White paper

Cerba Research

Precision medicine for non-small cell lung cancer (NSCLC):

Emerging trends in molecular analysis

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About the author

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Rania Gaspo earned her B.Pharm and Ph.D. at the University of Montreal, Faculty of Pharmacy. She served as a post-doctoral fellow at Montreal Heart Institute before working as a senior scientist at Merck Research Laboratories. Rania then joined Pfizer where she held positions of increasing responsibilities in medical affairs, clinical development, and medical communications in various therapeutic areas, most notably in oncology. She has also supported the launch of many novel medications, led a global team of experienced medical communications managers, and authored more than 25 peer reviewed publications and 60 scientific communications. Rania is also our Cerba Research Publications Committee Chair.

Of all types of cancer, lung cancer has caused more deaths worldwide than any other type of cancer.[1] It also causes more deaths than breast and colorectal cancers combined.[1] Patients with the most common lung cancer, non-small cell lung cancer (NSCLC), have higher survival rates than patients with small-cell lung cancer (SCLC), but the outcomes for both remain bleak. According to the American Cancer Society, the 5-year relative survival rate for lung cancer across all stages is 32% for NSCLC and 9% for SCLC.[2]

NSCLC patients also have more promising and more precise treatment options today compared to 10 years ago. Advances in biomarker and precision medicine have led to the development of immunotherapies and targeted novel treatments that have the potential to improve patient outcomes. In the United States, the FDA has approved dozens of biomarker-driven therapies for NSCLC, including ALK, EGFR, RET and ROS1 inhibitors.[3] Meanwhile, more than 1,200 treatments are in development.[4]

With precision medicine becoming a more integral component of NSCLC treatment, molecular testing is an important step to help researchers, pathologists, and oncologists understand the genetic underpinnings of this disease. Pathologists commonly use immunohistochemistry (IHC) and/or next-generation sequencing (NGS) to characterize lesions and refine diagnoses, circulating tumor DNA (ctDNA) analysis has emerged as a promising and increasingly standard non-invasive approach for detecting certain biomarkers.

This white paper explores the roles IHC, NGS, and ctDNA play in NSCLC precision medicine therapy development, as well as how they help healthcare providers determine the most effective treatment regimens for their patients.

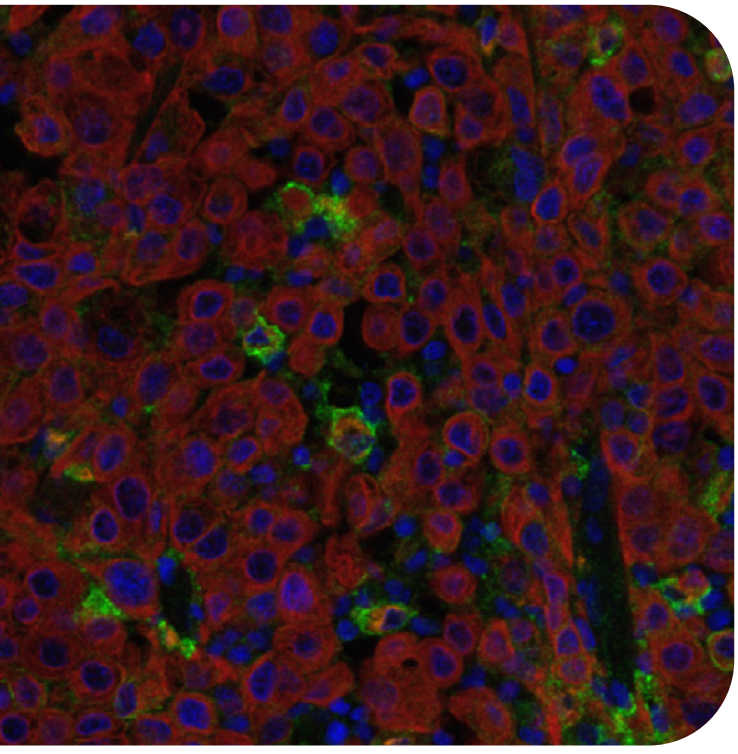
The need for broad molecular profiling

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines provide a robust framework for molecular testing. Specifically, the NCCN recommends that patients with metastatic NSCLC, regardless of histologic subtype, undergo comprehensive biomarker testing to determine eligibility for targeted therapies or immunotherapy, which have been shown to improve clinical outcomes.

The NCCN clinical practice guidelines recommend broad panel molecular profiling for patients with metastatic non-small cell lung cancer (NSCLC) to identify actionable biomarkers.

This test includes, but is not limited to, alterations in ALK, EGFR, ERBB2 (HER2), KRAS, MET exon 14 skipping, NTRK1/2/3, RET, ROS1, and expression of PD-L1. Identifying these biomarkers helps determine eligibility for targeted therapies and immunotherapies, which can significantly improve patient outcomes.

Understanding programmed death-1/programmed-death-ligand 1 (PD-1/PD-L1) levels is especially integral to treatment planning. First-line treatment strategies exist for patients with both negative and positive PD-1/ PD-L1 expression, including combinations of surgical intervention, chemotherapy, radiation, and PD-1/PD-L1 inhibitors.[6]



PD-L1 multiplex panel. NSCLC.

Immunohistochemistry: a cost-effective screening method for biomarker detection

Pathologists across the globe use IHC to identify and quantify biomarkers for precision medicine treatment and research. Many cancer centers choose conventional, single marker IHC stains for their simplicity, speed of execution, and cost-effectiveness. However, multiplex IHC offers the following additional benefits for NSCLC precision medicine treatment and research.

- **Patient-centric approach:** view and review multiple biomarkers on one slide - no need for patients to undergo additional invasive, often painful rebiopsies.
- **Verify co-expression and spatial organization:** view multiple targets within a preserved tissue architecture.
- **Immune profiling:** characterize tumors and identify predictive biomarkers for immunotherapy response.
- **Move from preclinical to clinical:** use multiplex IHC to validate targets, select patients, and characterize efficacy and response. This creates an iterative feedback loop where the ability to predict responses from IHC improves as healthcare providers incorporate the data associated with patient outcomes.

Selected examples of available lung biomarkers at Cerba Research in IHC

PD-L1, PD-1, **ALK**, **c-MET**, **ROS1**, **HER2**, **panTRK**, **MEK**, **RET**, IL-1α, Nkp46, FoxP3, Treg*, MDSC*, NK cells*, CD163, CD56, Ki-67.

Bold = Targetable Biomarker
* = Multiplex Assay

Preferred IHC panels for NSCLC

For efficient NSCLC analysis, Cerba Research recommends two immuno-oncology panels:

- The checkpoint inhibitor (CKI) multiplex panel, which consists of CD3, CD8, PD-1, PD-L1 and a custom marker of your choice.
- The PD-L1 multiplex panel, which consists of CD68, panCK, and PD-L1 markers.

Both panels contain druggable targets and have been appropriately validated on lung specimen. Then, based on the results of these panels, clinical trialists can design a treatment regimen that's optimally targeted to the patient's makeup and cancer type.

Available IHC immuno-oncology multiplex panels at Cerba Research

Tumor Microenvironment Marker Panels (these panels help characterize different components of the tumor microenvironment (TME)):

Macrophage and epithelial interaction:

CD68, CD163, PD-L1, EP4R, PanCK

Suggests profiling of tumor-associated macrophages (TAMs), immune checkpoint expression, and epithelial cells.

Prostaglandin pathway and epithelial cells:

EP4R, COX-2, mPGES-1, PanCK

Indicates inflammatory signaling and prostaglandin E2 synthesis in tumor cells.

Chemokine signaling:

MCP-1 (CCL2)

Key for monocyte recruitment and macrophage polarization.

Prostaglandin synthesis enzyme:

mPGES-1 (PTGES)

Focused on a single enzyme involved in PGE2 production.

Stemness and dendritic cell marker:

TCF4, CD123

May indicate plasmacytoid dendritic cells or progenitor-like cells.

PD-L1 Localization Panel:

CD68, PD-L1, PanCK

Designed to localize PD-L1 expression on macrophages (CD68+) vs tumor cells (PanCK+).

Activated Cytotoxic T Cell Phenotype:

Ki-67, Granzyme B, CD8

Proliferating cytotoxic T cells:

NKp46, CD8, Granzyme B, TCRγδ

Mixed NK and γδ T cell cytotoxic profile.

Macrophage Polarization (M1/M2):

pSTAT1, cMAF, CD68, CD163

pSTAT1: M1 marker

cMAF and CD163: M2 markers

CD68: pan-macrophage marker

Next-generation sequencing: broad-panel technique (Oncopanels)

Using NGS, pathologists and researchers observe the order of nucleotides in targeted DNA or RNA regions or the entire genome of both germline and cancer cells, depending on the scope of the investigation or study, from molecular biomarkers research to identification of actionable mutations. When developing targeted NSCLC therapies, NGS allows researchers to detect important gene alterations with high throughput, scalability, and speed.

According to the NCCN clinical practice guidelines, broad-panel NGS is strongly recommended for patients with metastatic NSCLC to identify actionable genetic alterations and guide treatment decisions.

Key recommendations from NCCN:

Broad-panel NGS (e.g., oncopanels) is preferred over single-gene testing because it can detect a wide range of oncogenic driver mutations and gene fusions in a single assay.

Actionable alterations include:

Gene fusions: ALK, ROS1, RET, NTRK1/2/3.

Mutations: EGFR, BRAF, KRAS, HER2 (ERBB2), MET exon 14 skipping.

Amplifications: high-level MET amplification (considered exploratory but clinically relevant in some contexts).

These biomarkers are critical for selecting targeted therapies or immunotherapies, which have been shown to significantly improve outcomes in biomarker-positive patients.[5]

With patients' genetic information, clinical trialists can recommend effective drugs already available or steer patients to appropriate clinical trial options. Until recently, NGS was reserved for reference laboratories and large cancer centers due to cost. Now that the cost to implement NGS has dropped, more hospitals are bringing the technology in-house.[7] Although generally more expensive and less accessible than IHC, both techniques ideally complement themselves to give a full characterization of the tumor.

NGS use case

A physician performs a biopsy to obtain a sample of a patient's lung lesion. A molecular pathologist and his team run the sample through a broad-panel NGS validated assay – either DNA, RNA, or both. The result demonstrates that the patient suffering from metastatic NSCLC has an ALK rearrangement. The physician may opt to prescribe ceritinib, an ALK inhibitor approved for use in metastatic NSCLC.[8]

Most commonly deployed techniques for NSCLC biomarkers[5]

Biomarker	Most commonly deployed techniques	Additional techniques
Biomarker	NGS, RT-PCR	Sanger sequencing, single gene
ALK	NGS, IHC, Liquid Biopsy	FISH (reflex), RT-PCR
ROS1	NGS	FISH (reflex), IHC, RT-PCR
BRAF	NGS, RT-PCR	IHC
KRAS	NGS, RT-PCR	
MET	NGS, RNA-based NGS	
RET	NGS, RNA-based NGS	FISH, RT-PCR
NTRK1/2/3	NGS, RNA-based NGS	FISH, IHC, PCR
EGFR T790M	NGS, Liquid Biopsy	
PD-L1	IHC	
ERBB2 (HER2)	NGS, FISH	IHC, single gene

The future is now: circulating tumor DNA (liquid biopsy)

One of the newer testing methods in oncology, ctDNA, is attracting significant attention due to its non-invasive nature and practicality for early detection, ongoing monitoring, and rapid treatment.[8,9] ctDNA refers to cancer cell DNA that breaks down and releases into the bloodstream. Analyzing genetic alterations and mutations using a ctDNA approach, aka liquid biopsy, helps reduce the need for an invasive tissue biopsy or rebiopsy.

Aside from the ability to obtain genetic information via a blood draw, ctDNA testing offers the following advantages:

Serial sampling: use in conjunction with or without tissue samples (matched specimens)

- **Ease of use:** requires less staff to implement
- **Patient comfort:** patients can provide a sample during an outpatient visit
- **Invasive:** reduces the need for biopsy or rebiopsy
- **Tissue is the issue:** 1/5 patients don't have enough tissue
- **Monitor:** sometimes used to monitor tumor burden longitudinally

Currently, ctDNA diagnostics do not always provide the specificity and/or sensitivity of IHC or NGS on tissue biopsy; however, researchers are currently working to improve the performance of these techniques to meet or exceed IHC and NGS in both dimensions. In addition, ctDNA diagnostics continues to be expensive, reserving the assay to large cancer centers or central laboratories such as Cerba Research. However, the cost effectiveness and specificity/sensitivity are expected to improve over time, much like NGS for tissue biopsy.

Cerba Research services for NSCLC

With fully equipped histopathology services across the U.S., Europe, and Asia, Cerba Research offers the technology and expertise for expedited NSCLC diagnostics. Serving preclinical to clinical research, Cerba Research has over 250 IHC biomarkers/protocols available and a biobank with a large number of blocks available and growing. We also develop and validate custom biomarkers according to clinical trial needs.

We perform both conventional and multiplex IHC, with the ability to detect up to eight biomarkers in one multiplex IHC panel. Additionally, an international network of board-certified pathologists and consultants analyzes IHC results on demand.

Cerba Research also offers global NGS capabilities with multiple comprehensive oncopanels available for analysis. Our capacity for high throughput, with the ability to sequence more than 1,000 whole human genomes in as little as 10-15 days, provides the information needed to bring targeted medicines to patients faster. We are also one of the few diagnostics solutions providers to offer ctDNA analysis.

Wide range of comprehensive platforms for your NGS needs

Cerba Research has experience in a variety of NGS applications, including the following:

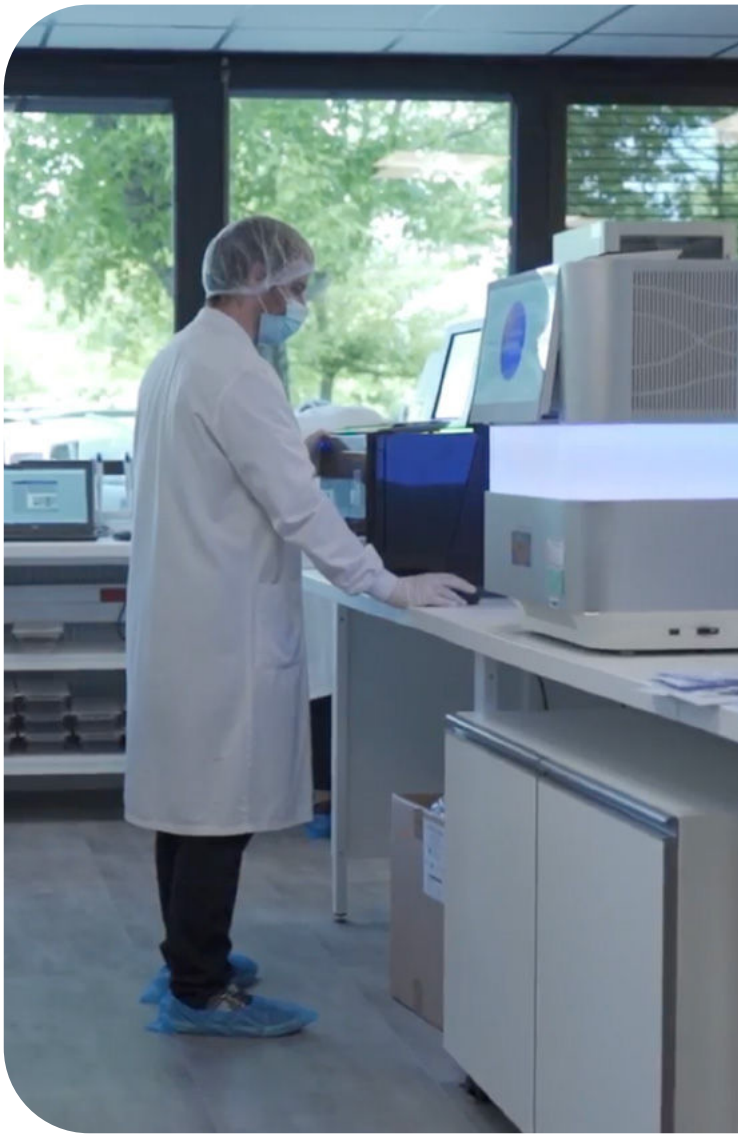
- Solid tumors: targeted panels for somatic oncology in solid tumors including but not limited to our OncoSign FFPE, OncoSign ctDNA, and OncoSign 600+ broad panel assays. These panels cover alterations with established, emerging and exploratory value across lung, ovarian, breast, colon, melanoma, bladder, GIST, rare tumors and more
- Liquid tumors: targeted panels for somatic oncology in hematological malignancies. These panels cover mutations with established and emerging value for myeloproliferative neoplasms, chronic myelomonosystic leukemia, myelodysplastic syndroms, acute myeloid leukemia (AML) and more
- Hereditary cancers: oncogenetic panels for hereditary cancers, such as the OncoStar, cover mutations within breast, ovarian, prostate, colon, GI, pancreatic, kidney, neuroendocrine tumors and more
- Rare disorders: germline sequencing such as, but not limited, to BRCA1/BRCA2 with more than 100 off the shelf panels available for numerous rare disorders
- Constitutional genomics: whole exome sequencing (WES) for your constitutional genomic assessments
- Pathogens identification: whole genome sequencing (WGS) for various pathogens identification
- Viral & microbiome sequencing: various sample types may be analyzed, including but not limited to feces
- Translocations & fusions: with RNA-based NGS sequencing, targeted FISH and IHC screening
- Cell & Gene Therapy: TCR/BCR immune repertoire sequencing, HLA typing and more for your Cell & Gene Therapy trials

A full range of library preparation platforms

- Perkin Elmer Sciclone® G3 LiquidHandling Workstations
- Agilent Bravo A & B
- Perkin Elmer Zephyr G3
- Hamilton NGS Star
- Hamilton Microlab Nimbus

And a broad range of high throughput sequencing platforms

- Ilumina (MiSeqDx, NextSeq500, NextSeq2000, NextSeq 550Dx)
- PacBio
- Ion Torrent
- Nanopore



Practice guidelines aligned with Cerba Research NGS offerings

An example of non-small cell lung cancer (NSCLC)

According to the NCCN Guidelines, broad-based genomic testing, particularly next-generation sequencing (NGS), is emphasized as a preferred approach for patients with advanced cancers, including non-small cell lung cancer (NSCLC).

The guidelines state:

"Broad-based genomic testing approaches that efficiently utilize limited biopsy tissue while maximizing diagnostic genomic information are most commonly NGS-based."

"Broad genomic profiling may be the most informative approach to examining potential mechanisms of resistance."[1]

This supports the use of comprehensive oncopanels, which map relevant lung cancer biomarkers (e.g., EGFR, ALK, ROS1, MET, RET, KRAS, BRAF, HER2, NTRK) to actionable therapies and resistance mechanisms. Check out the table below that outlines relevant lung cancer biomarkers mapped against what Cerba Research may offer.

Lung Cancer Biomarkers	Cerba Research NGS†	Cerba Research IHC†*	Cerba Research FISH†
EGFR	✓	✓	
ALK	✓	✓	✓
ROS1	✓	✓	✓
BRAF	✓	✓	
KRAS	✓	MEK1	
MET	✓	✓	✓
RET	✓	✓	✓
NTRK1/2/3	✓	✓	✓
EGFR T790M	✓		
PD-L1		✓(clones 22C3, SP142, SP263, multiplexed)	
HER2	✓	✓	✓

1. NCCN guidelines 2024; **2.** Bebb *et al.* Curr Oncol 2021; **3.** Cabillic *et al.* ESMO Open 2018;3(6):e419; **4.** Li *et al.* J Nat Cancer Center 2021; †Cerba Research Data In-house mostly available through the ACTOnco®/Cerba France/Cerba US NGS panels or CR Montpellier/NY (IHC) or Cerba France (FISH); *Validation level may vary; IHC=immunohistochemistry; NGS=next-generation sequencing; FISH=fluorescence in situ hybridization

Cerba Research offers a suite of advanced genomic profiling tools such as OncoSign FFPE, OncoSign ctDNA, and OncoSign600+, designed to detect a wide range of genetic alterations across multiple tumor types, including lung, ovarian, breast, colon, melanoma, bladder, GIST, and rare tumors.

Key features of Cerba Research panels:

- OncoSign FFPE & ctDNA Panels
- **Sample types:** formalin-fixed paraffin-embedded (FFPE) tissue and circulating tumor DNA (ctDNA)
- **Coverage:** mutations with established, emerging, and exploratory clinical relevance
- **Tumor types:** broad applicability across solid tumors
- **Routine use:** OncoSign FFPE is used in routine clinical practice in France, often alongside HRD (homologous recombination deficiency) testing, which is CE-IVD marked
- OncoSign600+ Panel
- **Gene coverage:** analyzes 638 genes
- **Variant types:** detects SNVs, indels, CNVs, and gene fusions
- **Clinical utility:** enables detection of rare and actionable driver mutations, supporting precision oncology strategies

These panels are designed to support both clinical diagnostics and clinical trials, offering flexibility and depth in molecular profiling.

Conclusion

As researchers identify more druggable targets using highly specific and sensitive methods like IHC, NGS, and ctDNA-based panels, the development of targeted therapies for lung cancer is expected to accelerate. This progress will lead to incremental improvements in patient care, offering those living with this devastating disease a greater chance at a higher quality of life and potentially longer periods without disease progression.

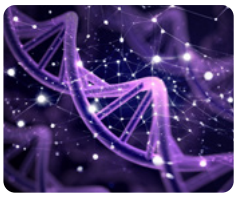
About Cerba Research

Cerba Research is a leading specialty laboratory services provider with the capacity and breadth of a global central laboratory network. Our highly qualified scientists provide insight on the latest biomarkers, assays, and testing approaches and develop innovative solutions for unique challenges across all research phases for pharmaceutical, biotechnology, medical device, government, public health, and CRO organizations.

Cerba Research's extensive capability in laboratory testing and global logistics, including Bioanalysis, Flow Cytometry, HistoCytopathology, and Next-Generation Sequencing, enables us to drive operational agility at scale in a wide range of therapeutic areas, with recognized expertise in Virology, Immunology, Oncology, and Cell & Gene Therapy.

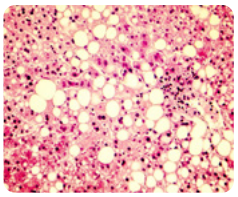
Cerba Research is part of the Cerba HealthCare Group with 15,000 employees on five continents, driven to advance diagnosis and health.[2]

A Cerba Research snapshot in NSCLC precision medicine



DNA

- NGS
- Oncopanels
- Custom panels
- ctDNA panels
- DNA extraction
- Strek tubes
- ddPCR
- qPCR
- Whole exome
- Single gene

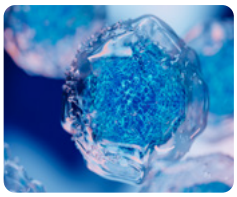


Tissue

- Multiplex/Simplex IHC
- 250+ biomarkers/ protocols centralized pathology reading
- Large biobank
- FISH, ISH protocols
- Strong immuno-oncology simplex & multiplex panels
- Full histopath service
- Spatial analysis in the tumor microenvironment
- Nanostring®

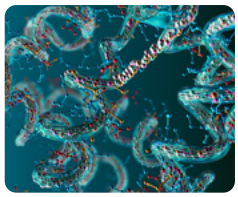
RNA

- RNAseq (fusion genes)
- NGS
- Oncopanels
- Custom panels
- RT-PCR
- PaxGene® RNA extraction
- Nanostring®



Cell

- Immunophenotyping
- Lymphocyte infiltration
- Marker analysis (cell surface/cytoplasmic)
- Receptor occupancy
- Custom FCM panels
- Minimal residual disease (MRD) detection for multiple myeloma
- Intracellular cytokine detection
- PBMC/BMMC isolation
- Immunogenicity



Protein

- Electrophoresis
- Multiplex cytokine

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