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Performance Characteristics of a tissue-agnostic genome-wide methylome enrichment MRD assay for head and neck malignancies

Geoffrey Liu[1], Martha Pienkowski[1], Shao Hui Huang[1], Laurie Ailles[1], Katrina Rey-McIntyre[1], Jun Min[2], Yarong Wang[2], Justin Burgener[3], Ben Brown[2], Junjun Zhang[3], Owen Hall[2], Shu Yi Shen[3], Jeremy B. Provance[2], Eduardo Sosa[2], Joshua T. Jones[2], Brian Allen[2], Abel Licon[2], Jing Zhang[2], Anne-Renee Hartman[2], Daniel D. De Carvalho[3]

[1]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

[2]Adela, Inc., Foster City, CA

[3]Adela, Inc., Toronto, ON, Canada

Key Takeaways

- Head and Neck Cancers (HNC) are molecularly and etiologically heterogeneous tumors with high relapse rates
  - Early detection of recurrences can lead to earlier intervention and potentially better outcomes
- Blood-based approaches to detect recurrences that do not use tumor tissue (tissue-agnostic approaches) would be advantageous
  - No requirement for access to original tumor tissue or new biopsy
  - Quicker turnaround time / More efficient
- Here we demonstrate the use of a **tissue-agnostic genome-wide methylome enrichment platform** that predicts and detects recurrence and provides relative quantification in all HNC, including HPV-positive and HPV-negative subtypes

Background and benefits of MRD detection in head and neck cancer

- Head and neck cancer (HNC) consists of etiologically and molecularly distinct subtypes, including:
  - Smoking/Alcohol related HPV-negative subtypes
  - HPV-driven subtype
- Up to half of patients will relapse. Prognosis remains suboptimal due to:
  - the challenges of delivering **effective** curative intent treatment while managing **toxicities**
  - and the lack of standardized **surveillance** to detect recurrence
- Early detection of recurrent disease can help route patients to potentially novel approaches to early intervention and therapeutics
  - Molecular residual disease (MRD) assays

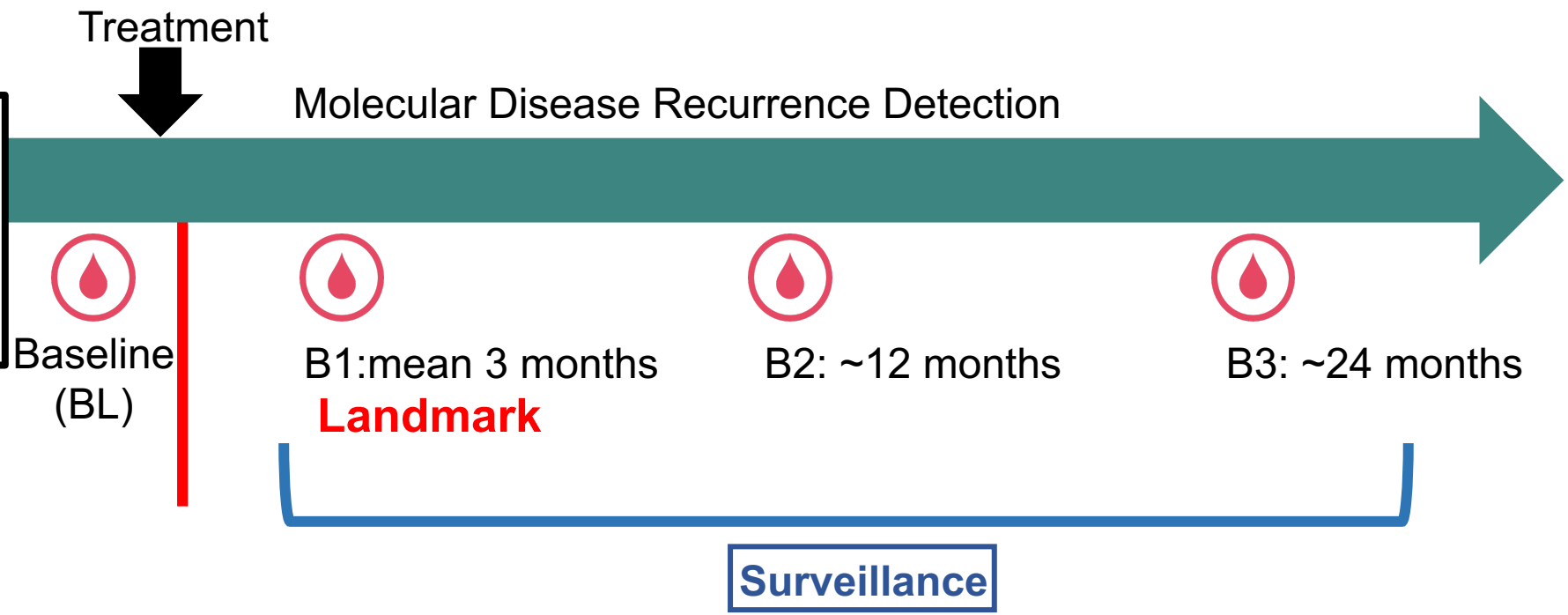
Study Design

Patient population:

Curative intent

- Total: 325 stage I-IVB pts
- Pre-defined subgroup:
  125 stage I-III HPV+ OPC pts

Single center:
Princess Margaret Hospital (PMH)
Staging 8th edition



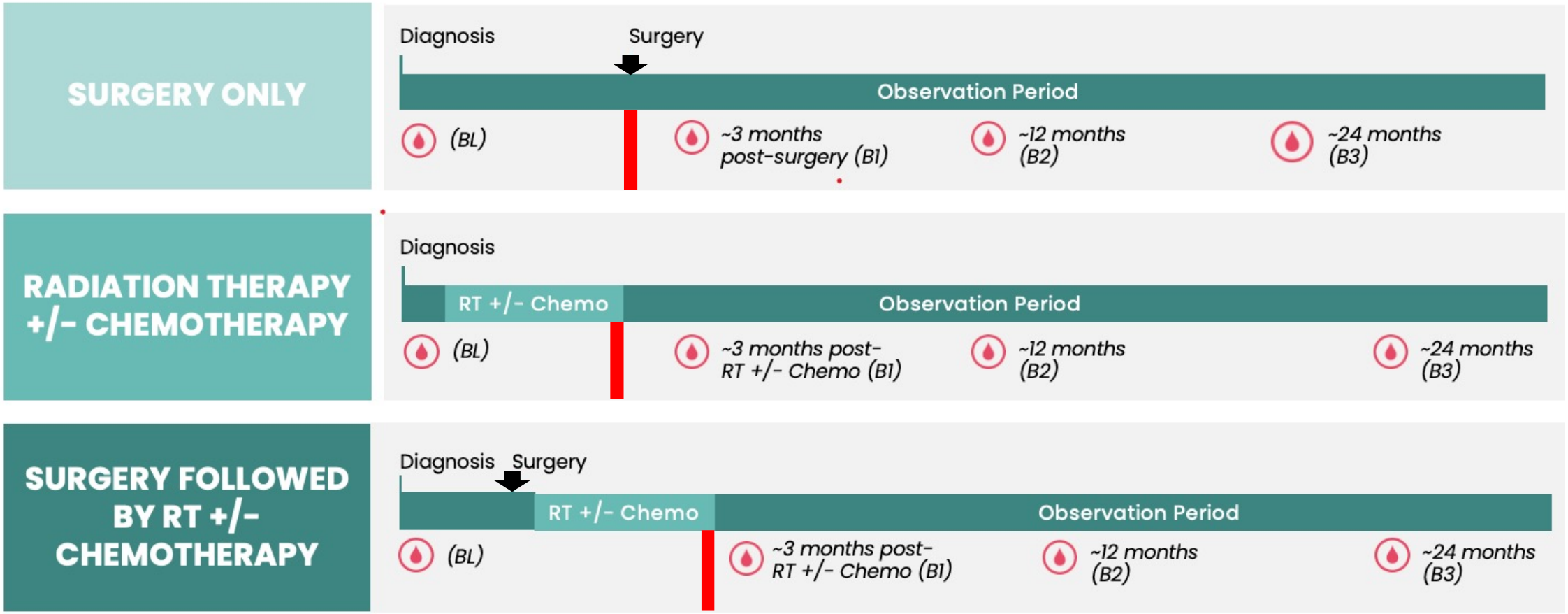
Plasma collected and cfDNA extracted

cfDNA profiled using a tissue-agnostic genome-wide methylome assay.

Plasma samples were split into distinct sets to train and test a classifier consisting of differentially methylated regions.

Curative intent treatment regimens in PMH cohort

Patients fall into one of three different treatment pathways:



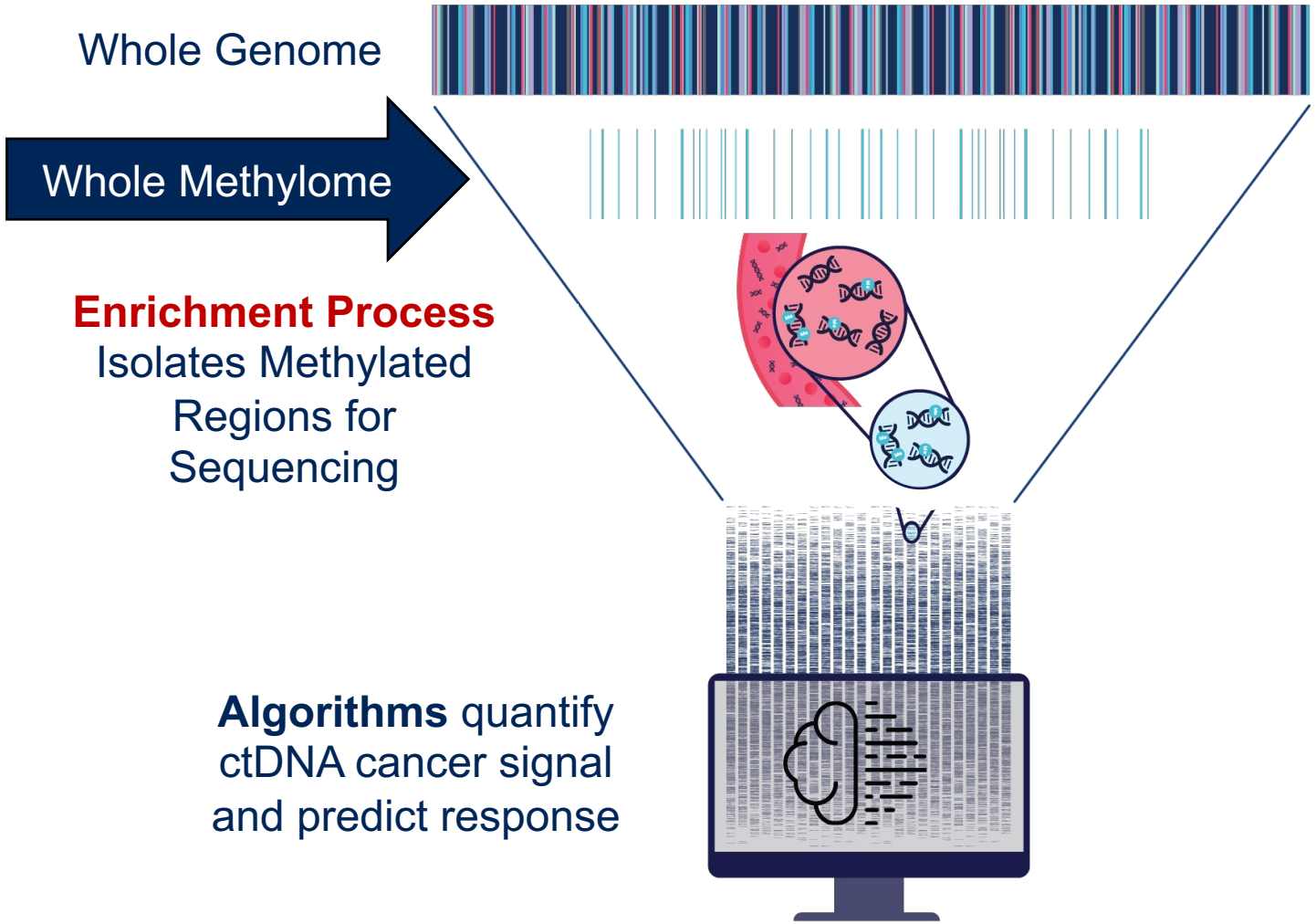
Training Cohort

Overall:
Patients (N=130)
Samples (N=432)
Recurrence (N=45)
Non-Recurrence (N=85)

Held out test set ~ (517 samples):
157 patients:
59 recurrences
98 non-recurrences

Characteristic		Mean	[SD]
Age		61	[10.53]
Characteristic		**N**	**(%)**
Sex	Female	27	(21%)
	Male	103	(79%)
Stage (AJCC 8th Edition)	Stage I	43	(33%)
	Stage II	19	(15%)
	Stage III	29	(22%)
	Stage IVA/B	39	(30%)
Histology	Squamous Cell Carcinoma (SCC)	124	(95%)
	Non-SCC	6	(5%)
Cancer Site	Oropharynx	70	(54%)
	HPV +	58	(83%)
	HPV -	12	(17%)
	Lip & Oral Cavity	29	(22%)
	Larynx	17	(13%)
	Other	14	(11%)
Smoking History	Yes	76	(58%)
	No	35	(27%)
	Unknown	19	(15%)

Genome-Wide Methylome Enrichment Platform Utilizing cfMeDIP-seq[1]

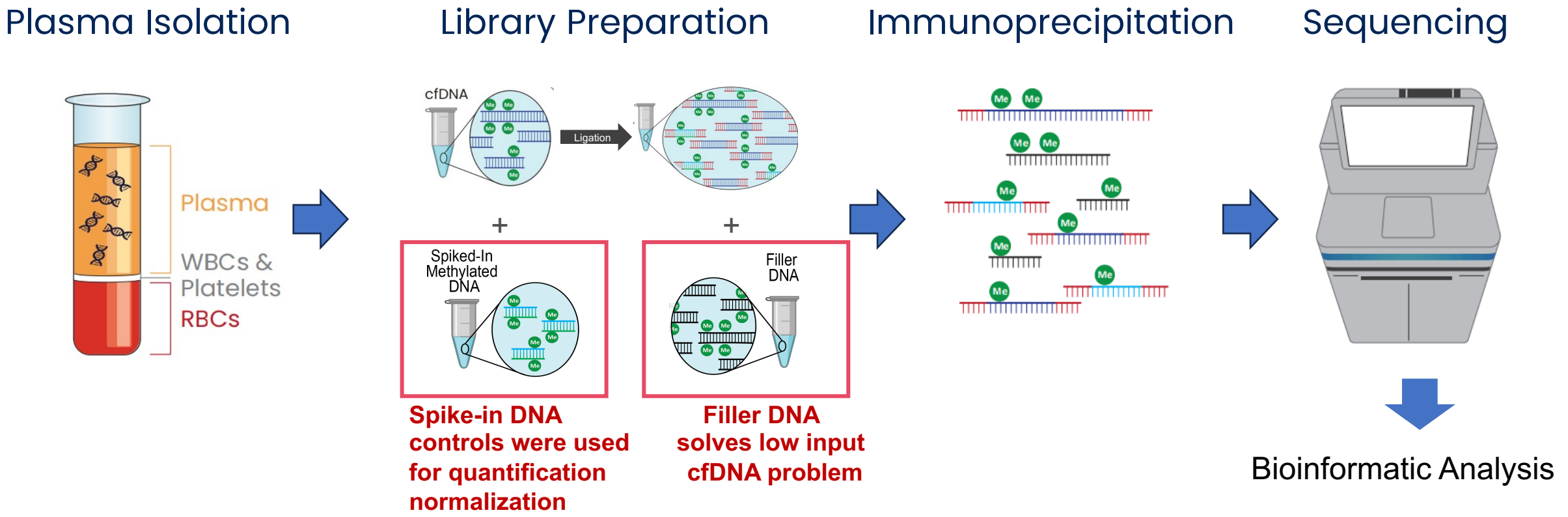


An efficient, comprehensive approach to detecting cancer and its underlying biology

[1]Utilizing Adela's cfMeDIP-seq platform

Genome-Wide Methylome Enrichment Platform Enables High Specificity for Recovery of Methylated cfDNA

Utilizes cfMeDIP-seq platform



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Statistical Methods

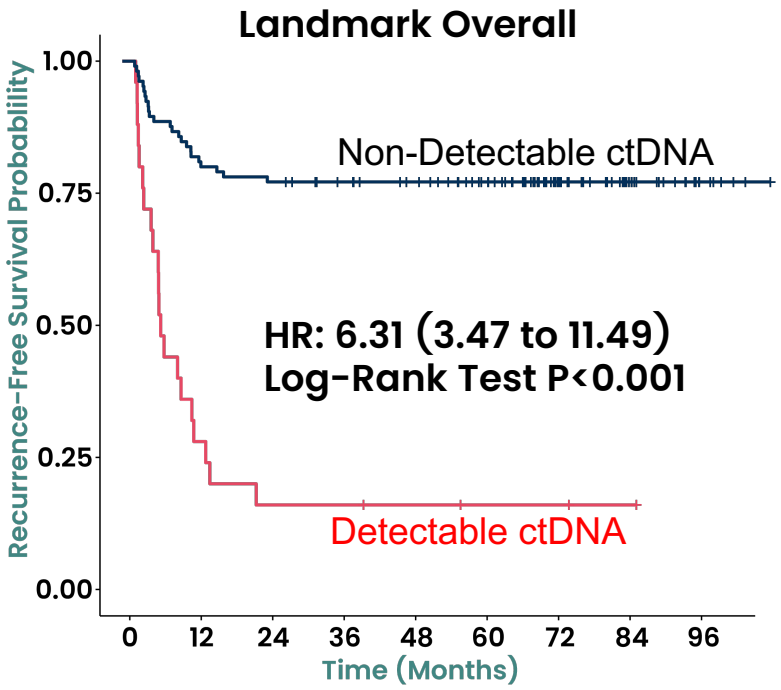
- Preliminary performance of the MRD assay to detect recurrence within the training set.
  - Kaplan-Meier curves plotted for ctDNA detected vs not detected (threshold-based).
  - Recurrence-free survival differences evaluated using a log-rank test.
  - Hazard Ratio estimated using a Cox proportional hazards model.

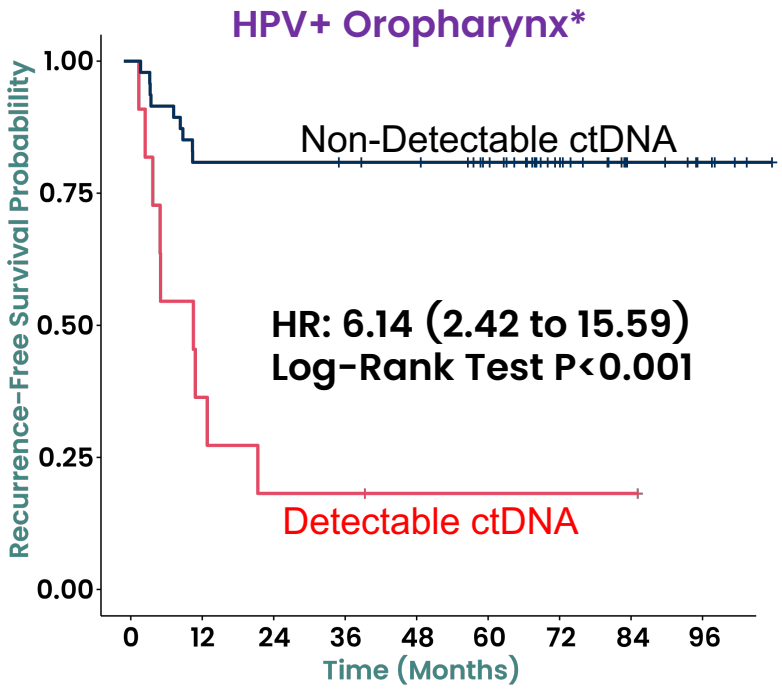
- Analyses performed:
  - At **landmark** timepoint.
  - Incorporating all **surveillance** blood draws.
  - In sub-groups to assess utility in **HPV+ oropharynx vs all other HNCs**.

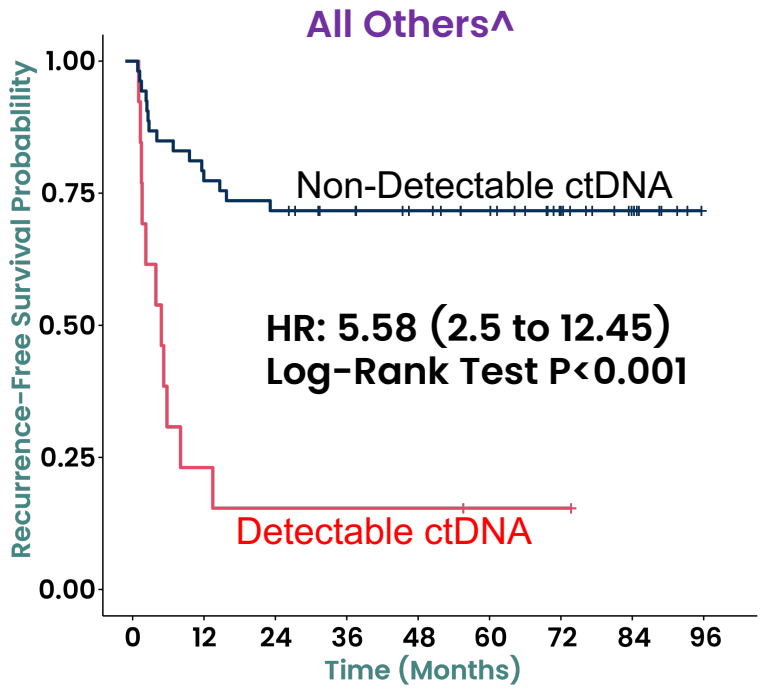
- Relative ctDNA quantification plotted over time to demonstrate the ability to monitor ctDNA kinetics.

Results: Landmark (mean 3 months after end of treatment): Detectable ctDNA above the threshold is predictive of poor survival outcomes in curative intent treated patients with HNC

ctDNA positivity correlates with RFS in both HPV positive and negative disease



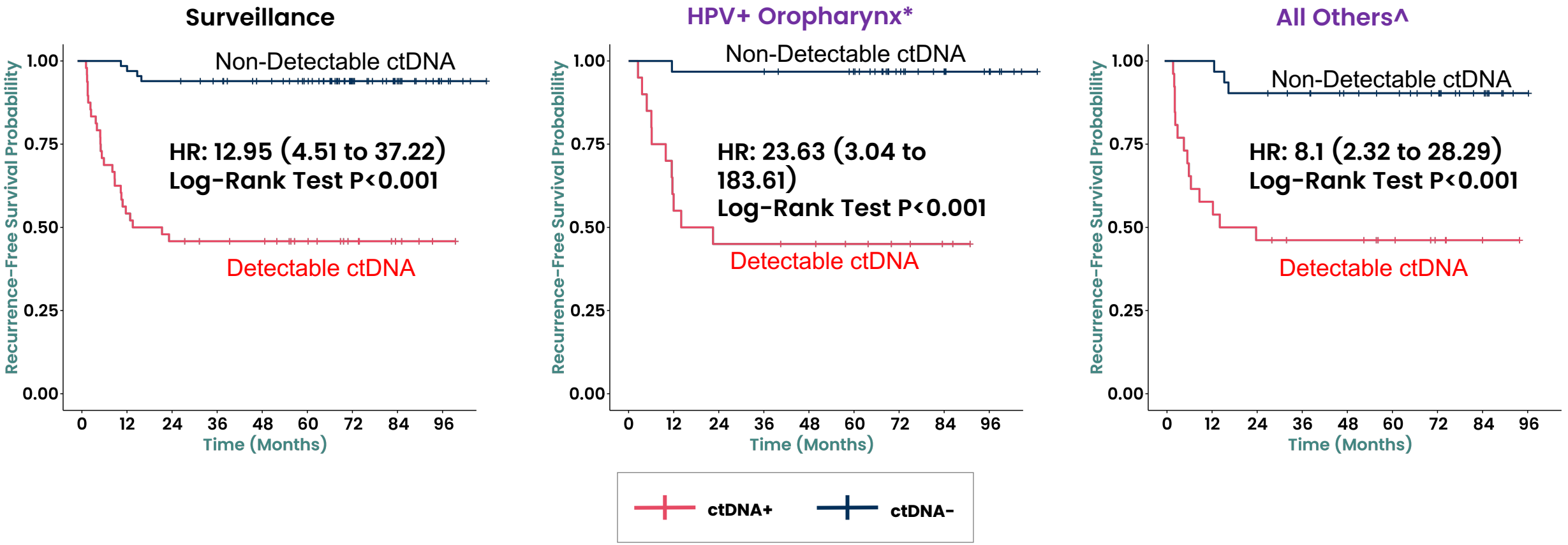




*Only squamous histology was included in this analysis
^*HPV- oropharynx and other subtypes

Results: Surveillance: Detectable ctDNA above threshold is predictive of survival outcomes in curative intent treated patients with HNC

ctDNA positivity correlates with RFS in both HPV positive and negative disease



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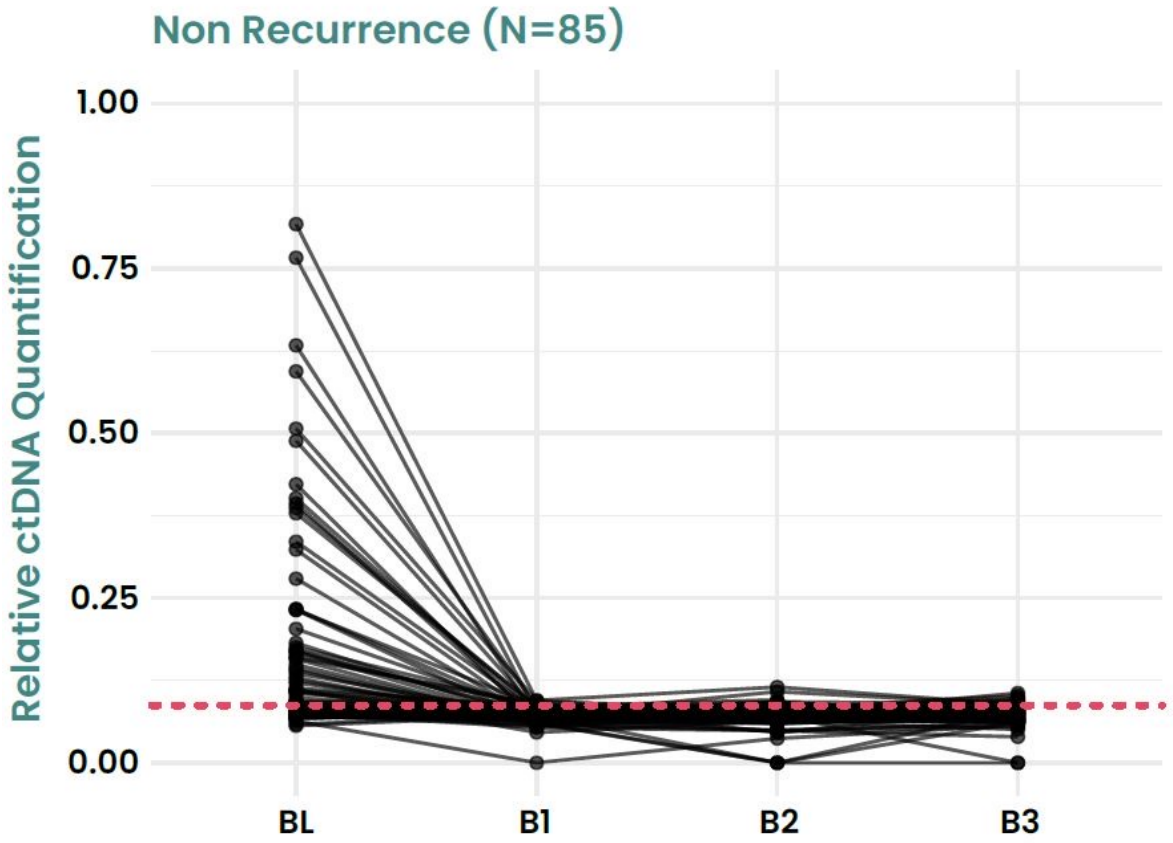
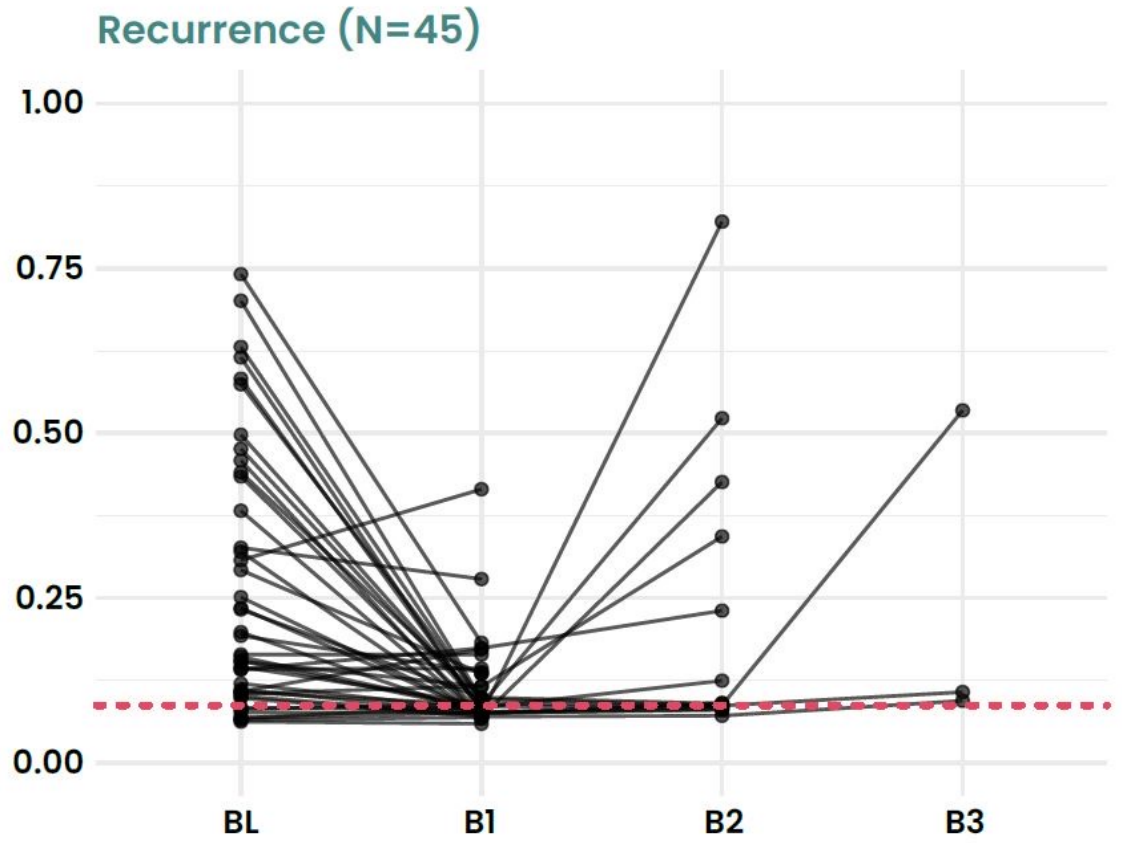
Changes with ctDNA Correlate with Outcomes

Demonstrates Feasibility of Monitoring Tumor Burden



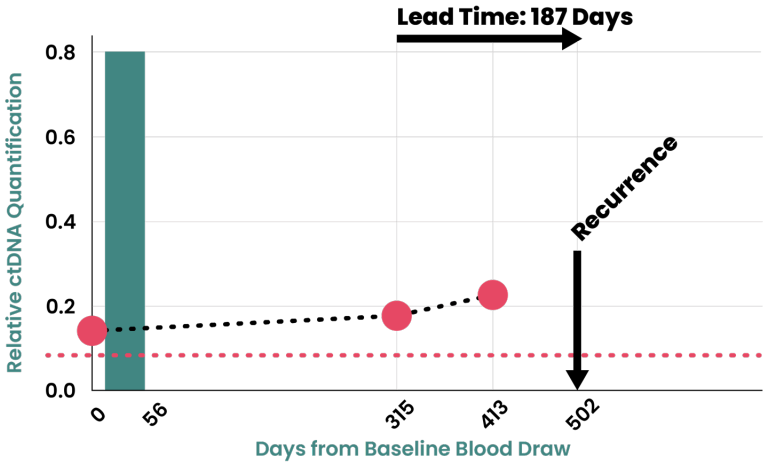


For non-recurrences, ctDNA relative quantification dropped at 3M and remained low at 12M & 24M.

For most recurrences, ctDNA relative quantification dropped at 3M but increased at 12M & 24M.

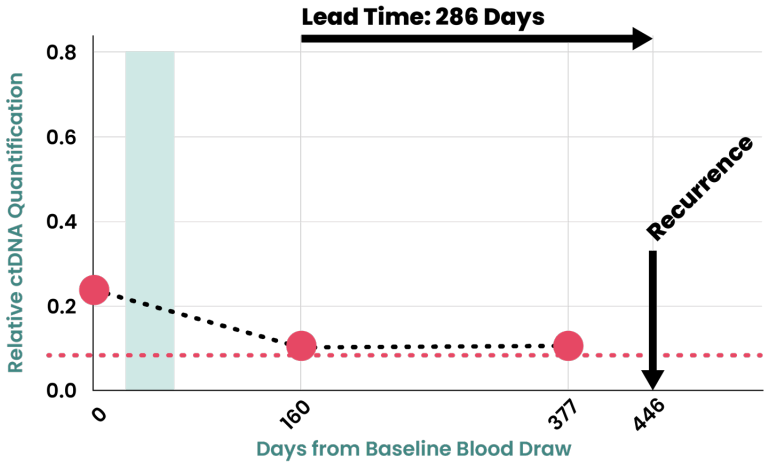
In relation to curative intent treatment: BL = pre-treatment B1 = ~3 months post B2 = ~12 months post B3 = ~24 months

Representative case studies of ctDNA kinetics in patients before and after curative intent treatment



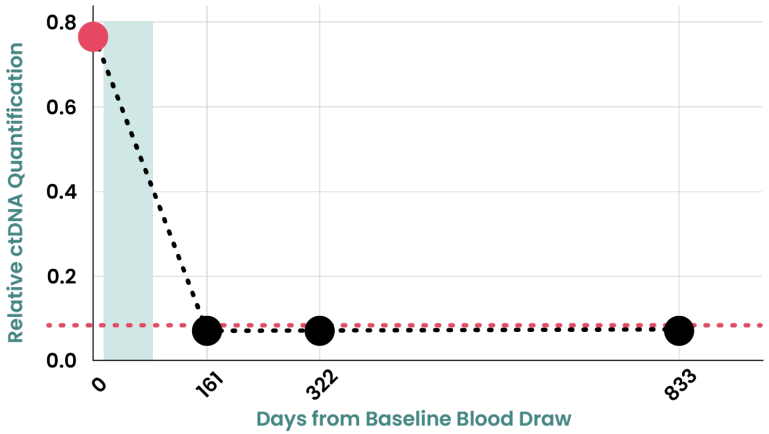
Patient A

Head and Neck Cancer, Stage: III
HPV-negative
Lead time of 187 days



Patient B

Oropharynx, Stage I
HPV-positive
Lead time of 286 days



Patient C

Non-Recurrence
Oropharynx, Stage I
HPV-positive

Conclusions and Next Steps

Conclusions: Here we demonstrate the use of a tissue-agnostic genome-wide methylome enrichment platform that predicts and detects recurrence and provides relative quantification in all HNC, including HPV-positive and HPV-negative disease.

Limitations

- A limited number of surveillance blood draws were available in the cohort.
  - This results in a potential underestimation of detectability and lead time.
- Cross-fold validation was used to reduce the bias of the performance estimate.
  - Assessing test performance in an independent set of samples will provide a more accurate validation of results.

Future Studies

- Final training and validation of the assay in a held-out test set is ongoing and will be reported in the future.

- After completion of clinical validation, the detection of cfDNA cancer signal has numerous practical advantages in both research and clinical settings; to guide curative intent treatment and detect recurrence before current standard of care.