

performance was assessed using sensitivity, specificity, and potential clinical utility in ruling out MSS patients.

**Results:** The models were validated on 5 (CRC), 2 (GC), and 2 (EC) external cohorts. At sensitivity thresholds aligned with clinical standards (CRC: 0.95; GC/EC: 0.90), specificities reached 0.62 (CRC), 0.69 (GC), and 0.44 (EC). Based on disease prevalence, the models could directly rule out MSI testing for 56% of CRC, 62% of GC, and 33% of EC patients, indicating significant triage potential.

**Conclusions:** This study demonstrates the robust performance of AI models in predicting MSI status across multiple external datasets. These models could lead to up to 60% of patients being directly ruled-out from further MSI testing. These models offer a scalable, potentially cost-effective solution to optimize MSI testing workflows, ultimately increasing the number of patients being tested.

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### 1757eP Tumor fraction, tumor volume, and anthropometry on CT scans as key determinants of prognosis in metastatic disease

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**Background:** Total tumor volume (TTV) on CT scans, circulating tumor DNA (CTDNA) from liquid biopsy, known as tumor fraction (TF), as well as 3D anthropometric measurements, are indicators for predicting overall survival (OS) in metastatic patients.

**Methods:** Metastatic patients who had a baseline CT scan and liquid biopsy (STING, NCT04932525, Gustave Roussy) were included from January 2021 to December 2023 in this retrospective study. Data collected include age, sex, cancer type, treatment line, and date of death. CT scans were anonymized and manually annotated in 2D by senior radiologists on the SPYD platform, with a 3D tumor volume estimate calculated (Tumor volume = 2/3 x Mesh surface area x Minor axis). TF was reported as a percentage. The Anthropometer3DNet software provided 3D measurements for muscle, superficial, and deep fat masses; combined with TTV and with Cox model coefficients to generate a CT scan risk score. Patients were grouped based on TF ( $\geq 0\%$ ) and then divided into two subgroups according to the CT scan risk score (below or above the median). OS was the primary endpoint, and the analyses were carried out using Kaplan-Meier estimators and log-rank statistics.

**Results:** Among 720 patients 38,283 metastases were annotated. The median OS was 13.11 months (95% CI: 11.50-15.11). The median TF was 3.30% (IQR 20%), and the median TTV was 91.61 cm<sup>3</sup> (IQR 213.68 cm<sup>3</sup>). Of these patients, 213 (29.58%) had a TF of 0%, despite showing tumor burden on the CT scan, with a median TTV of 35.34 cm<sup>3</sup> (IQR 84.00 cm<sup>3</sup>). For those with TF=0%, the median OS was 10.15 months (95% CI: 8.71-11.60), compared to 25.46 months (95% CI: 21.26-30.09) for those with TF > 0%. In the TF=0% group, patients with a low CT-scan risk score had a median OS of 35.35 months (95% CI: 27.10-44+ months), while those with a high CT-scan risk score had a median OS of 19.35 months (95% CI: 13.37-25.36). In the TF > 0% group, those with a low CT-scan risk score had a median OS of 13.24 months (95% CI: 6.54-13.24), whereas patients with a TTV above the median had a median OS of 7.46 months (95% CI: 6.54-13.24). The survival curves for these groups were significantly different ( $p=0.003$  vs  $p<0.001$ ).

**Conclusions:** TTV and anthropometric measurements, when combined with TF offer a more precise prediction of OS.

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### 1758eP An advanced cell-free DNA assay for prostate cancer early detection established by machine learning algorithm using whole-genome sequencing fragmentomic features

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**Background:** Early detection of prostate cancer is challenged by the limited specificity of prostate-specific antigen (PSA)-based screening. Circulating cell-free DNA (cfDNA) fragmentomics may offer a promising non-invasive approach to improve screening accuracy and risk stratification.

**Methods:** This study retrospectively enrolled 106 patients with prostate cancer and 114 high-risk non-cancer individuals (training cohort) to develop a fragmentomics-based cfDNA assay for prostate cancer screening via plasma whole-genome sequencing. The fragmentomic features of copy number variant and fragmentation size profile were involved in machine learning algorithms for model training, followed by performance assessment in an independent cohort (validation cohort) including 83 cancer patients and 76 non-cancer individuals. We further combined the cfDNA assay with PSA to establish an integrated algorithm and evaluated its performance.

**Results:** The fragmentomics-based algorithm achieved an area under the curve (AUC) of 0.939 (66.0% sensitivity at 95.6% specificity; 51.9% sensitivity at 98.2% specificity) when distinguishing cancer from non-cancer samples in the training cohort, with good calibration (slope, 1.371; intercept, -0.036). Similar discrimination was observed in the validation cohort using the threshold fixed in the training cohort (57.8% sensitivity at 92.1% specificity; AUC, 0.887), exhibiting a trend of elevating predictive probabilities ( $p=0.058$ ) and decreased sensitivity (I, 27.3%; II, 55.3%; III, 68.0%; IV, 77.8%) across increased disease stages. Notably, the fragmentomics-based assay demonstrated outstanding performance within individuals having PSA between 4 and 10 ng/mL (AUC, 0.865; 69.0% sensitivity at 81.8% specificity). The integrated algorithm had higher AUC (0.915) and sensitivity at 98% specificity (I, 30.0%; II, 66.7%; III, 76.0%; IV, 87.5%) within the validation cohort.

**Conclusions:** We developed an advanced cfDNA assay utilizing plasma cfDNA fragmentomic features, which reached high accuracy for prostate cancer early detection, offering a promising tool in clinical practice.

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### 1759eP Fast and simple biomarker testing qPCR platform for simultaneous DNA and RNA variant detection in non-small cell lung cancer clinical trials using tissue or liquid biopsies

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**Background:** Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related deaths worldwide, necessitating the development of tools for early sensitive detection and personalized treatment. Current methods for biomarker testing, particularly those using FFPE tissue or liquid biopsies, are often time-consuming and complex. Aspyre® Lung is a rapid and sensitive assay that addresses gaps in multiplexed testing by simultaneously analyzing DNA and RNA from FFPE or liquid biopsies, detecting 114 somatic variants across 11 clinical practice recommended genes (*EGFR*, *BRAF*, *KRAS*, *ERBB2*, *ALK*, *ROS1*, *RET*, *MET*, *NTRK1-3*). The technology utilizes targeted multiplex (RT)-PCR amplification, pyrophosphorolysis reaction and real-time rolling circle amplification to detect somatic single nucleotide variants, insertions, deletions, exon skipping and fusions associated with NSCLC.

**Methods:** The assay is commercially available as a Research Use Only product (Cat n° AS-001-02-04, Biofidelity Ltd.), which CellCarta has implemented, in close collaboration with Biofidelity Ltd., as a clinical trial assay (CTA) according to ISO 13485 (IVD) regulations. Hence, CellCarta is able to offer the assay for patient management decisions in NSCLC clinical trial testing.

**Results:** Assay validation of Aspyre® Lung was performed at CellCarta Antwerp (EU) and CellCarta Naperville (US). Analytical sensitivity determined by Biofidelity Ltd. was verified on a total of 30 blank FFPE and plasma samples in compliance with CLSI EP17A2. Trueness data was generated by comparing Aspyre® Lung results to NGS data from 48 FFPE and 32 plasma samples. Precision was evaluated by assessing the consistency of measurements within and across runs and sites. All performance characteristics met initial acceptance criteria established by Biofidelity Ltd. resulting in successful assay implementation.

**Conclusions:** The Aspyre® Lung is now available at CellCarta, supporting patient management studies across both Europe and the United States (assay will be

available in China 2026). This offering leverages the clinically validated CTA, ensuring high-quality, reliable data for research and clinical decision-making.

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### 1760eP Multi-cohort analysis reveals diagnostic potential of intratumoral microbiota across cancer types

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**Background:** While large-scale pan-cancer studies have extensively characterized host genomic and molecular features, systematic analyses of microbial signatures across diverse cancer types remain scarce. This study aims to address this gap by employing 16S rRNA sequencing to profile intratumoral microbiota across multiple tumor types.

**Methods:** We integrated microbiome data from 16 published studies and one large validation cohort, encompassing 2,839 samples across nine cancer types and normal controls. In addition, we included an independent validation set consisting of 541 tumor samples collected at the Cancer Hospital, Chinese Academy of Medical Sciences. Using QIIME2 for preprocessing and DADA2 for ASV detection, we performed microbial diversity analysis, co-occurrence network construction, taxonomic and functional annotation (via PICRUSt2 and KEGG), and supervised machine learning classification with Random Forest and other models.

**Results:** Significant differences in both alpha and beta diversity were observed across cancer types, with colorectal cancer (CRC), oral cancer (OC), and bladder cancer (BCa) showing high microbial diversity, while gastric cancer (GC) exhibited reduced diversity. LEfSe analysis (LDA > 2, p < 0.05) identified tumor-specific microbial signatures, including the enrichment of genera such as *Ralstonia* and *Treponema* in the breast cancer (BC) group, and *Fusobacterium* in Bca group. Additionally, metabolic pathway analysis revealed significant differences across cancer types, with the lung cancer (LC) group primarily enriched in metabolism-related pathways, while CRC showed associations with immune-related pathways. The Random Forest model achieved the highest classification performance (AUC = 0.92), with *Cutibacterium* and *Pelomonas* as key contributors. Grouping strategies based on tumor biology or anatomical origin further enhanced classification performance.

**Conclusions:** Our findings highlight the ecological and functional diversity of intratumoral microbiomes and support the development of microbiome-informed diagnostic tools.

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### 1762eP Canine olfaction as a non-invasive tool for lung cancer detection

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**Background:** Lung cancer (LC) is the leading cause of cancer-related death, with an estimated 1.8 million deaths worldwide each year. Recently, low-dose CT screening has been shown to reduce mortality by enabling the detection of early-stage lesions. However, the widespread implementation of this screening method is costly and primarily limited to current or former smokers. Dogs have demonstrated a remarkable ability to detect lung cancer through their highly sensitive sense of smell. Studies suggest they can identify cancer-related volatile organic compounds with notable accuracy, offering a potentially low-cost, non-invasive alternative for early detection that could be extended to the general population.

**Methods:** We conducted a double-blind study with five domestically raised dogs of various breeds and ages (four males and one female), with no prior experience in olfactory detection. They were trained over a six-month period using operant conditioning to perform a specific behavioral response to the scent of cancer, with food used as a positive reinforcer. Exhaled breath samples from LC patients and from control donors (either healthy individuals or those with other respiratory diseases) were randomly placed in an eight-position carousel, containing zero, one, or two cancer samples per trial. A positive indication was defined as the execution of the trained behavior in response to a cancer sample.

**Results:** A total of 5845 trials were conducted (1169 per dog), using 174 samples from cancer patients and 995 samples from healthy volunteers or individuals with other respiratory diseases. Dogs showed a sensitivity of 0.99 and a specificity of 0.99 in detecting LC. The positive predictive value was 0.99 and the negative predictive value was 0.99.

**Conclusions:** Our results are consistent with previous findings on the ability of dogs to detect cancer with high accuracy and highlight the strong effectiveness of our conditioning-based training method. Since early-stage detection has been shown to significantly impact survival through LC screening, a study is being planned to explore the detection of small pulmonary lesions. This prospective work will examine the potential complementarity of canine olfaction with other techniques, such as liquid biopsy.

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### 1764eP A multi-omic liquid biopsy for early colorectal cancer detection

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**Background:** Colorectal cancer (CRC) is one of the most common and deadliest cancers worldwide, and incidence rates are rising. However, early detection and intervention can improve the survival rates and quality of life of affected patients. The preferred screening choice is still debated, due to the lack of available resources and the invasiveness of colonoscopy, and the relatively low sensitivity of stool-based tests. Blood-based CRC detection offers an attractive screening strategy.

**Methods:** The Dxcover Liquid Biopsy Platform is a rapid multi-omic liquid biopsy that interrogates a blood sample with infrared (IR) radiation and produces a distinctive signature that represents the whole biomolecular profile of the sample. The technique analyzes the full range of diagnostic information from both the tumor and the non-tumor response. CREATE-2 is a prospective, multicenter, case-control study, with collection sites across the USA and the UK. Blood was drawn either pre-colonoscopy or pre-surgery. Streck plasma samples were analyzed and the spectral data has been used to generate machine learning algorithms. Diagnostic models have been trained by cross-validation strategies to independently predict the presence of disease in unknown samples. The nature of the technology also allows for the diagnostic models to be tailored towards higher sensitivity (or specificity) depending on clinical priorities and international healthcare markets.

**Results:** The US data (n=960) generated a receiver operating characteristic curve (ROC) curve with an area under the curve (AUC) of 0.96, with 91% for both sensitivity and specificity. Furthermore, 100% of stage I and II CRC were detected (n=18). For