AI enabled whole exome/transcriptome liquid biopsy addressing MCED, MRD, and therapy selection on a single platform

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Abstract

Background: cancer diagnosis, treatment and management are possible through the usage of multidisciplinary platforms. Herein, we present a unique Artificial Intelligent (AI)-enabled liquid biopsy platform that can provide sensitive and specific signals for the purpose of multi-cancer early detection (MCED), diagnosis, and therapy selection to minimal residual disease (MRD) and monitoring.

Methods: We utilized the Caris database composed of genetic data from over 350,000 tissue Whole Exome Sequencing (WES)/Whole Trasnscriptome Sequencing (WTS) of solid malignancies to train deep learning neural networks aimed at uncovering the molecular drivers of cancer. Additionally, WES/WTS sequencing was performed on 4,276 samples to develop a set of cell free DNA (cfDNA) specific features. One hundred and sixty-six of these samples had paired tissue sequenced WES/WTS to facilitate liquid biopsy variant validation. These features were organized into 'pillars' and integrated into the Assure Blood-based Cancer Detection AI (ABCDai) for early detection (binary classifier with 20-fold cross-validation) and tissue-of origin determination (multiclass classifier with 20-fold cross-validation). Subsequently, these models were evaluated using survival analysis on MRD and Monitoring samples.

Results: The Assure workflow detected CHIP mutations in 27% of samples, many of which were in clinically actionable genes (**Figure 1**). By leveraging CHIP subtraction, the detection of driver mutations from blood collected within 30 days of matched tumor tissue showed high concordance, with a Positive Percent Agreement (PPA)of 93.8% and a Positive predictive value (PPV) of 96.8%. Assure Plasma-derived features were independently significant for MCED (examples in **Figure 3**). When combined with tissue-identified features through ABCDai, we achieved an overall sensitivity of 87.4% at 99.5% specificity (**Figure 4**). ABCDai applied to plasma extracted before (MRD) and after (Monitoring) therapy showed significant stratification ($p<0.05$) for patient Disease-Free Survival (DFS), even when controlling for common clinicopathological variables (**Figure 5**). Tissue of origin is focused on those tumor types that are most common and thus provide the most utility (breast, CRC, gastric, H&N, NSCLC, ovarian, pancreatic, and prostate cancers). Among these cancers, we were able to determine the tissue of origin for 100% of the positive calls with an accuracy within the top three predictions of 84%.

CHIP Identification vital for therapy selection

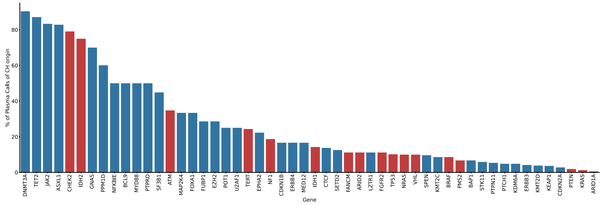


Fig. 1 -For each gene listed, the value shown is the percentage of the time that the variant is of CH origin. Variants Genes that are clinically relevant in solid tumors are marked in red.

Features powering the Assure Blood-based Cancer Detection AI - ABCDai

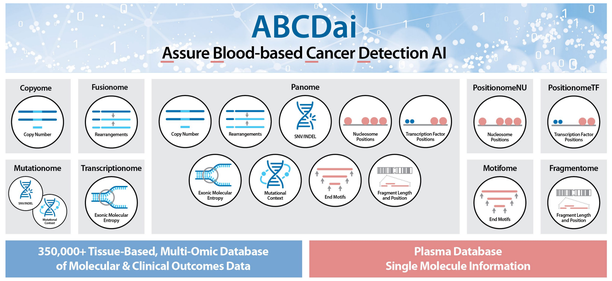


Fig. 2 - Pillars are derived from traditional tissue based bioinformatic features (left side) or from biologically relevant characteristics unique to cfDNA sequencing (right side). Machine learning models are trained separately using features from each pillar, and subsequently, these features are combined to train a comprehensive 'Panome' model and a ABCDai final layer that provides the final call and risk score.

Diverse patient and sample data used for development and validation

Table 1– Demographic and tumor origin distribution tables for the ABCDai, MRD and Monitoring cohorts.

Patient Characteristics	Early Detection *n* = 4,276	MRD *n* = 446	Monitoring *n* = 335
Patient Age at Diagnosis			
Median Age (range), years	61 (19-95)	62 (21-88)	62 (30-88)
Age <50, n(%)	811 (19.0)	84 (18.7)	61 (17.2)
Age 50-59, n(%)	1,134 (26.5)	112 (24.9)	86 (24.2)
Age 60-69, n(%)	1,396 (32.6)	134 (29.8)	111 (31.3)
Age >=70, n(%)	932 (21.8)	119 (26.5)	97 (27.3)
Unknown, n(%)	3 (0.1)	-	-
Gender			
Male, n(%)	2,082 (48.7)	97 (21.6)	79 (22.3)
Female, n(%)	2,194 (51.3)	352 (78.4)	276 (77.7)
Stage			
I, n(%)	596 (13.9)	123 (27.4)	95 (26.8)
II, n(%)	319 (7.5)	149 (33.2)	111 (31.3)
III, n(%)	344 (8.0)	169 (37.6)	142 (40.0)
IV, n(%)	1,170 (27.4)	2 (0.4)	2 (0.6)
Normal, n(%)	1,847 (43.2)	-	-
Unknown, n(%)	-	6 (1.3)	5 (1.4)
Body Mass Index (BMI)			
Median BMI (range)	-	25 (15-49)	25 (15-49)
Underweight, n(%)	-	11 (2.4)	8 (2.3)
Healthy Weight, n(%)	-	203 (45.2)	166 (46.8)
Overweight, n(%)	-	149 (33.2)	113 (31.8)
Obesity, n(%)	-	81 (18.0)	66 (18.6)
Unknown, n(%)	-	5 (1.1)	2 (0.6)

Cancer Origin Tissue	Early Detection *n* = 4,276	MRD *n* = 446	Monitoring *n* = 335
Bladder Cancer, (%)	61 (1.4)	5 (1.1)	4 (1.1)
Brain Cancer, (%)	14 (0.3)	-	-
Breast Carcinoma, (%)	94 (2.2)	204 (45.4)	159 (44.8)
Colorectal Cancer, (%)	226 (5.3)	109 (24.3)	83 (23.4)
Cancer of Unknown Primary, (%)	18 (0.4)	-	-
Cholangiocarcinoma, (%)	70 (1.6)	3 (0.7)	2 (0.6)
Esophageal Cancer, (%)	58 (1.4)	-	-
Gastric Cancer, (%)	518 (12.1)	8 (1.8)	6 (1.7)
Head and Neck Cancer, (%)	115 (2.7)	1 (0.2)	-
Kidney Cancer, (%)	278 (6.5)	-	-
Liver Cancer, (%)	16 (0.4)	-	-
Lung Cancer, (%)	191 (4.5)	17 (3.8)	14 (3.9)
Lymphoma, (%)	32 (0.7)	-	-
Melanoma, (%)	26 (0.6)	-	-
Neuroendocrine Tumors, (%)	13 (0.3)	-	-
Normal, (%)	1,847 (43.2)	-	-
Other, (%)	40 (0.9)	12 (2.7)	6 (1.7)
Other Female Genital Tract Malignancy, (%)	321 (7.5)	20 (4.5)	19 (5.4)
Ovarian Cancer, (%)	63 (1.5)	36 (8.0)	31 (8.7)
Pancreatic Cancer, (%)	94 (2.2)	27 (6.0)	25 (7.0)
Prostate Cancer, (%)	79 (1.8)	1 (0.2)	1 (0.3)
Small Bowel Cancer, (%)	40 (0.9)	6 (1.3)	4 (1.1)
Thyroid Cancer, (%)	30 (0.7)	-	1 (0.3)
Uveal Melanoma, (%)	32 (0.7)	-	-

cfDNA derived features show significant cancer signal

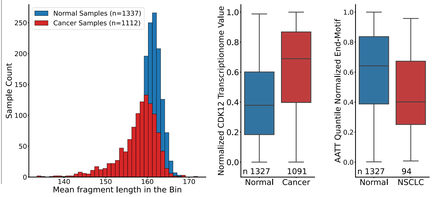


Fig. 3- A) Median fragment length across approximate 5MB bins for normal samples *vs.* late-stage cancer samples. B) Normalized Transcriptionome Entropy for *CDK12* shows a significant difference after multiple hypothesis correction C) The AATT Motifs shown to have significance between NSCLC and Normal cfDNA [(1)].

ABCDai detects cancer across a wide variety of cancer types and stages

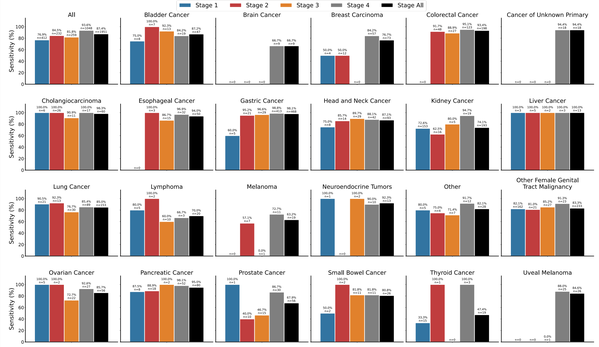
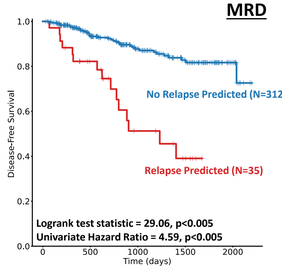


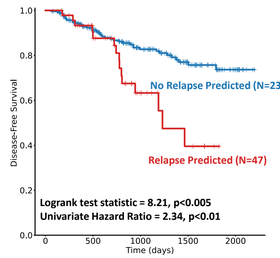
Fig. 4 - Sensitivity of ABCDai by Tumor Type and Stage. Bar plots representing the ABCDai sensitivity on aggregated held-out folds from 20-fold cross-validation.

ABCDai identifies residual disease and stratifies recurring patients



	MV Hazard Ratio	95% Confidence Interval	*p*-value
Model Prediction			
Recurrence Free	1.00	-	-
Recurrence	6.44	(3.33-12.45)	<0.001
Patient Age at Diagnosis			
<50*	1.00	-	-
50-59	1.43	(0.42-4.88)	0.56
60-69	3.52	(1.15-10.75)	0.03
>=70	1.89	(0.60-5.93)	0.28
Gender			
Male	1.00	-	-
Female	0.51	(0.26-0.99)	0.05
BMI Group			
Healthy Weight	1.00	-	-
Underweight	1.86	(0.55-6.33)	0.32
Overweight	0.41	(0.21-0.82)	0.01
Obesity	0.25	(0.09-0.70)	0.01
Stage			
1	1.00	-	-
2	1.19	(0.45-3.13)	0.72
3|4	2.86	(1.24-6.61)	0.01

(-): reference class



	MV Hazard Ratio	95% Confidence Interval	*p*-value
Model Prediction			
Recurrence Free	1.00	-	-
Recurrence	1.96	(1.04-3.68)	0.04
Patient Age at Diagnosis			
<50*	1.00	-	-
50-59	1.38	(0.46-4.17)	0.56
60-69	3.05	(1.14-8.11)	0.03
>=70	2.48	(0.89-6.93)	0.08
Gender			
Male	1.00	-	-
Female	0.77	(0.41-1.43)	0.40
BMI Group			
Healthy Weight	1.00	-	-
Underweight	3.15	(0.88-11.23)	0.08
Overweight	0.49	(0.25-0.96)	0.04
Obesity	0.55	(0.25-1.22)	0.14
Stage			
1	1.00	-	-
2	2.09	(0.82-5.31)	0.12
3|4	3.38	(1.45-7.87)	<0.001

(-): reference class

Fig. 5 - Kaplan-Meier survival curves depict MRD (top), or Monitoring (bottom) samples categorized into risk groups using an ABCDai pillar's model. Multivariate (MV) hazard ratios in tables account for common clinicopathological variables, with an event defined as patient relapse or death post-surgery.

ABCDai adresses important clinical needs

	Sensitivity	PPV	Specificity
Metastatic, Driver SNV/INDEL Variants	93.8	96.8	100
Multi-cancer Early Detection	87.4	99.5	99.5

	Univariate HR	Multivariate HR	Logrank Statistic
MRD	4.59	6.44	29.06
Monitoring	2.34	1.96	8.21

Fig. 6 – Performance Metrics of the ABCDai platform towards selection of molecularly targeted therapies, MCED, and MRD and monitoring. (HR): Hazard Ratio.

Conclusions

- We demonstrate that a comprehensive whole-exome and transcriptome-wide liquid biopsy is a versatile solution to address the entire continuum of blood-based clinical applications, including early detection and potential screening for cancer, molecularly based cancer diagnosis, monitoring of MRD and recurrence in the early-stage curative approach setting, and precision selection of therapy for patients with advanced metastatic disease with targetable driver mutations.
- Our approach is unique in that we performed high-depth sequencing of white blood cells in addition to cfDNA/RNA from plasma. This provides an important capability to detect mutations derived from clonal hematopoiesis. Equally importantly, this approach also allows for the detection of incidental germline alterations that can have both therapeutic and familial implications.
- We demonstrated the detection of malignancies at their earliest stages across various solid tumor types with a PPV higher than any other clinical platform to date.
- Our results illustrate the application of our liquid biopsy by leveraging a model built to predict MCED in the MRD setting. Patients who were MRD-positive had significantly inferior DFS than those who were MRD-negative. Importantly, the approach employed to detect MRD does not rely on a priori genomic information from the primary tumor.
- Proper clinical intervention requires knowledge of the tissue of origin, and the molecular information provided by Caris Assure can assist in this determination as ABCDai was able to determine the tissue of origin for 100% of the positive calls with a top three accuracy of 84%.

References

1. Guo W, Chen X, Liu R, et al. Sensitive detection of stage I lung adenocarcinoma using plasma cellfree DNA breakpoint motif profiling. EBioMedicine. 2022;81:104131. doi:10.1016/j.ebiom.2022.104131