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HGF/MET Signaling

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DISCOVER MET
A Pathology Resource

The *MET* gene encodes the c-Met (also known as MET or HGFR) receptor tyrosine kinase, a protein that influences cell growth, survival, and migration when activated by its ligand, HGF.[1-4]

The HGF/MET pathway plays an important role in various vital cell processes, including embryonic development, tissue repair, carcinogenesis, and tumor progression. It can also interact with other ligands or cellular receptors.

AKT=protein kinase B (or PKB); CD44=cluster of differentiation 44; EGFR=epidermal growth factor; ERK=extracellular signal-regulated kinases; Gab1=GRB2-associated-binding protein 1; Grb2=growth factor receptor-bound protein 2; HER2=human epidermal growth factor receptor 2; HGF=hepatocyte growth factor; HGFR=hepatocyte growth factor receptor; MEK=mitogen-activated protein kinase; MST1R=macrophage-stimulating protein receptor 1; mTOR=mammalian target of rapamycin; NFkB=nuclear factor kappa-light-chain-enhancer of activated B cells; P=phosphate; PIK3=phosphatidylinositol 3-kinases; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma virus proteins; ROR1=receptor tyrosine kinase-like orphan receptor 1; RTK=receptor tyrosine kinase; Shc=Src homology 2 domain-containing (adaptor protein); SOS=son of sevenless protein (or guanine nucleotide exchange factor); STAT3=signal transducer and activator of transcription 3; VEGFR=vascular endothelial growth factor.

Image adapted from Spitaleri G, et al. *Cancers (Basel)*. 2023;15(19):4779.

References: 1. Altintas DM, Comoglio PM. *Cancers (Basel)*. 2023;15(18):4672. **2.** Liang H, Wang M. *Onco Targets Ther*. 2020;13:2491-2510. **3.** Park S, et al. *Histol Histopathol*. 2012;27(2):197-207. **4.** Sun W, et al. *J Biomed Res*. 2013;27(3):220-230.

FOLD

MET Biomarkers in NSCLC

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In NSCLC, HGF/MET signaling can be dysregulated through various aberrations associated with the receptor, including:

MET Exon 14 Skipping Mutations (*MET*ex14 Skipping)

- Caused by **genetic alterations, primarily point mutations or insertions/deletions (indels)**[1]
- Typically identified via **genetic sequencing, including DNA and RNA NGS** methods[1]

Increased c-Met Protein Expression

- Refers to **elevated levels of the c-Met receptor** on the surface of tumor cells compared to normal cells[2]
- Measured via **immunohistochemistry (IHC)** staining intensity of tumor cells[3]

MET Focal Gene Amplification (*MET* Amp)*

- Refers to **increase in *MET* gene copies** without an accompanying rise in chromosome 7 copies[4]
- Can be detected via:[4,5]
  - **Fluorescence *in situ* hybridization (FISH)** using *MET*:*CEP7* ratio
  - **DNA and RNA NGS** methods to assess gain in *MET* copy number

*Emerging biomarker.

CEP7=centromeric portion of chromosome 7; HGF=hepatocyte growth factor; NGS=next-generation sequencing; NSCLC=non-small cell lung cancer.

References: 1. Socinski MA, et al. *JCO Precis Oncol*. 2021;5:653-663. **2.** Sierra JR, Tsao MS. *Ther Adv Med Oncol*. 2011;3(1 Suppl):S21-S35. **3.** Ding C, et al. *BMC Pulm Med*. 2023;23(1):240. **4.** Coleman N, et al. *ESMO Open*. 2021;6(6):100319. **5.** Qin K, et al. *Cancers (Basel)*. 2023;15(3):612.

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c-Met Protein Expression

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	0	1+	2+	3+
	Negative	Weak	Moderate	Strong
10x				
20x				

Images for illustrative purposes only. Contents herein should not be considered as a replacement for assay-specific interpretation manuals or guides.

References: 1. VENTANA MET (SP44) RxDx Assay Interpretation Guide for Non-Squamous Non-Small Cell Lung Cancer. 1018336US Rev A. 2025-05-14. **2.** Images are provided by Caris Life Sciences. **3.** Yin W, et al. *Cancers (Basel)*. 2022;14(10):2433.

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Key MET IHC Considerations

Tissue[1,2]

Types of specimen
Includes resections, biopsies, and cell blocks*

Section considerations
4–5 µm sections with ≥100 viable tumor cells

Fixation considerations
Immediate fixation in 10% NBF for 6–72 hours†

IHC Positive Control Examples[1,3]

External control
Non-neoplastic gallbladder

Internal controls
Bronchial epithelium or type II pneumocytes

MET IHC Staining Patterns[1,2]

Tumor cell staining intensities
Weak (1+), moderate (2+), and/or strong (3+)

Cellular components

Membrane staining

Images for illustrative purposes only. Contents herein should not be considered as a replacement for assay-specific interpretation manuals or guides.

*FNA or other cytology samples that can be spun into cell blocks. †Zinc formalin can also be acceptable.

FNA=fine-needle aspirate; IHC=immunohistochemistry; NBF=neutral-buffered formalin; NSCLC=non-small cell lung cancer.

References: 1. VENTANA MET (SP44) RxDx Assay Interpretation Guide for Non-Squamous Non-Small Cell Lung Cancer. 1018336US Rev A. 2025-05-14. **2.** Yin W, et al. *Cancers (Basel)*. 2022;14(10):2433. **3.** AbbVie Data on File REF-1383355.

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