performance on par with current modalities.
- For cancers without a paradigm or diagnostic pathway:
  - Aim to reduce false positive rate while ensuring sensitivity is clinically meaningful.
- We developed a blood-based solid tumor screening assay. Here we present feasibility data on four cancer types with differing screening clinical utility as examples.

Clinical Utility to balance risk and benefit

	Cancer Type	USPSTF rating Population	Currently available screening options	Assessment of overall benefits and harms	Screening Adherence Rate	Target Specificity for this analysis
Cancers with population screening recommendation	**Colorectal Cancer[1]**	**A / B** Asymptomatic adults aged 45 - 75	• Colonoscopy • Fecal Immunohistochemical stool test (FIT) • Multi-target stool DNA test • Methylated Sept9 blood test	**Risk-to-benefit ratio supports screening**	66%	90%
	Lung Cancer[2]	**B** Asymptomatic adults aged 50-80 with 20 pack-year history and currently smoke, or quit within last 15 years	• Low Dose CT (LDCT)	**Risk-to-benefit ratio supports screening**	14%	90%
Cancers without population screening recommendations	**Pancreas Cancer[3]**	**D** Asymptomatic adults	• Endoscopic Ultrasound (EUS) • Magnetic resonance cholangiopancreatography (MRCP)	**Risk-to-benefit ratio does NOT support screening, except in limited scenarios***	-	95%+
	Bladder Cancer	Not Reviewed	None	**No screening available**	-	95%+

*Individuals with a known pathogenic / likely pathogenic germline mutation in a pancreas cancer susceptibility gene or strong family history of pancreas cancer

USPSTF, United States Preventive Services Task Force. 1. US Preventive Services Task Force. *JAMA*. 2021;325(19):1965-1977. 2. US Preventive Services Task Force *JAMA*. 2021;325(10):962-970. 3. US Preventive Services Task Force. *JAMA*. 2019;322(5):438-444.

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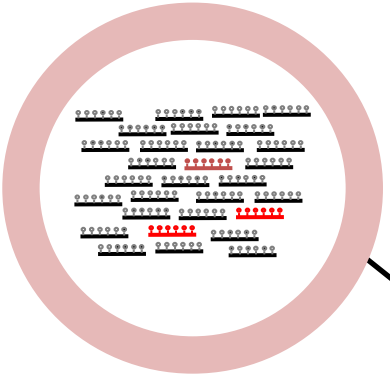
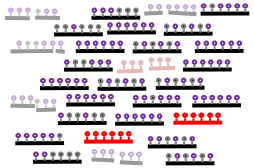
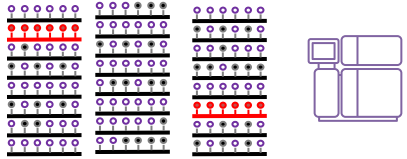
Conventional Methylation Technology: Low fidelity resulting in degraded performance



Conventional Bisulfite Methylation Assessment



DNA Degraded
with harsh chemical treatment



Sequencing without preferential enrichment of tumor molecules

Single and degraded signal output only

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Novel Epigenomic Technology: Higher Signal-to-Noise Ratio at Lower Sequencing Costs

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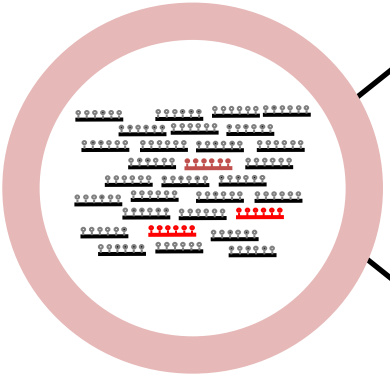
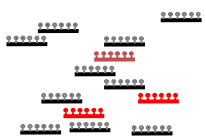
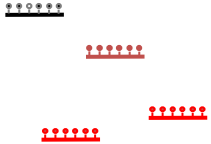


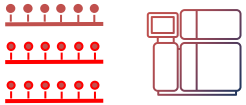
Novel Methylation Signal Enrichment



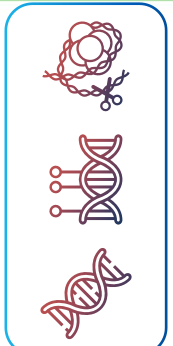
Efficient methylated molecule partitioning



Background depletion to improve signal-to-noise ratio



Low-cost sequencing of tumor molecules



Multi-modal signal output

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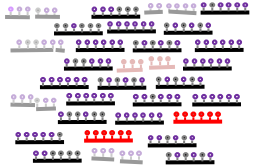

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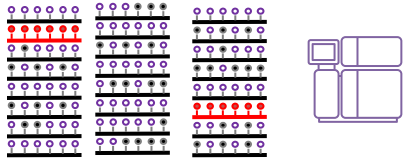

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Methylation Technology Development: Higher Signal-to-Noise Ratio at Lower Sequencing Costs

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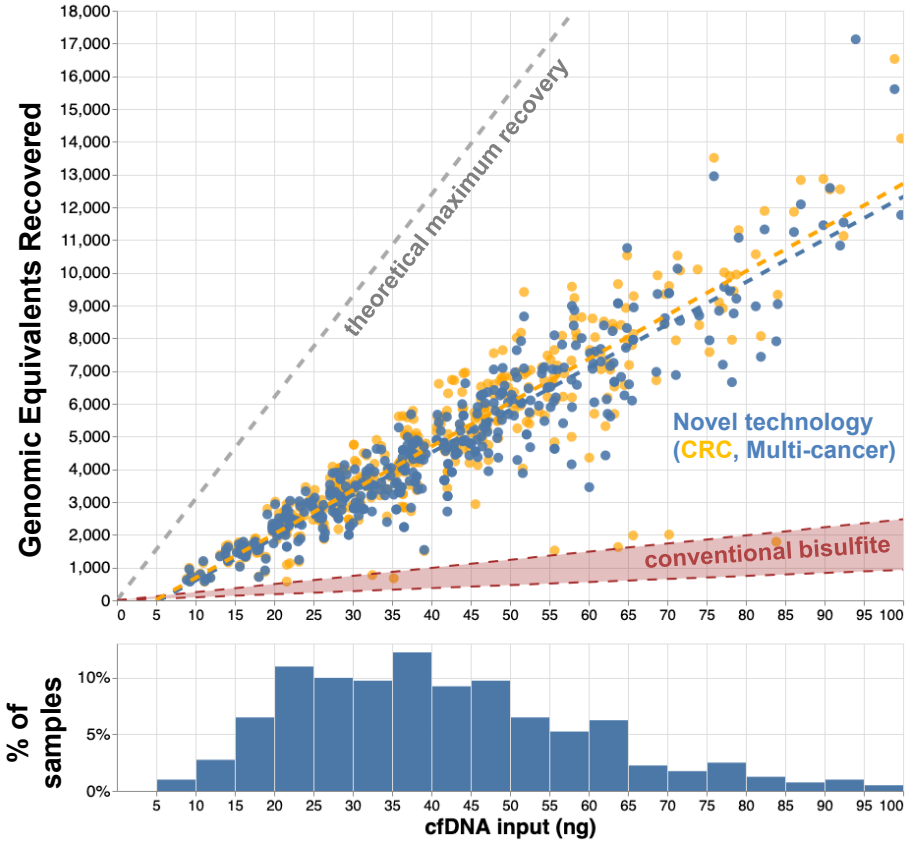
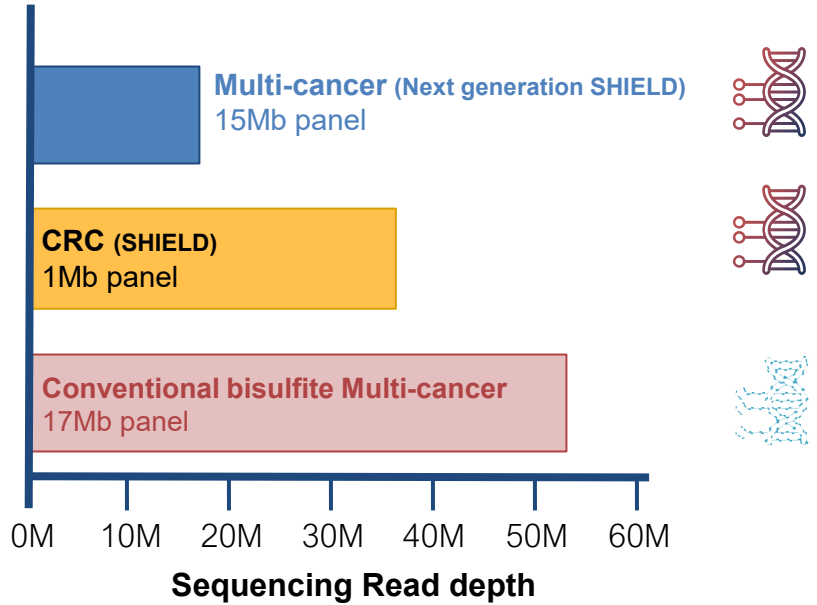


Technology utilizes a broad genomic panel to capture and sequence only tumor-associated molecules enabling high molecular recovery with low sequencing costs



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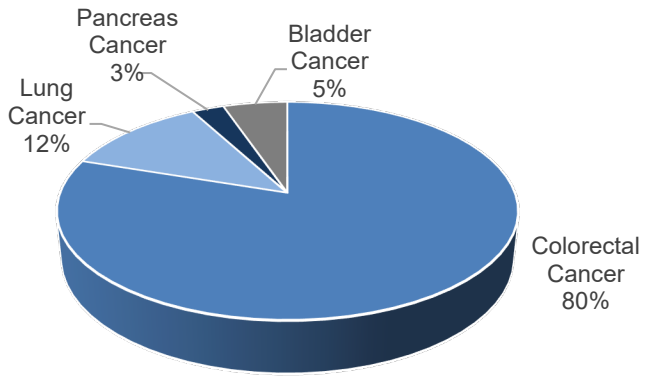
Methods: Clinical Cohorts

Cohort Demographics						
		Cancer – free (N = 1,862)	Colorectal Cancer (N = 1,274)	Lung Cancer (N = 191)	Pancreas Cancer (N = 42)	Bladder Cancer (N = 84)
Cancer Stage	I / II	-	54%	29%	26%	27%
	III / IV	-	46%	71%	74%	73%
Age (years)	Median (Range)	57 (18 – 86)	65 (19 - 93)	67 (23 – 93)	67 (39 – 83)	65 (35 – 94)
Number of unique cohorts		17	12	6	2	3

Cancer Distribution Across Cases



Results: Cancers with Population Screening Recommendations

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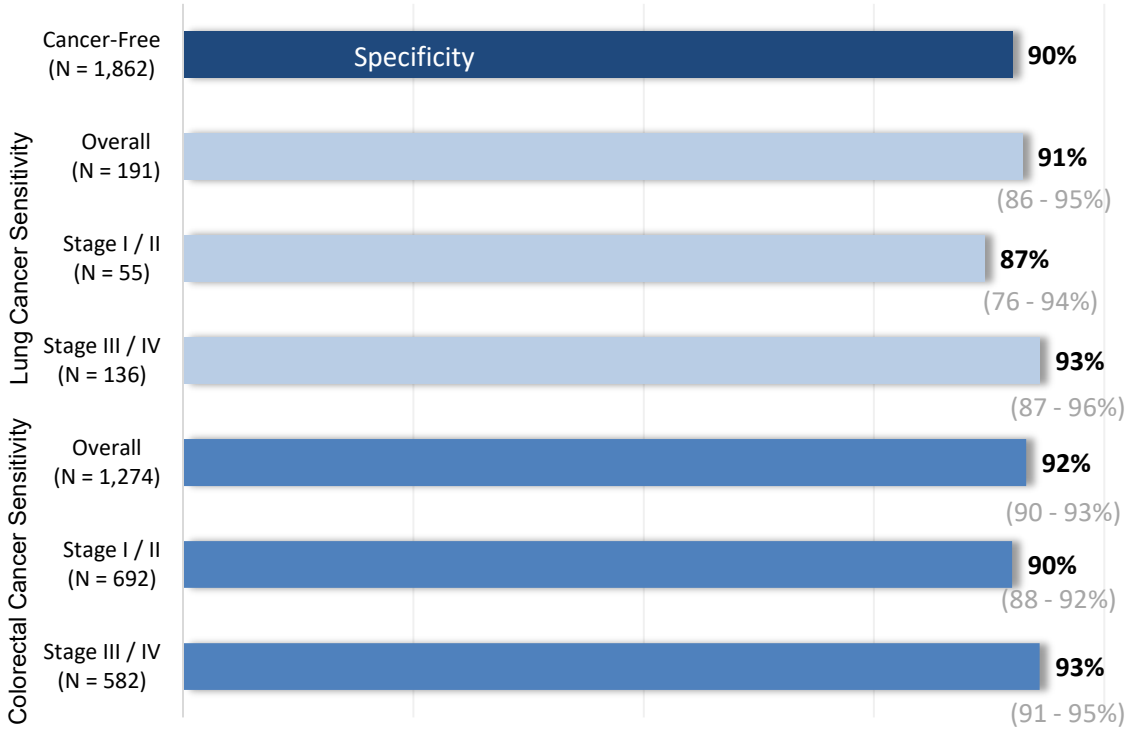

Current Cancer Screening Methods	
Low Dose CT[1]	Specificity 76% Sensitivity 80%
Colonoscopy[2]	Specificity 86% Sensitivity 95%
Fecal Immunohistochemistry[2]	Specificity 96% Sensitivity 74%
Multi-target stool DNA[2]	Specificity 87% Sensitivity 92%
Methylated Sept9 blood[2]	Specificity 81% Sensitivity 72%

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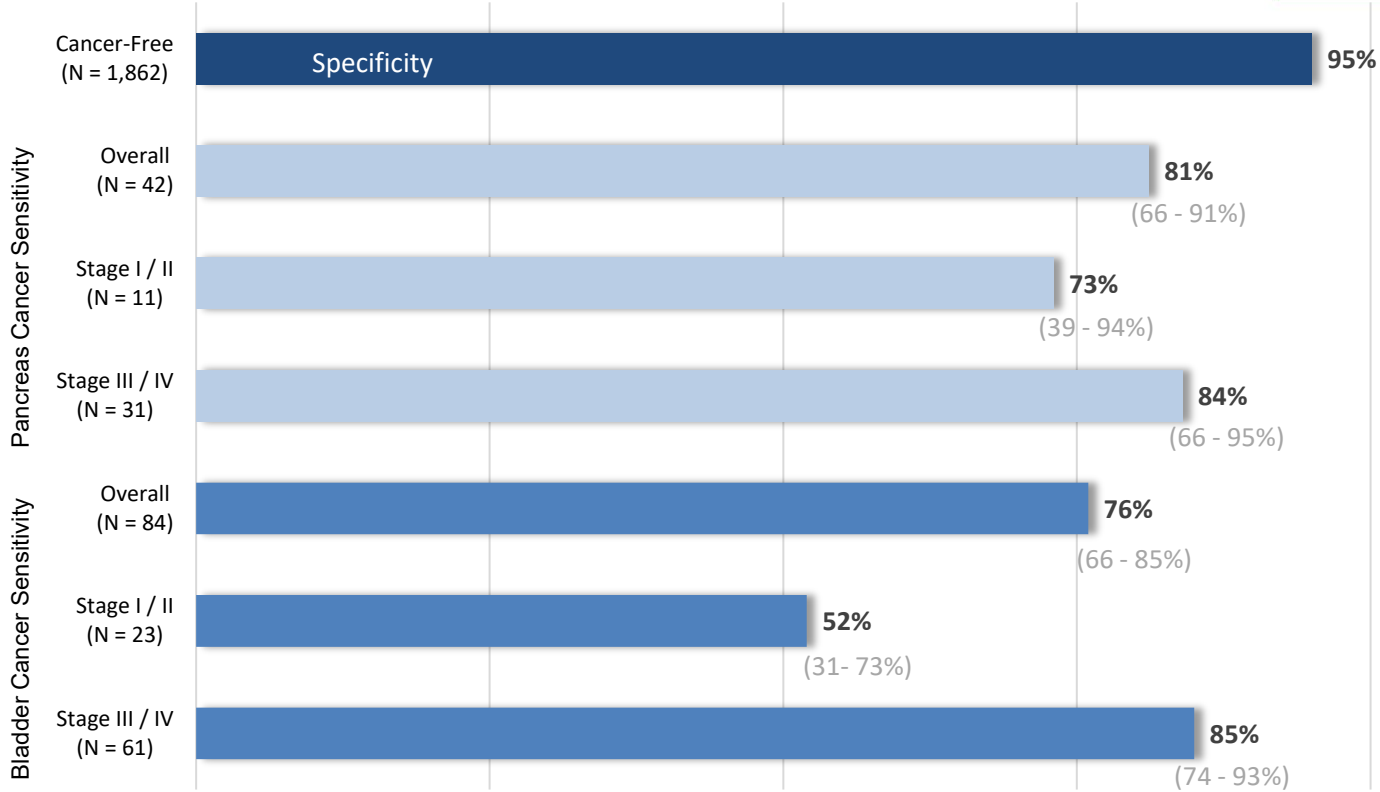

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Results: Multi-Cancer Assay with Accurate Tissue of Origin Prediction

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- Highly accurate tissue of origin (TOO) prediction is needed when more than one cancer type is evaluated as part of a single assay.
- The tissue of origin prediction evaluated at 98% specificity.

Accuracy Matrix*

Predicted Cancer Type	True Cancer Type: Colorectal Cancer	Lung Cancer	Bladder Cancer	Pancreas Cancer
Colorectal Cancer	0.99	0.05	0.0	0.03
Lung Cancer	0.0	0.94	0.12	0.1
Bladder Cancer	0.0	0.01	0.88	0.0
Pancreas Cancer	0.0	0.0	0.0	0.86

*Accuracy matrix: Percentage of true cancer types accurately predicted

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Limitations

- Cancer cases include screen detected and symptomatically detected cases
  - Not reflective of intended use screening population
- Self-reported healthy individuals were all-comers not reflective of intended use screening population in terms of age and risk factors

Conclusions

- This multi-cancer targeted screening assay provides robust and sensitive detection of early-stage cancer at thresholds optimized for current screening paradigms with accurate tissue of origin identification.
- The assay is undergoing further data development studies in additional cancer types where screening can save lives.
- Clinical evaluation in registrational screening trials is ongoing (NCT05117840).

Thank you

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- Questions?
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