Immediate Biomarker Profiling of Actionable NSCLC Panel from a Digitized H&E Biopsy Image

Nurit Paz-Yaacov[1], Efrat Ofek[2], Razan Haj[2], Yossef Molchanov[2], Rinat Yacobi[2], Chen Mayer[2], Camila Avivi[2], Jonathan Zalach[1], Inbal Gazy[1], Nir Peled[1,3], Jair Bar[4], Dov Hershkoviz[5,6] and Iris Barshack[2,6]

[1] Imagene AI LTD., [2] Institute of Pathology, Sheba Medical Center, [3] Department of Oncology, Shaare Zedek Medical Center, [4] Institute of Oncology, Sheba Medical Center, [5] Pathology Department, Tel Aviv Sourasky Medical Center, [6] Sackler Faculty of Medicine, Tel Aviv University

Background

- Optimal non-small cell lung cancer (NSCLC) patient management rely on comprehensive molecular testing to identify driver alterations that guide therapeutic decisions.
- Limited accessibility, long turnaround times and inadequate tissue for molecular testing all result in undertesting and suboptimal clinical management of lung cancer patients.
- An AI solution that uses the diagnostic H&E-stained slide to detect genomic alterations offers an accessible solution that can overcome many of the aforementioned barriers to molecular testing.

Aim

To evaluate the accuracy of an AI-based solution that uses the diagnostic H&E-stained slide to detect the NSCLC actionable genomic alterations compared to clinically diagnostic tests.

Method

- Training and testing was performed on pan-cancer FFPE H&E digital whole slide images (WSIs) from both public and commercial databases as well as medical centers using self-supervised learning (SSL) with dynamic data augmentation and multiple instance learning (MIL) algorithms.
- The model performance was evaluated on an independent lung cancer WSI dataset (including samples from multiple sites, led by Sheba Medical Center) using a 5-fold cross-validation scheme, and comparing the inference results to the official reported results of the reference methods (NGS, FISH, etc.) for each biomarker.
- For every sample, each gene was assigned either a “positive” or a “negative” status for high confidence biomarker scores, or “inconclusive” status for low confidence biomarker scores.

Data

- **1,915 retrospective samples** were used for the evaluation of the model:
  - Multiple medical centers and reference labs, from the USA and Israel, led by the Pathology Institute at Sheba Medical Center.
  - Various digital slide scanners, including Philips and Leica devices.
  - Needle biopsies as well as surgical resection specimens.
  - Specimens from both primary and metastatic sites.
- All collected samples from NSCLC patients with an available WSI and an official result were included in the study. Each case was was represented by a single slide.

Results

AI-based NSCLC actionable biomarker panel performance:

Biomarker	N cohort*	N pos	N neg	AUC	Sensitivity	Specificity	Accuracy	% of cohort	Prevalence
ALK fusion	1513	88	1425	0.979	0.974	0.962	0.962	53	0.05
BRAF V600E	1748	43	1705	0.983	0.941	0.973	0.973	65	0.02
EGFR mut	1870	318	1552	0.973	0.901	0.917	0.914	44	0.15
ERBB2 mut	1642	46	1596	0.990	1.000	0.973	0.973	43	0.03
MET ex14 skipping	1330	67	1263	0.946	0.952	0.921	0.923	25	0.04
NTRK1-3 fusion	1082	25	1057	0.852	0.824	0.944	0.942	94	0.01
RET fusion	1308	43	1265	0.941	0.923	0.920	0.920	55	0.02
ROS1 fusion	1304	46	1258	0.984	1.000	0.970	0.970	51	0.02
Average				**0.956**	**0.939**	**0.947**	**0.947**	**54**	

* Number of samples with official results for each biomarker.

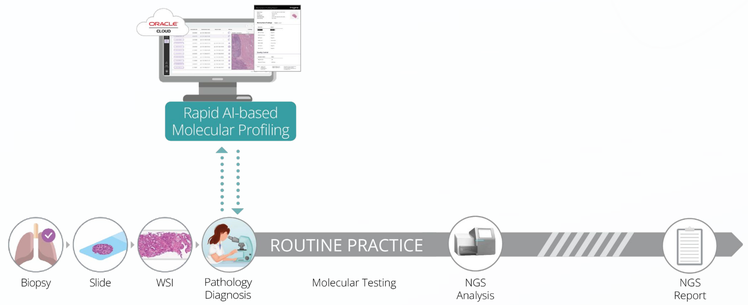
KRAS G12C biomarker was not included in the panel yet as it’s performance values were: 91.7% specificity, 82.4% sensitivity, 91.2% accuracy and an AUC of 0.842 for ~0.25 of the cohort’s patients.

NCSLC inference performance, in the high-confidence cases, demonstrated an **average of:**

AUC	Sensitivity	Specificity	Accuracy
0.956	**93.9%**	**94.7%**	**94.7%**

Discussion

- The NSCLC panel performances demonstrated **generalization** in detecting genomic alterations directly from diagnostic H&E-stained WSIs with **high accuracies**, comparable to those of diagnostic tests.
- We demonstrate that he NSCLC actionable alterations are **identifiable using image-based AI algorithms**. Imagene is currently researching the boundaries of AI solutions capabilities such as the ability to distinguish between different variants within a specific gene.
- Further studies evaluating the practical benefits of **incorporating NSCLC panel into the clinical workflow** are currently underway. Such studies will assess how a rapid, robust, scalable AI biomarker profiling panel can optimize and improve the diagnostic workflow and enhance accessibility for molecular testing.



Schematic representation in the diagnostic workflow