touchPANEL DISCUSSION

MET mutations: The next frontier in NSCLC testing

An expert panel discussion recorded in July 2020

This educational activity is supported by an independent grant from the Healthcare business of Merck KGaA, Darmstadt, Germany

touch RESPIRATORY®

NSCLC, non-small cell lung cancer.

Disclaimer

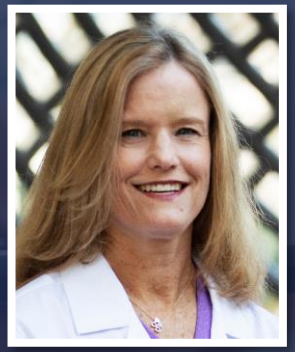
Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions.

The presenting faculty have been advised by touchIME to ensure that they disclose any such references made to unlabelled or unapproved use.

No endorsement by touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in touchIME activities.

touchIME accepts no responsibility for errors or omissions.

Expert panel



Professor Karen Reckamp (Chair)
Cedars-Sinai Cancer Center,
Los Angeles, CA

Professor Keith Kerr
Aberdeen University
Medical School, UK

Dr Paul K Paik
Memorial Sloan
Kettering Cancer Center,
New York, NY

Agenda

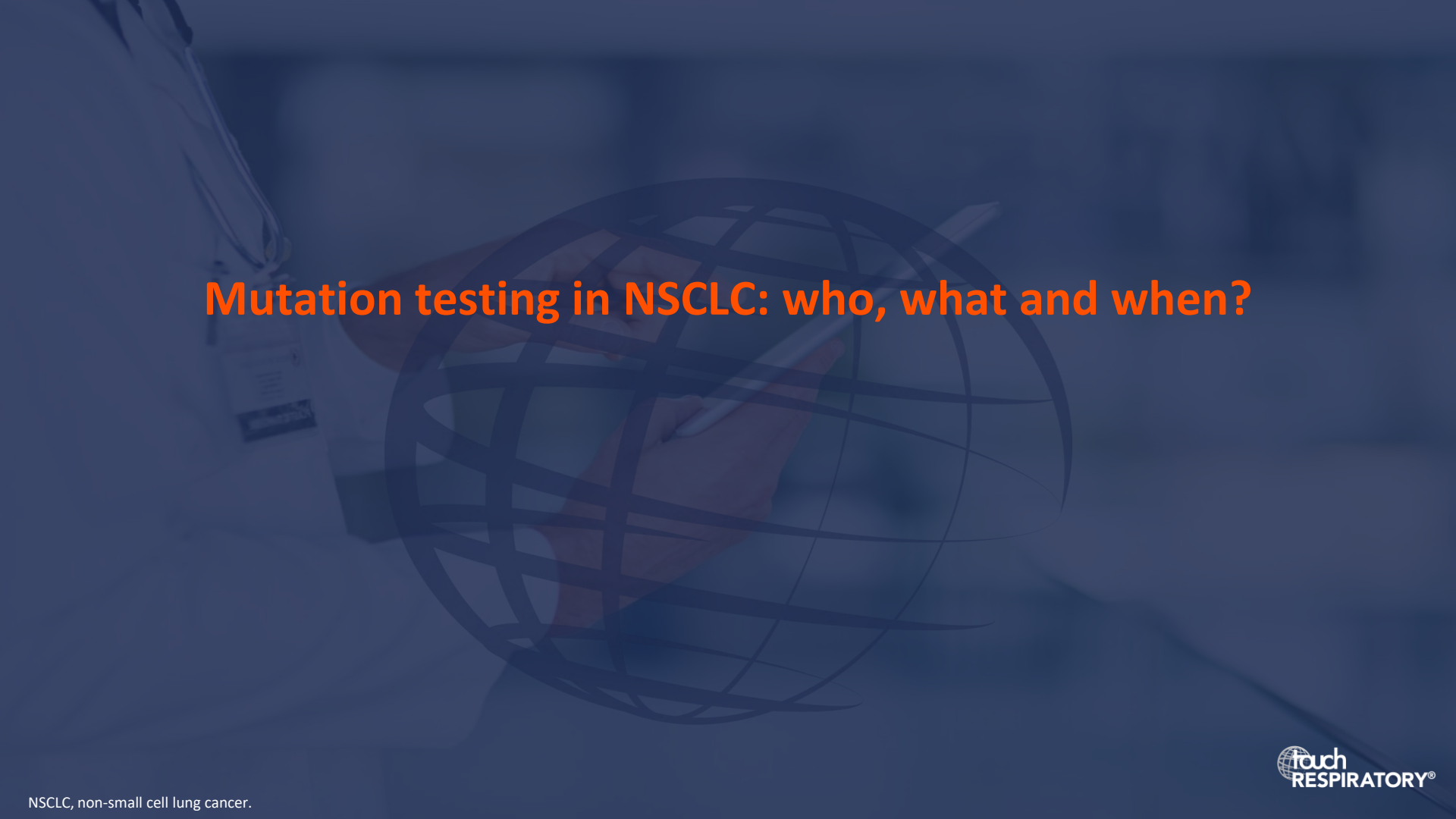
Mutation testing in NSCLC: who, what and when?
Presentation: Karen Reckamp
Panel discussion: Paul Paik and Keith Kerr; moderated by Karen Reckamp

How is molecular testing in NSCLC evolving?
Presentation: Karen Reckamp
Panel discussion: Paul Paik and Keith Kerr; moderated by Karen Reckamp

NSCLC, non-small cell lung cancer.

touch RESPIRATORY®

Mutation testing in NSCLC: who, what and when?



NSCLC, non-small cell lung cancer.

NCCN guidelines for biomarker testing in NSCLC

Patients with advanced or metastatic NSCLC

Establish histologic subtype with adequate tissue for molecular testing (consider rebiopsy if appropriate); smoking cessation or counselling; integrate palliative care

Squamous cell carcinoma

Molecular testing

- **Consider** *EGFR* mutation and *ALK* testing in never-smokers or small biopsy specimens, or mixed histology
- **Consider** *ROS1, BRAF, MET* exon 14 skipping, and *RET* testing in small biopsy specimens, or mixed histology
- Testing should be conducted as part of broad molecular profiling

PD-L1 testing

Adenocarcinoma, large cell, NSCLC not otherwise specified

Molecular testing

- *EGFR* mutation testing (Category 1)
- *ALK* testing (Category 1)
- *ROS1* testing
- *BRAF* testing
- ***MET* exon 14 skipping mutations**
- *RET* testing
- Testing should be conducted as part of broad molecular profiling

PD-L1 testing

FDA-approved agents are available for these biomarkers
Other testing, e.g., for *NTRK* or *HER2* mutation, or MET amplification, may also be performed

- *MET* ex14 skipping mutations occur in **3–4% of patients with adenocarcinoma** and in 1–2% of patients with other NSCLC histologies

ALK, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; FDA, US Food and Drug Administration; *HER2*, human epidermal growth factor receptor 2; *MET* exon 14, mesenchymal–epithelial transition exon 14; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tropomyosin receptor kinase; PD-L1, programmed death-ligand 1; *RET*, rearranged during transfection.

NCCN Guidelines (Non-Small Cell Lung Cancer, Version 6.2020). Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed June 2020)

Timing of biomarker analysis in NSCLC

Before first-line therapy

- The NCCN panel emphasizes that molecular testing results for actionable biomarkers should be obtained before first-line therapy

At progression on targeted therapy

- Re-testing of a sample that is actively progressing while exposed to targeted therapy can shed light on appropriate next therapeutic steps

NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.
NCCN Guidelines (Non–Small Cell Lung Cancer, Version 6.2020). Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed June 2020)

Other biomarker testing guidelines in NSCLC

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Therapy-predictive biomarker testing in patients with metastatic NSCLC[1]

- *EGFR* mutations
- *ALK* rearrangements
- *ROS1* rearrangements
- *BRAF* mutations
- PD-L1 expression

CAP/IASLC/AMP Guidelines[2]

- Include *MET*, *RET*, *HER2,* and *KRAS* in larger testing panels either initially or when negative for routine *EGFR*, *ALK*, *BRAF*, and *ROS1* testing

The National Lung Cancer Roundtable[3]

Guideline-concordant	Recommended	Optional as part of a larger panel	
EGFR, including *T790M*	MSI	*RET*	*KRAS*
ALK	PD-L1	*MET*	TMB
BRAF	*NTRK*	*HER2*	
ROS1			

ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; CAP, College of American Pathologists; *EGFR*, epidermal growth factor receptor; FDA, US Food and Drug Administration; *HER2*, human epidermal growth factor receptor 2; IASLC, International Association for the Study of Lung Cancer; *MET* ex14, mesenchymal–epithelial transition exon 14; MSI, microsatellite instability; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tropomyosin receptor kinase; PD-L1, programmed death-ligand 1; RET, rearranged during transfection; TMB, tumor mutational burden.

1. ESMO Clinical Practice Guidelines, updated 18 September 2019. Available at: www.esmo.org/content/download/227453/3874538/1. (accessed June 2020);
2. Kalemkerian GP, et al. *J Clin Oncol.* 2018;36:911–9; 3. Kim ES, et al. *J Thorac Oncol*. 2019;14:338–42.

touch RESPIRATORY®

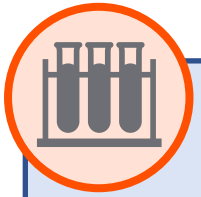
How is molecular testing in NSCLC evolving?

NSCLC, non-small cell lung cancer.

Tissue versus liquid biopsy testing in clinical practice

Tissue biopsy[1]

- Historical standard of care
- Invasive; potential for bleeding and infection
- Difficulty obtaining adequate samples
- Not all patients suitable for biopsy
- Tumor DNA preserved in FFPE blocks
- Single-site tissue biopsies may miss genetic heterogeneity



Liquid biopsy (plasma ctDNA)[1,2]

- Non-invasive; highly acceptable
- Potentially reduced cost and risk of complications
- An alternative when tissue biopsy specimens are insufficient or unfeasible
- Assesses DNA from all tumor sites; potentially bypasses intra-tumoral heterogeneity
- Can obtain serial samples at diagnosis and at acquired resistance
- Issues with sensitivity, specificity and standardization?

ctDNA, circulating tumor DNA; FFPE, formalin-fixed paraffin embedded.

1. Pennell NA, et al. *Am Soc Clin Oncol Educ Book.* 2019;39:531–42; 2. Rolfo C, et al. *J Thorac Oncol*. 2018;13:1248–68.

touch RESPIRATORY®

The evolving role of NGS testing in NSCLC

NGS is increasingly utilized in clinical laboratories[1]

Benefits of NGS

- ✓ Simultaneously tests for multiple alterations using a single tissue sample[2]
- ✓ Should ultimately reduce costs and increase availability for patients, reducing the need for rebiopsy versus single-gene tests[3]
- ✓ Single-gene test sequences are time-consuming and may require a relatively large tissue sample, which is not always available[3]

Challenges of implementing NGS

- Limited access, lack of awareness in medical care teams, limited coverage, and low reimbursement rates[2]
- Interpretation of NGS reports and use of results to guide treatment decisions[3]
- Careful consideration of limitations – e.g. not all assays that include *MET* will detect all known *MET* exon 14 skipping variants[4]

MET exon 14, mesenchymal–epithelial transition exon 14; NGS, next-generation sequencing; NSCLC; non-small cell lung cancer.

1. Ettinger DS, et al. *J Natl Compr Canc Netw.* 2018;16:807–821; 2. Pennell NA, et al. J *Clin Oncol.* 2018;36 (suppl; abstr 9031); 3. Pennell NA, et al. *Am Soc Clin Oncol Educ Book.* 2019;39:531–42; 4. Davies KD, et al. *J Thorac Oncol.* 2019;14:737–41.

DNA-based and RNA-based NGS testing in NSCLC

NGS panel assays can identify mutations, such as *MET* ex14 skipping events, to guide selection of targeted therapy[1,2]

DNA sequencing[2]

- Detects genomic variants that alter or ablate a splicing site, or delete a whole exon

RNA sequencing[2]

- Detects the results of altered splicing (e.g. "fusion" of *MET* exon 13 to 15) regardless of the underlying genomic event
- RNA is more fragile than DNA, and high-quality RNA is harder to acquire from clinical cases

In a study of 286 samples:[2]

- RNA analysis detected *MET* ex14 skipping at 4.2% versus 1.3% with DNA analysis*
- Six of 10 positives by RNA analysis were not detected by DNA analysis
- RNA analysis was highly reliant on RNA quality

*DNA-based NGS assay using amplicon-mediated target enrichment; RNA-based NGS assay using anchored multiplex PCR for target enrichment.
MET, mesenchymal–epithelial transition, NGS, next-generation sequencing; PCR, polymerase chain reaction.
1. Qin D. *Cancer Biol Med.* 2019;16:4–10; 2. Davies KD, et al. *J Thorac Oncol.* 2019;14:737–41.

touch RESPIRATORY®

Thank you for watching this on-demand event

touchoncology.com/education-zone/

touch RESPIRATORY®