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EMERGING MOLECULAR TESTING PARADIGMS IN NON-SMALL CELL LUNG CANCER (NSCLC) MANAGEMENT – CURRENT PERSPECTIVES AND RECOMMENDATIONS

SELECTED HIGHLIGHTS

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THIS PROGRAMME HAS BEEN DEVELOPED BY A GROUP OF EXPERTS

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EDUCATIONAL OBJECTIVES

1. Have an awareness of the current **biomarker landscape in lung cancer**

2. Understand the **current testing strategies** for precision oncology in lung cancer, **associated challenges** and how to **implement these into clinical practice**

3. Explore potential **future opportunities** related to **precision oncology for lung cancer**

CLINICAL TAKEAWAYS

- **Precision medicine in patient care requires** specialised knowledge that is best delivered via **a well-coordinated and well-educated MDT**, up to date with the latest developments in lung biomarker research and testing technology
- **Molecular testing** should be performed in clinical situations where there is evidence that **targeting particular molecular alterations makes a clinical difference**
- Specimen acquisition and processing of tissue should follow well-established standard procedures and protocols. **Genomic testing with NGS using multigene panels is highly recommended**
- Besides methodological aspects, **effective collaboration and communication** within the MDT are paramount
- Patients should be evaluated by MDTs implementing **rapid on-site evaluation (ROSE) and reflex testing to improve testing efficiency** and reduce the time to treatment initiation

MDT, multi-disciplinary team; NGS, next-generation sequencing

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INTRODUCTION

- **Advances in molecular testing and precision oncology** have **transformed the clinical management of lung cancer**, especially non-small cell lung cancer (NSCLC), enhancing diagnosis, treatment, and outcomes
- **Practical guidelines offer insights into selecting appropriate biomarkers and assays**, emphasising the importance of comprehensive testing
- However, **real-world data reveal underutilisation of biomarker testing and consequently targeted therapies**, with molecular testing often occurring late in diagnosis or not at all in clinical practice, leading to delayed or inadequate treatment
- **Enhancing precision requires adherence to best practices** by all healthcare professionals involved, which can ultimately improve lung cancer patient outcomes
- This review presents the **currently known actionable mutations in lung cancer** and **new upcoming ones that are likely to enter clinical practice soon**, and provides an overview of established and emerging concepts in testing methodologies
- **Challenges are discussed and best practice recommendations are made** that are relevant today, will continue to be relevant in the future, and are likely to be relevant for other cancer types too

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ACTIONABLE MUTATIONS IN NSCLC (1)

Gene	Frequency	ESCAT[a]	Genetic alteration	Detection method	Sample type	FDA and/ or EMA approved targeted therapies
ALK	~5%	IA	Fusions (mutations as mechanism of resistance)	Ventana-D5F3 IHC Break-apart FISH (for rearrangements) RT-PCR detection of specific fusions DNA or RNA-based NGS	FFPE tumour tissue, liquid biopsy or cytology specimen	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
BRAF	~2%	IB	V600E, deletion mutations, fusions, exon 11 mutations	IHC as a screening tool dd-PCR RT-PCR NGS Only for the V600 mutation: Cobas 4800 *BRAF* V600 Mutation Test and THxID-BRAF kit, monoclonal antibody VE1	FFPE tumour tissue, liquid biopsy (blood)	dabrafenib + trametinib, encorafenib + binimetinib
EGFR	~15% ~50-60% Asian	IA	Common: ex19del, L858R	Sanger sequencing Mutation-specific PCR; dd-PCR, NGS	FFPE tumour tissue, plasma	afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, osimertinib + pemetrexed + platinum chemotherapy, erlotinib + ramucirumab, erlotinib + bevacizumab
	~50-60% of NSCLC cases with acquired resistance to 1st and 2nd generation EGFR-TKIs	IA	Acquired T790M exon 20 (TKI resistance)	Mutation-specific PCR (re-biopsy of the tumour tissue or liquid biopsy)	Plasma (ctDNA-detection), FFPE tumour tissue	osimertinib
	10%	IB	“Uncommon” TKI-sensitising mutations (G719X in exon 18, L861Q in exon 21, S768I in exon 20)	Mutation-specific PCR NGS	FFPE tumour tissue, liquid biopsy (blood)	afatinib
	4-10%	IIB	Exon 20 insertions	NGS PCR only for specific variants	FFPE tumour tissue, liquid biopsy (blood)	amivantamab-vmjw, amivantamab-vmjw + carboplatin + pemetrexed

[a] The ESMO Scale of Clinical Actionability of molecular Targets (ESCAT) provides evidence-based criteria to prioritise markers and to select patients for targeted therapies. ESCAT defines six levels of clinical evidence for targets in relation to their implications for patient management, ranging from tier I (ready for implementation in routine clinical decisions) to tier X (lack of evidence for actionability).

ctDNA, circulating tumour DNA; dd-PCR, droplet digital PCR; EMA, European Medicines Agency; ESCAT, ESMO Scale of Clinical Actionability for molecular Targets; ESMO, European Society for Medical Oncology; ex19del, exon 19 deletion; FDA, Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase PCR; TKI, tyrosine kinase inhibitor

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ACTIONABLE MUTATIONS IN NSCLC (2)

Gene	Frequency	ESCAT[a]	Genetic alteration	Detection method	Sample type	FDA and/ or EMA approved targeted therapies
ERBB2 (*HER2*)	2-5%	IIB	Hot spot mutations, amplifications, overexpression	RT-PCR (mutations) IHC FISH (amplifications) NGS (mutations)	FFPE tumour tissue, liquid biopsy (blood)	fam-trastuzumab deruxtecan-nxki
KRAS p.G12C	12% 25-33% all *KRAS* mutations	IIB	Mutation	Mutation-specific dd-PCR PCR pyrosequencing NGS (SiRe® panel)	FFPE tumour tissue, liquid biopsy (blood), plasma (cfDNA)	sotorasib, adagrasib
KRAS	~35%	IIIA	Amplification	Mutation-specific PCR NGS FISH IHC for amplification/overexpression	FFPE tumour tissue, liquid biopsy (blood)	None yet
MET	~3%	IB	Exon 14 skipping	IHC FISH Amplicon-based NGS Hybrid capture-based NGS Various modifications of PCR (e.g. RT-PCR)	FFPE tumour tissue, liquid biopsy (blood), plasma	capmatinib, tepotinib
	1-6% of treatment-naïve NSCLC	IIB	Amplifications (de novo or due to acquired resistance on TKIs in patients with various NSCLC mutations)	FISH (MET/CEN7 or MET/CEP7 ratio) NGS assays capable of measuring gene copy number dd-PCR NanoString nCounter	FFPE tumour tissue, liquid biopsy (blood), plasma	None yet
	< 0.5%	Not determined	MET fusions	DNA-based NGS RNA-based NGS (amplicon- or hybridisation-based) FISH RT-PCR	FFPE tumour tissue, liquid biopsy (blood)	None yet

[a] The ESMO Scale of Clinical Actionability of molecular Targets (ESCAT) provides evidence-based criteria to prioritise markers and to select patients for targeted therapies. ESCAT defines six levels of clinical evidence for targets in relation to their implications for patient management, ranging from tier I (ready for implementation in routine clinical decisions) to tier X (lack of evidence for actionability).

CEN7, centromere 7; CEP7, centromere of chromosome 7; cfDNA, cell-free DNA;

dd-PCR, droplet digital PCR; EMA, European Medicines Agency; ESCAT, ESMO Scale of Clinical Actionability for molecular Targets; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase PCR; TKI, tyrosine kinase inhibitor

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ACTIONABLE MUTATIONS IN NSCLC (3)

Gene	Frequency	ESCAT[a]	Genetic alteration	Detection method	Sample type	FDA and/ or EMA approved targeted therapies
MSI	0.8-40%	Unknown	Microsatellite instability, Pattern of hypermutation	IHC PCR (Bethesda, Pentaplex) NGS	FFPE tumour tissue, liquid biopsy (blood)	pembrolizumab
NTRK 1/2/3	0.23-3%	IC	Fusions	IHC as a screening assay, followed by a validation test DNA- or RNA-based NGS Various modifications of PCR; FISH	FFPE tumour tissue, liquid biopsy (blood)	entrectinib, larotrectinib
PD-L1	28%: ≥50% TPS 38%: 1-49% TPS 33%: <1% TPS		Protein expression	IHC (Ventana SP142 and SP263 Dako 22C3 and 28-8 clones)	FFPE tumour tissue, liquid biopsy (blood), plasma cytology specimen	pembrolizumab, nivolumab + ipilimumab, nivolumab + platinum-based chemotherapy, atezolizumab, durvalumab, cemiplimab
RET	~1-2%	IC	Rearrangements, fusions	FISH Various modifications of PCR DNA- or RNA-based NGS methods of detection	FFPE tumour tissue, liquid biopsy (blood)	selpercatinib, pralsetinib
ROS1	1-2%	IB	Fusions (mutations as mechanism of resistance), rearrangements	IHC as screening assay followed by a validation test (NGS or FISH) FISH Various modifications of PCR DNA- or RNA-based NGS	FFPE tumour tissue, liquid biopsy (blood)	crizotinib, entrectinib, repotrectinib
TMB	Data not available	Not determined	High number of coding mutations	NGS	Liquid biopsy (blood)	pembrolizumab

[a] The ESMO Scale of Clinical Actionability of molecular Targets (ESCAT) provides evidence-based criteria to prioritise markers and to select patients for targeted therapies. ESCAT defines six levels of clinical evidence for targets in relation to their implications for patient management, ranging from tier I (ready for implementation in routine clinical decisions) to tier X (lack of evidence for actionability).

EMA, European Medicines Agency; ESCAT, ESMO Scale of Clinical Actionability for molecular Targets; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; MSI, microsatellite instability; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; PD-L1, programmed cell death-ligand 1; TMB, tumour mutational burden; TPS, tumour proportion score

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EMERGING LUNG CANCER BIOMARKERS

Gene	Frequency	ESCAT[a]	Genetic alteration	Detection method	Sample type
BRCA1/2	1.2%	IIIA	Mutations	NGS	FFPE tumour tissue, liquid biopsy (blood)
FGFR1	9-20%	Not determined	Fusions, amplification	NGS	FFPE tumour tissue, liquid biopsy (blood)
KEAP1	15%	Not determined	Mutation	NGS	Liquid biopsy (blood)
MTAP	15%	Not determined	Deletion	IHC, FISH	FFPE tumour tissue
NRG1	1.7%	IIIB	Fusions	RNA sequencing, FISH, NGS	FFPE tumour tissue
PIK3CA	1.2-7%	IIIA	Hotspot mutations	NGS	Plasma (cfDNA), cytology specimen
STK11/LKB1	18%	Not determined	Point mutations or deletions	NGS	FFPE tumour tissue, liquid biopsy (blood)
TMB	Data not available	Not determined	High number of coding mutations	NGS	Liquid biopsy (blood)

[a] The ESMO Scale of Clinical Actionability of molecular Targets (ESCAT) provides evidence-based criteria to prioritise markers and to select patients for targeted therapies. ESCAT defines six levels of clinical evidence for targets in relation to their implications for patient management, ranging from tier I (ready for implementation in routine clinical decisions) to tier X (lack of evidence for actionability).

cfDNA, cell-free DNA; ESCAT, ESMO Scale of Clinical Actionability for molecular Targets; ESMO, European Society for Medical Oncology; FFPE, formalin-fixed paraffin-embedded; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NGS, next-generation sequencing; TMB, tumour mutational burden

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OVERVIEW OF CURRENT RECOMMENDATIONS FOR MOLECULAR TESTING IN NSCLC[a] (1)

Molecular testing is mandatory in clinical situations where drugs are approved for routine use. Broader testing may be used to support early drug access or clinical trials

Molecular analyses should be performed in all histological subtypes of non-squamous NSCLC, including adenocarcinomas, NOS carcinomas, large-cell neuroendocrine carcinomas, adeno-squamous carcinomas and sarcomatoid carcinomas. NSCLC with neuroendocrine features should also be tested, as they are NSCLC

Molecular testing is recommended in eligible patients with stage IV disease and, for certain biomarkers, in eligible patients with resectable early-stage NSCLC. Testing should be considered in early-stage disease where therapies targeting EGFR and ALK are available

Molecular testing for oncogene drivers is recommended in eligible patients with advanced non-squamous-cell carcinoma, although in certain cases it is also recommended for patients with a diagnosis of squamous-cell carcinoma (e.g. young patients, light smokers or long-time ex-smokers)

Administration of therapy should be initiated once molecular testing results are available and based on clinical evidence as appropriate. There may however be exceptions where therapy should be initiated immediately based on patients' clinical condition

[a] As per ASCO, ESMO and NCCN clinical practice guidelines

NOS, not otherwise specified; NSCLC, non-small cell lung cancer

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OVERVIEW OF CURRENT RECOMMENDATIONS FOR MOLECULAR TESTING IN NSCLC[a] (2)

Tissue biopsy is the standard for molecular testing. Liquid biopsy can be a complementary approach, but negative results should be confirmed by tissue testing. Broad panel testing using NGS is preferable.

Adequate tissue material for histological diagnosis and molecular testing should be obtained to allow for individual treatment decisions, and re-biopsy should be performed, where possible, when initial sampling is inadequate

Tissue biopsy is the standard for molecular testing, however liquid biopsy (ctDNA) may be a complementary approach when there is insufficient tissue sample, if re-biopsy cannot be performed safely, when NGS fails, as an alternative to re-biopsy at disease progression or failure of targeted therapy, or potentially to provide a more rapid result

Negative ctDNA tests should be verified by tissue testing, if available. If feasible, testing should be performed via broad, panel-based molecular profiling; if available, multiplex platforms (NGS) for molecular testing are preferable

In some clinical situations, rapid testing may be warranted; but it should be followed up with broad-based genomic testing

[a] As per ASCO, ESMO and NCCN clinical practice guidelines

ctDNA, circulating tumour DNA; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer

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OVERVIEW OF CURRENT RECOMMENDATIONS FOR MOLECULAR TESTING IN NSCLC[a] (3)

Molecular alteration/ test	Recommendations
EGFR mutation	• *EGFR* FISH or EGFR immunohistochemistry (IHC) have no clinical utility and should not be used • *EGFR* mutation test methodology should have adequate coverage of mutations in exons 18-21, including those associated with resistance to some therapies • At a minimum, when resources or material are limited, exon 19 deletion, exon 21 L858R point mutation should be determined • T790M testing on disease relapse on first- or second-generation EGFR TKIs mandatory • Broader liquid biopsy panel to monitor the spectrum of resistance alterations
ALK rearrangements	Detection of the *ALK* translocation by FISH is the standard, but IHC with high performance ALK antibodies and validated assays may be used as a screening approach, or preferably RNA NGS.
ROS1 rearrangements	FISH is the standard or preferably, by RNA NGS.
NTRK rearrangements	May use IHC for screening but confirmation by molecular testing is mandatory (targeted RT-PCR or preferably RNA NGS).
Other oncogenic drivers	• *BRAF* V600 mutation (IHC is available), *MET*ex14 skipping mutations, *MET* amplifications, *RET* rearrangements, *KRAS* G12C mutations and *HER2* mutations • Tiered testing approaches may be employed i.e. certain mutations do not overlap, so testing for one may identify patients who do not benefit from further testing (e.g. *KRAS* and *ALK*, *BRAF* p.V600E, *EGFR, MET*ex14 skipping mutations, *RET* rearrangements, and *ROS1* rearrangements) • Preferably NGS (DNA and RNA) to cover all in one test
PD-L1	• IHC must be used • If cytology samples are used, individual laboratories should validate their assays in their own cytology preparations against tissue biopsy samples of the same tumour

[a] As per ASCO, ESMO and NCCN clinical practice guidelines

ASCO, American Society for Clinical Oncology; ESMO, European Society for Medical Oncology; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; METex14, MET exon 14; NCCN, National Comprehensive Cancer Network; NGS, next generation sequencing; RT-PCR, reverse transcriptase polymerase chain reaction; TKI, tyrosine kinase inhibitor

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CHALLENGES AND BEST PRACTICES OF TISSUE ACQUISITION AND QUALITY, BIOMARKER TESTING AND REPORTING (1)

Challenges	Best practices
Tolerability of procedure Patients' inability to tolerate biopsies hampers tissue collection.	Optimise topical anaesthesia, anaesthetic-led sedation, liquid biopsies as a less invasive procedure.
Specimen acquisition; quantity and quality Specimen acquisition procedure can yield limited or inadequate amounts of tissue for comprehensive molecular analysis. More specifically, core needle biopsies may provide insufficient specimen, with low tumour cell number.	Use larger gauge needle, if possible and/or apply multiple passes. EBUS-guided. ROSE can enhance diagnostic yield and accuracy, may reduce the number of biopsies, and rates of complications. Consider liquid biopsies or tumour enrichment. MDT/MTB input is helpful in selecting the most appropriate site for biopsy and biological sample for the molecular analysis, for example, histologic sample or liquid biopsy, and the molecular profiling, technologies, molecular test to use. The ratio of tumour cells to stromal cells should ideally be ≥20%. It is the responsibility of the pathologist to decide whether or not to attempt molecular assessment, as sometimes the technique can be successful even with low cellularity (5-10%). In the absence of molecular alteration, the conclusion of the molecular report should state that the result is inconclusive due to low cellularity.

EBUS, endobronchial ultrasound; MDT, multidisciplinary team; MTB, molecular tumour board; ROSE, rapid on-site evaluation

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CHALLENGES AND BEST PRACTICES OF TISSUE ACQUISITION AND QUALITY, BIOMARKER TESTING AND REPORTING (2)

Challenges	Best practices
Specimen processing Potential degradation of genetic material during processing. RNA prone to degradation; high failure rate of RNA extraction from FFPE. Specific issues include sample loss due to extended periods of ischaemia and fixation can impact suitability of samples; use of single cassette can contribute to tissue depletion, necrotic areas may be incompatible with test being used (PCR, NGS; 10-12% tumour nuclei are required for NGS).	Optimise and standardise operating procedures & ensure staff is trained sufficiently. Optimise tissue usage from small samples by dividing biopsies into multiple blocks per test, perform diagnostic IHC upfront, and minimise cutting sessions to reduce tissue waste (limit IHC to necessary tests only). Minimise formalin fixation time to limit nucleic acid damage. Minimise cold ischemia to less than 30 minutes for surgical specimens, and immediate fixation for biopsy and cytology. Divide tissues into more than one cassette. Microdissections may increase viable tumour fraction.
Testing methodology and platform diversity Multiple testing options/assays and platforms are available from different vendors, each with specific sample requirements that adds complexity and may lead to confusion and disorganisation, ultimately affecting laboratory workflow, efficiency and potentially resulting in longer turnaround times. Multigene NGS panels, more specifically, may identify many genetic variants, some with uncertain clinical relevance, necessitating additional investigation.	Optimise and standardise operating procedures & ensure staff is trained sufficiently. Standardise requests using a few testing platforms, centralise coordination for efficient sample transport, unify testing processes, and integrate results into Electronic Health Records. Initiate reflex testing. Combined DNA/RNA NGS is reliable and efficient for comprehensive detection of all approved and emerging biomarkers and is more cost-effective.

FFPE, formalin-fixed paraffin embedded; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction

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CHALLENGES AND BEST PRACTICES OF TISSUE ACQUISITION AND QUALITY, BIOMARKER TESTING AND REPORTING (3)

Challenges	Best practices
Reporting Lack of experience in reading genomic reports, especially muti-gene NGS panel reports, and determining clinical relevance. The increasing number of biomarkers and treatment options in NSCLC add to the complexity.	Standardised molecular genomic report. Provide training to enhance molecular genomic report interpretation skills. Continuously consult with the latest clinical practice guidelines (incl. ESMO, ASCO, NCCN etc.). MDT/MTB should be advised in the interpretation of complex genetic information. Introduce a genomic coordinator role (or patient navigator) for streamlined coordination.
Tumour biology Tumour clonal evolution, resistance, and intra-, or inter-tumour heterogeneity (genetic and molecular) may lead to biomarker discordance among tumour sites and between primary tumour and metastatic site.	Consider multiple site sampling; tissue biopsy, cytological samples, and liquid biopsies; particularly in cases involving multiple small primary tumours or metastases.
Data collection/collation Incompatibility between Laboratory Information System and Electronic Health Record systems may lead to operational challenges, errors and inefficiencies.	Implement checklists to streamline data capture and reporting. Enhance readability and searchability of reports within electronic systems.

ASCO, American Society for Clinical Oncology; ESMO, European Society for Medical Oncology; MDT, multidisciplinary team; MTB, molecular tumour board; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer

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CHALLENGES AND BEST PRACTICES OF TISSUE ACQUISITION AND QUALITY, BIOMARKER TESTING AND REPORTING (4)

Challenges	Best practices
Quality assessment and control Ensuring consistent and accurate interpretation of results.	Perform thorough internal and external validation.
Guidance and standardization Limited guidelines for respiratory physicians.	Develop/implement best practice guidelines on specimen acquisition for pulmonologist and pathologist (defining critical parameters such as IHC limits, sample marking, and maximising tissue use, etc.).
Collaboration and communication Diversity in composition and expertise often may affect effective communication and collaboration with the MDT/MTB	Establish clear roles and responsibilities and routes of communication. Introduce a genomic coordinator role (or patient navigator) for streamlined coordination. Foster a culture of continuous feedback and follow-up to enhance the precision of medical procedures.

IHC, immunohistochemistry; MDT, multidisciplinary team; MTB, molecular tumour board

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PROPOSED MINIMAL TESTING ALGORITHM WHERE COMPREHENSIVE MULTI-PANEL TESTING NOT POSSIBLE

Early-stage NSCLC
IB-IIIA and IIIB (T3N2)

MDT decision on testing

PD-L1 IHC, ALK by IHC +/- ISH, *EGFR* rapid testing by PCR or by NGS

Metastatic NSCLC

Reflex testing by pathologist OR MDT decision on testing

Treatment Emergency[a]:
EGFR (rapid testing by PCR)
PD-L1 IHC
ALK IHC +/- FISH,
ROS1 IHC (optional) + FISH),
RET by FISH (depending on drug availability)

[a] Warning this approach may be limited by tissue availability and not be cost-effective if all the tests are conducted. Furthermore, risk of under-detection by FISH (30% false negative) and PCR does not cover the rare gene variants)

Sequential testing[a]
(if limited resources)

Before 1L perform tests as outlined for **'Treatment Emergency'**

During 1L before 2L
$BRAF^{V600E}$ (by IHC)
KRAS by PCR

After 2L and beyond
HER2 by PCR, *MET*ex14 by PCR or Sanger, NTRK (IHC+FISH), *NRG1* (FISH) (depending on drug availability)

Preferred approach:
PD-L1 IHC
NGS DNA/RNA tissue
+/- concomitant liquid biopsy large panel (if reimbursement possible)

Monitoring during targeted therapy for identification of molecular alterations associated with resistance and to guide the next line of therapy.
Liquid biopsy: NGS or dd-PCR, if negative: tissue biopsy for histological verification of possible switch to SCC and NGS for identification of molecular alterations associated with resistance

1L, first-line; 2L, second-line; dd-PCR, droplet digital PCR; (F)ISH, (fluorescence) in situ hybridisation; IHC, immunohistochemistry; MDT, multidisciplinary team; METex14, MET exon 14 (skipping mutation); N, Nodes (staging); NGS, next-generation sequencing; NSCLC: non-small cell lung cancer; PCR, polymerase chain reaction; SCC, squamous cell carcinoma; T, Tumour (staging)

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PROPOSED MINIMAL TESTING APPROACH ACCORDING TO DISEASE STAGE

	Stage IA	Stage IB	Stage IIA	Stage IIB	Stage III	Stage IV before 1L or 2L	Stage IV ≥ 2L
PD-L1							
EGFR							
ALK							
ROS1							
RET							
KRAS							
BRAF							
HER2							
*MET*ex14							
MET other							
NTRK1/2/3							
NRG1							

All NSCLC

NSCLC with exceptions

1L, first-line; 2L, second-line; METex14, MET exon 14 (skipping mutation); NSCLC, non-small cell lung cancer

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FUTURE DIRECTIONS

- The future of precision oncology for **lung cancer is becoming even more personalised**
- **More complex targeted modalities therapies**, immunotherapies and combination treatments **will be used in earlier treatment lines**, faster than before
- **The role of alternate liquid samples** such as urine, sputum, effusions and FNA **will continue to advance** with the availability of high sensitivity, multi-detection genomic assays, and the growing recognition for validating unconventional cytologic substrates
- **Artificial intelligence is transforming patient care** and advancing not only diagnostic accuracy but also early cancer detection, prognosis prediction, and treatment evaluation through integration of patient data, ranging from CT scans to omics information like DNA, RNA, proteins, and microRNA
- Fundamentally though, enhancing **precision oncology for lung cancer requires adherence to current best practices**

CT, computed tomography; FNA, fine needle aspirate

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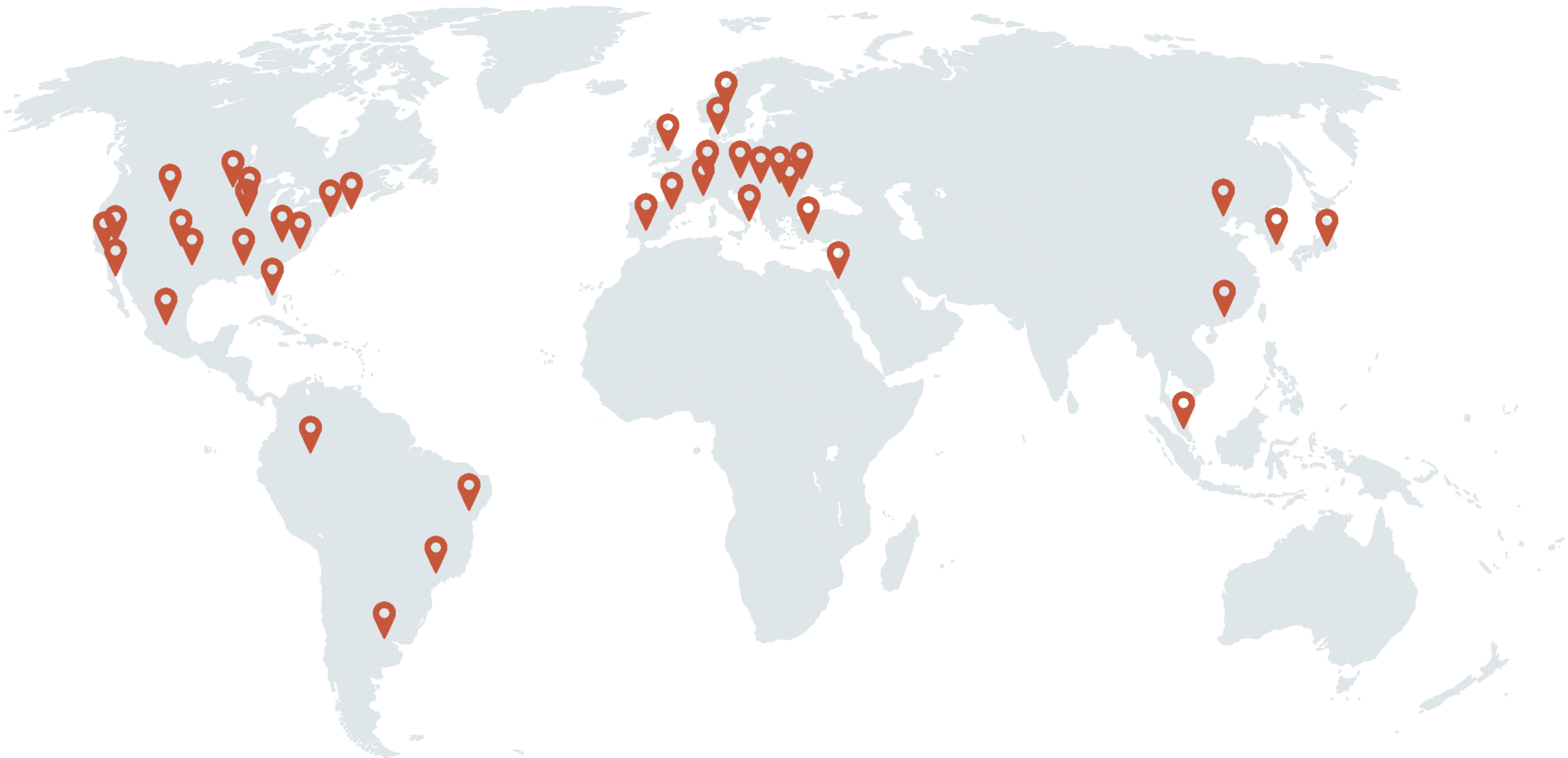

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