

#2822 Predicting Histology in Small Cell, Squamous Cell, and Adenocarcinoma of Lung using ctDNA: A Real-World Analysis



Jessica Zhang¹, Jack Shapiro¹, Samer Yassin¹, Dilsa M. Kaya², Liam I. Chung², Nisha A. Mohindra², Jacobi B. Hines², Bilal Anouti², Dean Tsarwhas², Young Kwang Chae²

¹Department of Medicine, Northwestern Medicine, Chicago, Illinois, USA

²Division of Hematology/Oncology, Department of Medicine, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois, USA



IASLC 2026 World Conference on Lung Cancer

SEPTEMBER 12 – 15, 2026
SEOUL, REPUBLIC OF KOREA

Background

Small cell and non-small cell lung cancer (SCLC and NSCLC) exhibit **distinct tumor biology and therapeutic approaches**, making the timely and accurate diagnosis of each essential.

Recently, the circulating tumor DNA (ctDNA) assay **Guardant G360 Liquid** has incorporated a DNA methylated-based model to predict **molecular tumor type (TT) and lung cancer subtype (ST)**.

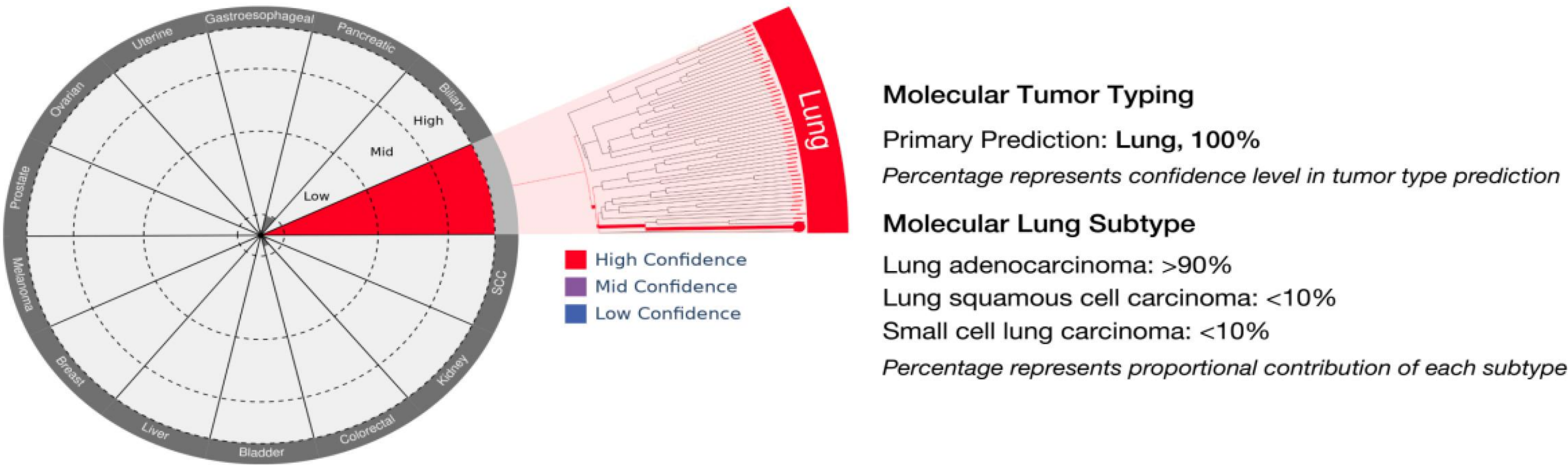
In this **real-world cohort**, we evaluated the **concordance between ctDNA histology prediction and conventional tissue pathology** in patients with small cell, squamous cell, and adenocarcinoma of the lung. We also explored clinical and molecular factors associated with successful histology prediction

Methods

- This **retrospective study** included patients with lung cancer who underwent G360 testing from May to October of 2025.
- G360 predicted TT and ST** (proportion of adenocarcinoma, squamous cell carcinoma, and small cell carcinoma) (Figure 1).
- TT was defined as the predominant tumor origin prediction. ST classification was defined as a proportion >80%.
- Agreement** between ctDNA TT/ST and tissue pathology was determined using **Cohen's kappa coefficient**.
- Demographic, clinical, and genomic characteristics were compared between patients with and without TT/ST prediction.

G360 Molecular Tumor Type and Lung Subtype Predictor

Figure 1. A sample G360 report of TT/ST prediction



Results

- A total of **150 patients** were included (145 patients with NSCLC, 5 with SCLC).
- The median age was 69 (IQR 63-76), 59% were female, and 79% had advanced NSCLC (stage III/IV).
- Of these 150 patients, 50 (33%) had ctDNA histology prediction, including 9 patients with TT prediction only and 41 with both.
- Patients with TT/ST prediction were **statistically** younger, had more advanced disease, and had higher ctDNA tumor fraction than those without TT/ST prediction (Table 1).
- There were no statistical differences in the mutational landscape of patients with and without ctDNA TT/ST prediction.

Table 1. Comparing patients with and without ctDNA histology prediction

	(+) ctDNA histology prediction (n=50)	(-) ctDNA histology prediction (n=100)	p-value
Median age (IQR)	68 (59-74)	71 (64-77)	0.02
Female (%)	28 (56.0)	61 (61.0)	0.56
Stage III/IV (%)	49 (98.0)	69 (69.0)	<0.0001
Extra-thoracic metastases (%)	37 (74.0)	21 (21.0)	<0.0001
Tumor fraction, %	4.6	0.7	0.01

Concordance Results

- ctDNA TT prediction demonstrated **100% agreement** with conventional pathology (50/50).
- The agreement between ctDNA ST prediction and tissue pathology, excluding 3 patients with poorly differentiated NSCLC, was 92% (35/38, k=0.74).
- The ctDNA accuracy of SCLC vs NSCLC classification was 95% (36/38, k=0.64).
- Overall, there were 3 discordant cases. One case was a patient with adenocarcinoma whose G360 at diagnosis predicted adenocarcinoma, but 4 months later predicted a **small cell component** (40%).
- All 3 patients with discordant subtyping died within 9 months of their discordant G360 result.

Conclusions

- In this real-world study, ctDNA was **highly accurate** in predicting tumor type, distinguishing NSCLC from SCLC, and predicting NSCLC subtype.
- However, only **a third of patients** had ctDNA TT/ST prediction, which was more likely in those with **more advanced disease and higher tumor burden**.
- Larger, prospective studies are needed to validate these findings, refine the clinical scenarios in which ctDNA-based histology prediction offers the greatest benefit, and clarify how discordant results should be incorporated into treatment decision-making.
- In the future, ctDNA-based TT/ST prediction may be a useful noninvasive tool to confirm primary lung cancer, classify histologic subtype, and identify **histologic transformation**, particularly during periods of **disease progression**, leading to earlier, better therapeutic decisions.

Contact information:
Jessica Zhang: Jessica.zhang1@northwestern.edu
Young Chae: young.chae@northwestern.edu