MTAP: How do we test it?

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Disclosures

- Abbvie: Honoraria
- Astra Zeneca: Honoraria, research funding
- Bayer: Honoraria
- Boehringer Ingelheim: Honoraria
- BMS: Honoraria
- Daiichi Sankyo: honoraria
- Janssen: Honoraria, research funding
- Lilly: Honoraria, research funding
- MSD: Honoraria
- Pfizer: Honoraria, research funding
- Roche: Honoraria, research funding
- Takeda: Honoraria
- Thermo Fisher: Honoraria, research funding

Contents

- Background
- Prognostic and therapeutic relevance
- Histology and molecular context
- Detection methods
- Conclusions

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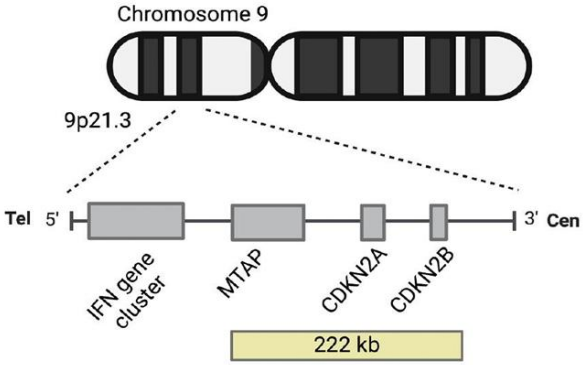
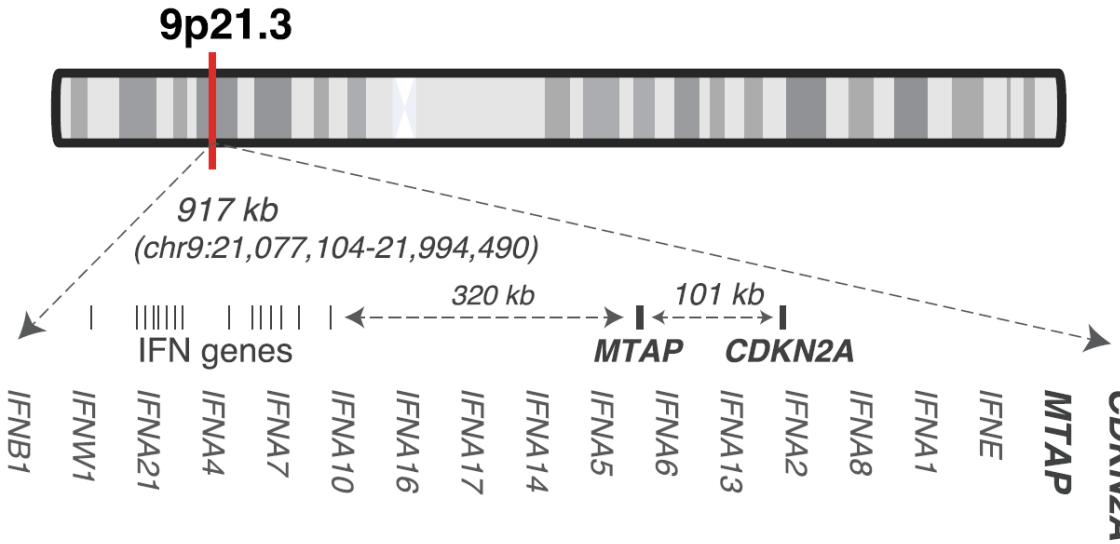
Background

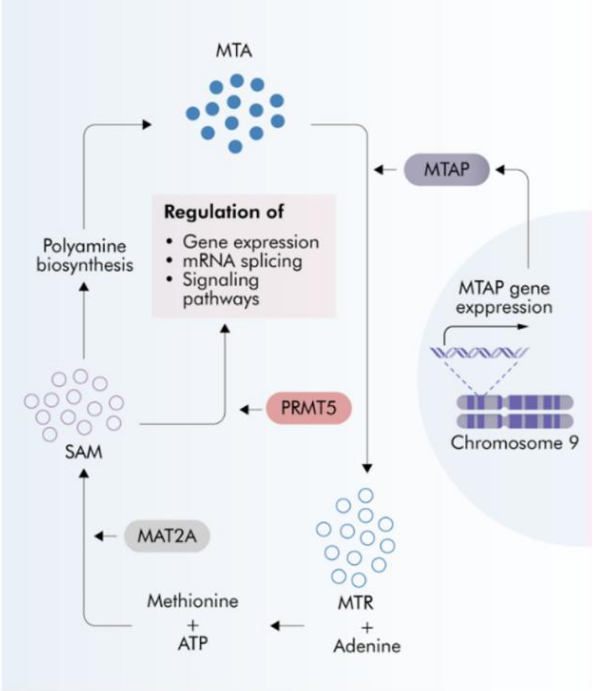
***MTAP* is located at 9p21, in the same genomic cluster as *CDKN2A* and several *IFN* genes, and encodes the enzyme methylthioadenosine phosphorylase**

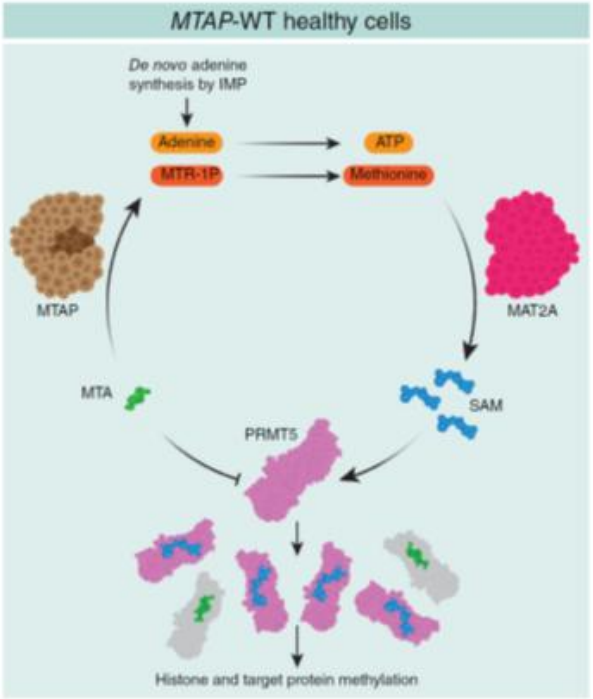




Background

MTAP is a key enzyme in the methionine salvage pathway that regulates PRMT5 activity





- MTAP degrades MTA, the PRMT5 by-product, keeping its levels low
- This allows PRMT5/MAT2A to drive normal protein methylation, splicing, and gene regulation

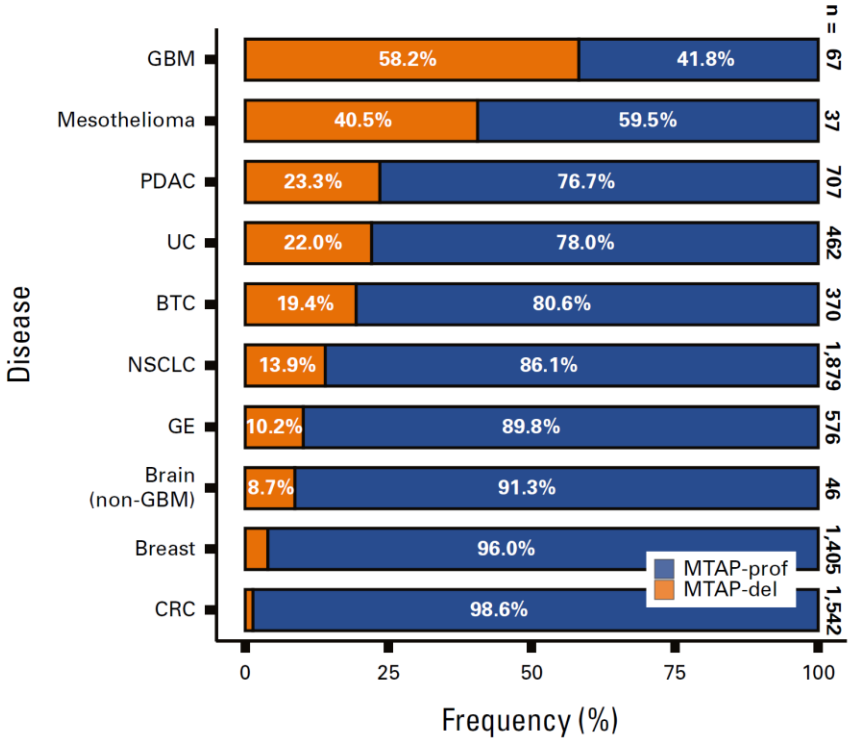
PRMT5:
protein arginin methyltransferase

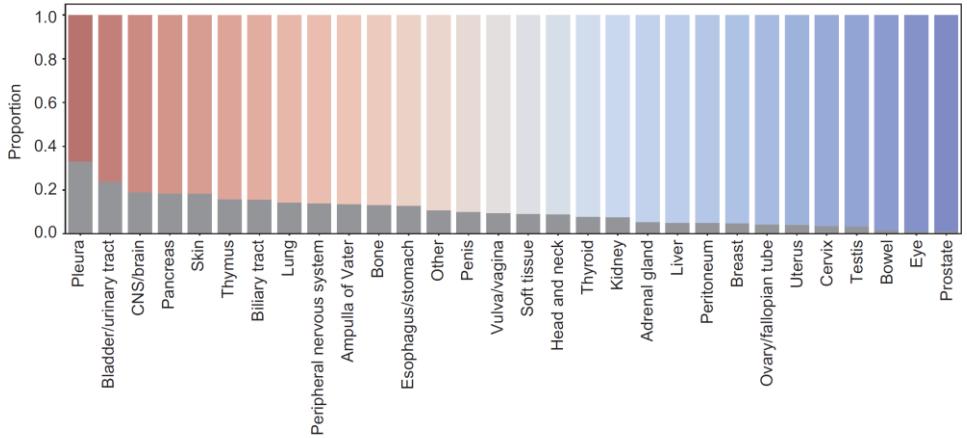
MAT2A:
methionine adenosyl transferase 2A

König D, *et al*. J Thorac Oncol 2026; Rodon J, *et al*. Cancer Res 2026

Background

MTAP homozygous deletion is observed in ≈10% of human cancers

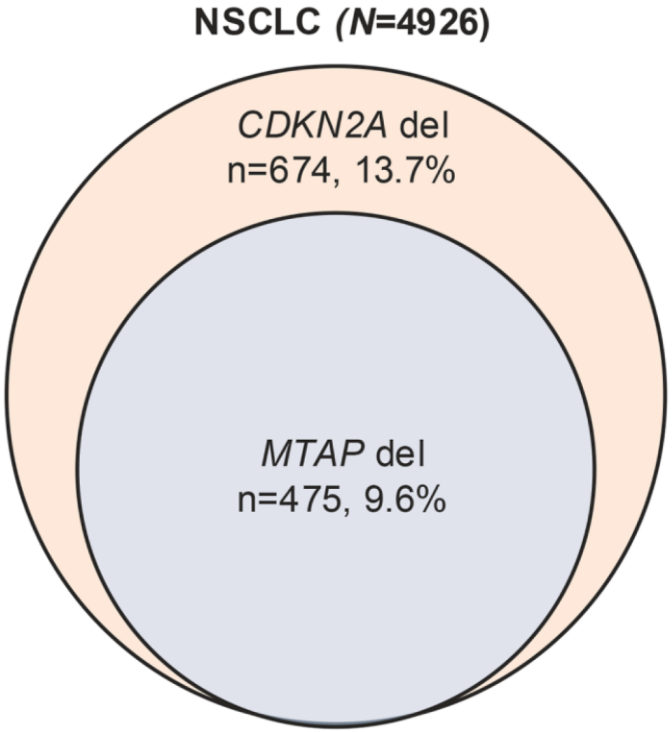




Ikushima H, *et al*. ESMO Open 2025; Best JT, *et al*. JCO Precis Oncol 2025

Background

MTAP is often co-deleted with *CDKN2A*



NSCLC (n=87,235)		$MTAP_{loss}$ +	$MTAP_{loss}$ -
$CDKN2A_{loss}$	+	14,235	6,681
	-	29	66,290

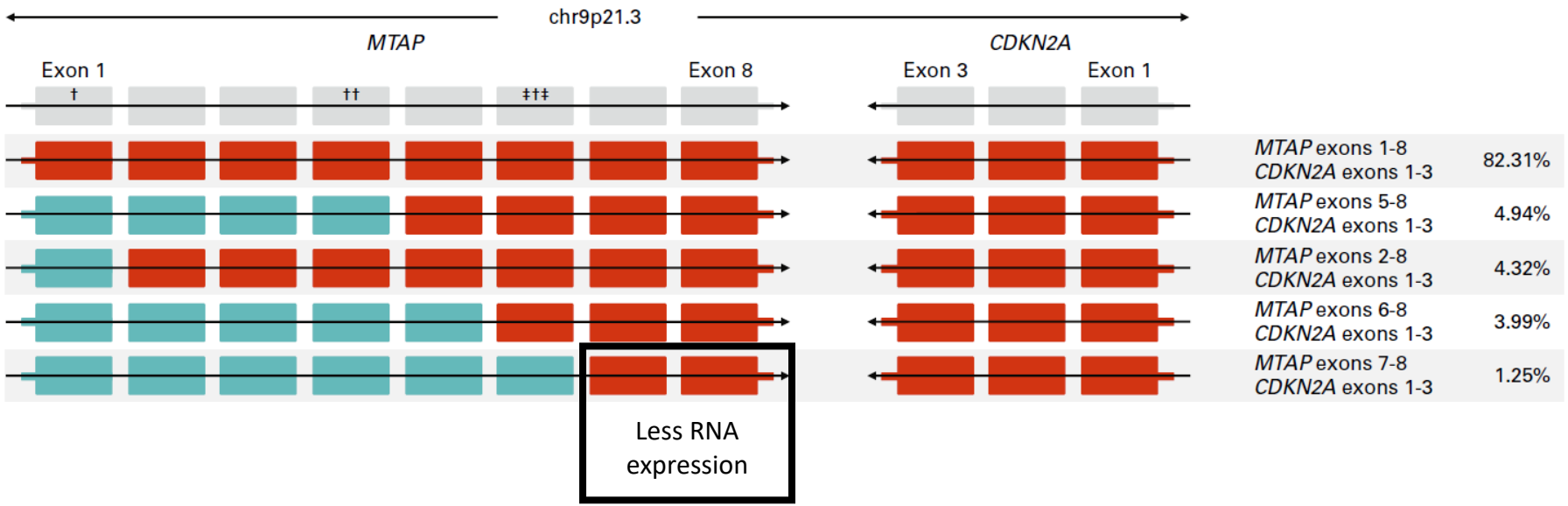
truth label:	$MTAP_{loss}$	$CDKN2A_{loss}$
Sensitivity (PPA)	0.9980	0.6806
Specificity (NPA)	0.9084	0.9996
PPV	0.6806	0.9980
NPV	0.9996	0.9084

Ross JS, *et al*. J Thorac Oncol 2025; Ikushima H, *et al*. ESMO Open 2025; Pavlick DC, *et al*. JCO Precis Oncol 2025

Background

MTAP is often co-deleted with *CDKN2A*

Pan-tumor



Ross JS, *et al*. J Thorac Oncol 2025; Ikushima H, *et al*. ESMO Open 2025; Pavlick DC, *et al*. JCO Precis Oncol 2025

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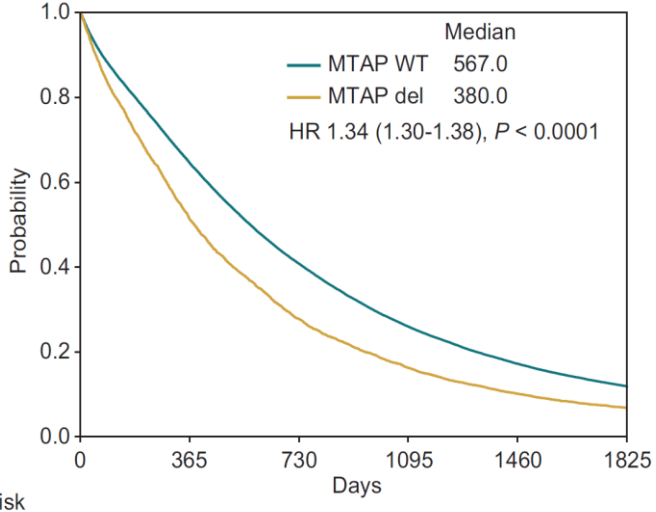
Prognostic relevance

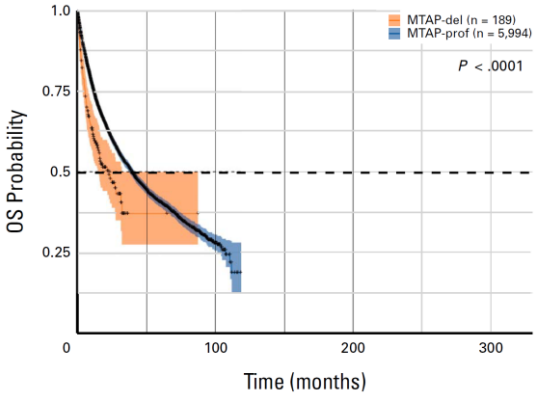
MTAP loss is associated with shorter OS across tumor types

Pan-tumor

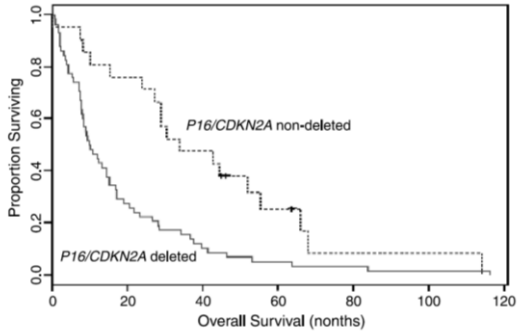


Number at risk

MTAP WT	42 824	27 663	17 499	11 143	7380	5114
MTAP del	4553	2340	1265	742	464	310



NSCLC



Mesothelioma

Ikushima H, *et al*. ESMO Open 2025; Best JT, *et al*. JCO Precis Oncol 2025; Lopez-Rios F, *et al*. Cancer Res 2006

Therapeutic relevance

Synthetic lethal target, resistance mechanism and possible predictor

Therapeutic target

MTA-cooperative PRMT5 inhibitors and MAT2A inhibitors

Acquired resistance mechanism

Acquired *MTAP* loss after osimertinib in *EGFR*-mut NSCLC

Predictor of response to IO

9p21 loss → cold immune microenvironment; lower PD-L1 expression and reduced TILs

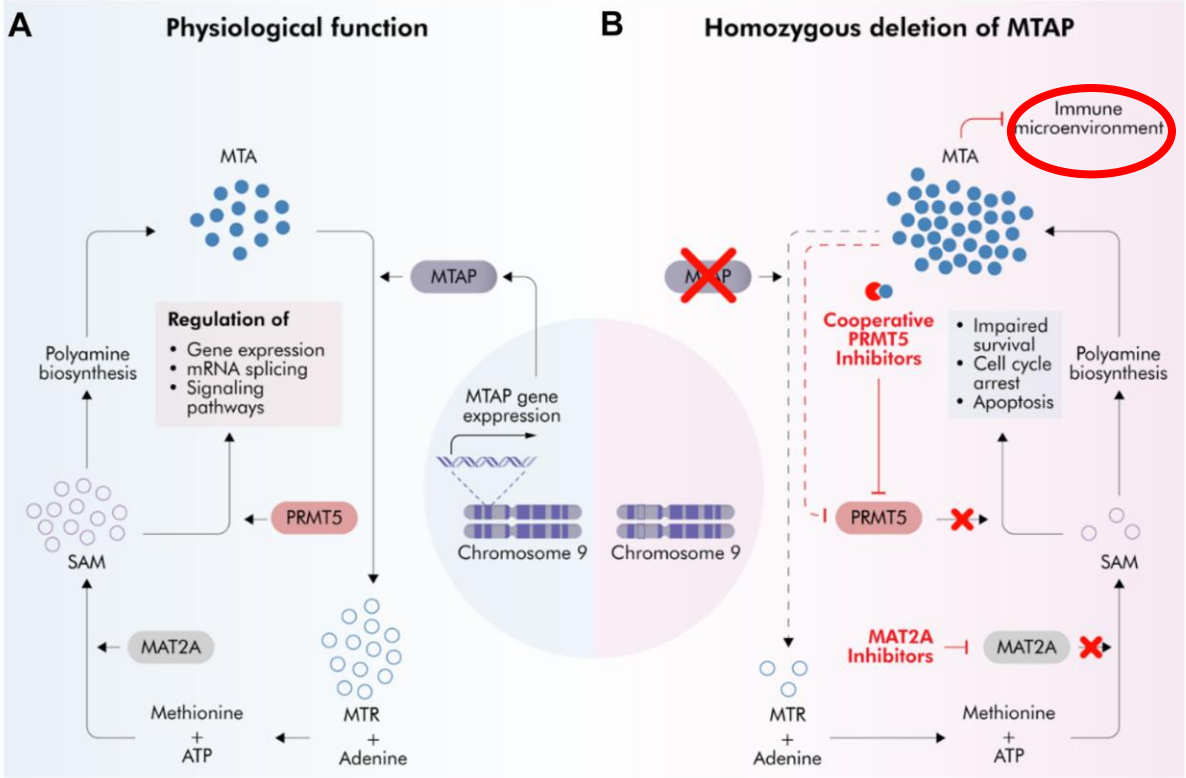
Predictor of response to chemo

MTAP loss linked to poorer response to pemetrexed, etc…

Rodon J 2026; König D 2026; Ross JS 2026; Han G 2021; Best JT 2025; Alhalabi O 2022

Therapeutic relevance

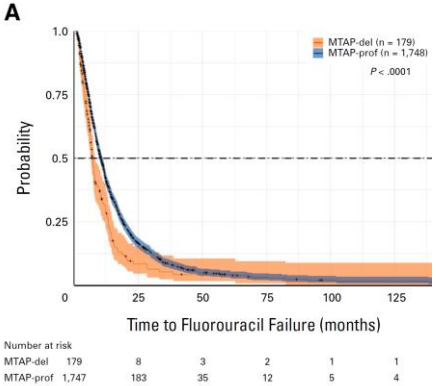
Synthetic lethality and IO

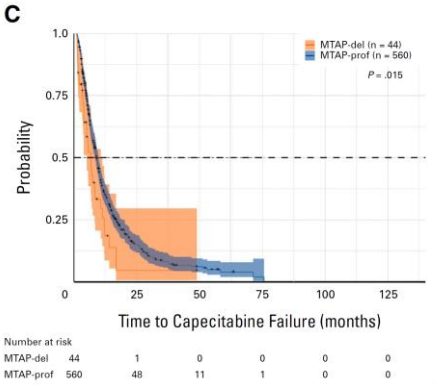


König D, *et al*. J Thorac Oncol 2026

Therapeutic relevance

Chemotherapy



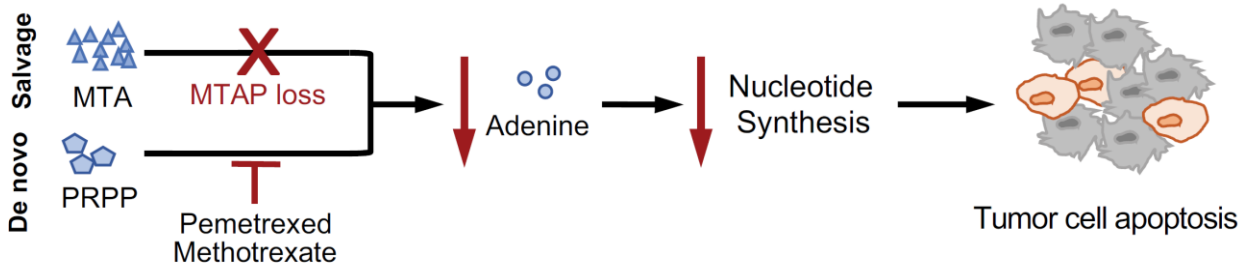


ARTICLE

Check for updates

https://doi.org/10.1038/s41467-022-29397-z OPEN

MTAP deficiency creates an exploitable target for antifolate therapy in 9p21-loss cancers

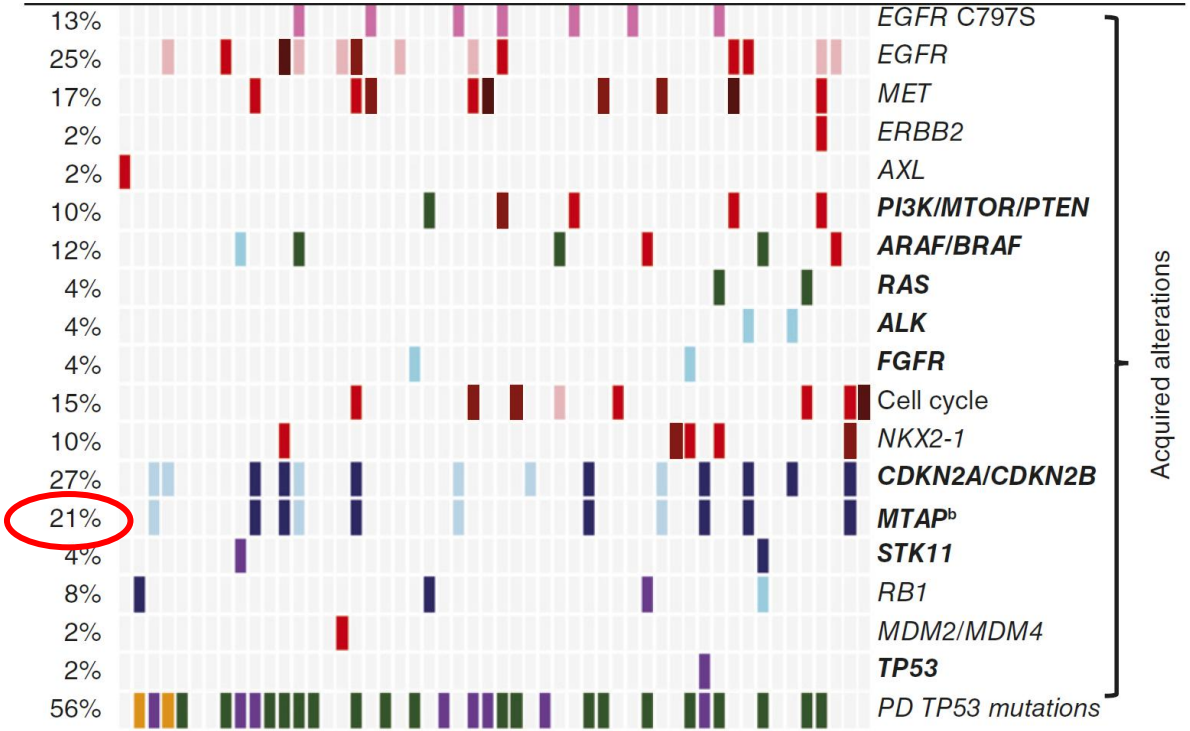


Alhalabi O, *et al*. Nat Commun 2022; Best JT, *et al*. JCO Precis Oncol 2025

Therapeutic relevance

Acquired resistance mechanism

Acquired molecular and pathologic changes at time of osimertinib resistance (*N*=69)	Total (%)
CDKN2A/CDKN2B del	15 (22%)
MTAP del	9 (13%)
SCLC transformation	9 (13%)
EGFR amp	7 (10%)
EGFR C797S	5 (7%)
MET gain/amp	4 (6%)
CDK4/MDM2 amp	4 (6%)
CCND1 gain/amp	3 (4%)
KRAS amp	2 (3%)
MYC amp	1 (1%)
BRAF V600E	1(1%)
PIK3CA E545K	1 (1%)
ERBB2 amp	1 (1%)
EGFR 718Q	1 (1%)
RB1 mutation	1 (1%)
FGFR2 amp	1 (1%)
MET fusion	1 (1%)
None identified	29 (42%)



Piotrowska Z, *et al*. Cancer Discov 2026; Ross JS, *et al*. J Thorac Oncol 2026

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Histology

MTAP deletion can occur beyond adenocarcinomas

Table 1. Clinical Parameters, Histologic Diagnosis, PD-L1 Expression, and CNV Analysis of *CDKN2A* in the Basel Cohort in Relation to Immunohistochemical MTAP Expression

Basel Cohort	Number of Cases	MTAP Proficient n (%)	MTAP Deficient n (%)	*p* Values
Subtype				
LUAD or NSCC, NOS	550	449 (81.6)	101 (18.4)	0.9
LUSC	148	122 (82.4)	26 (17.6)	

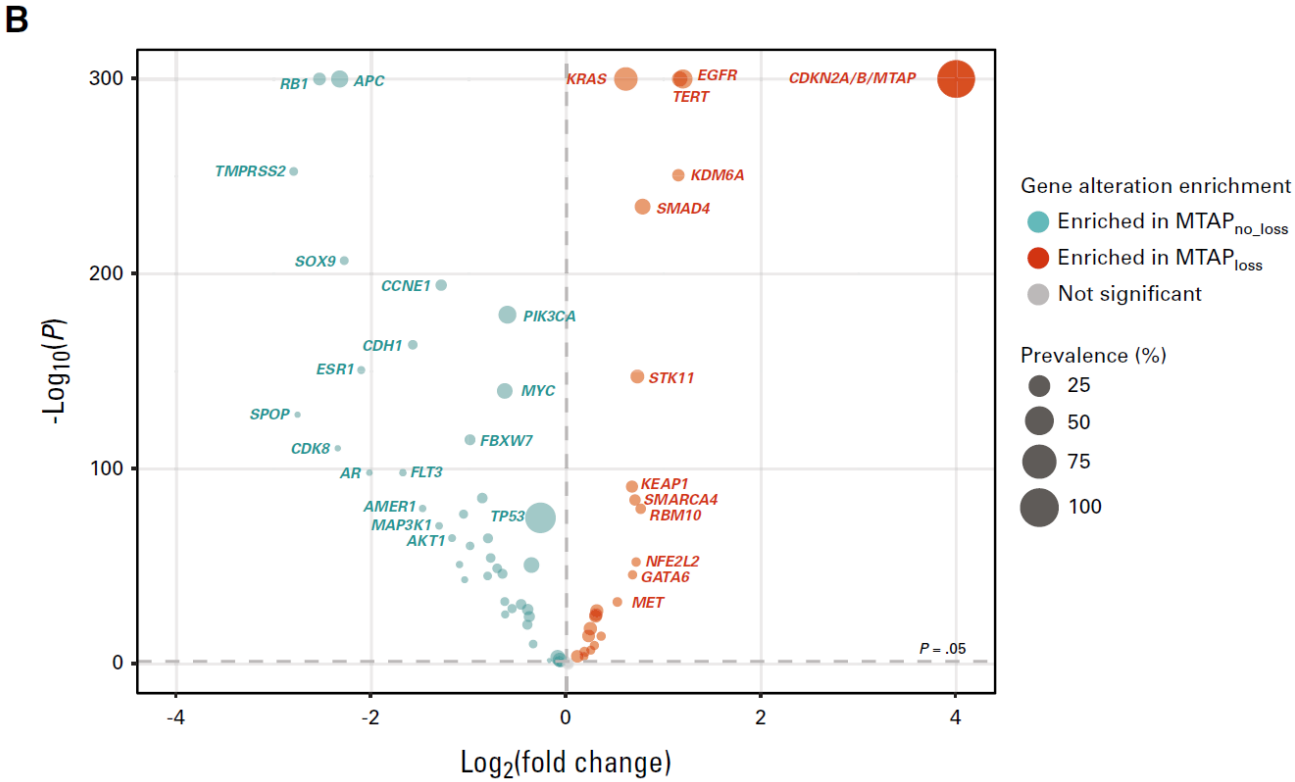
Table 1. Baseline Characteristics of the *MTAP*-del and *MTAP*-WT Cohorts

Patient Characteristics	Patients with *MTAP*-del stage IV NSCLC (*N* = 258) No. (%)
Age, median (range)	64 (18-95)
Sex	
Female	150 (58.1%)
Male	108 (41.9%)
Smoking status	
Never	126 (48.8%)
Former or current	130 (50.4%)
Unknown	2 (0.8%)
Histologic diagnosis	
Adenocarcinoma	228 (88.4%)
Squamous cell carcinoma	18 (7.0%)
NSCLC NOS	3 (1.2%)
Neuroendocrine	5 (1.9%)
Sarcomatoid/pleomorphic carcinoma	1 (0.4%)
Mixed histologic diagnosis	3 (1.2%)

Brune MM, *et al*. J Thorac Oncol 2025, Ross JS, *et al*. J Thorac Oncol 2026

Molecular context

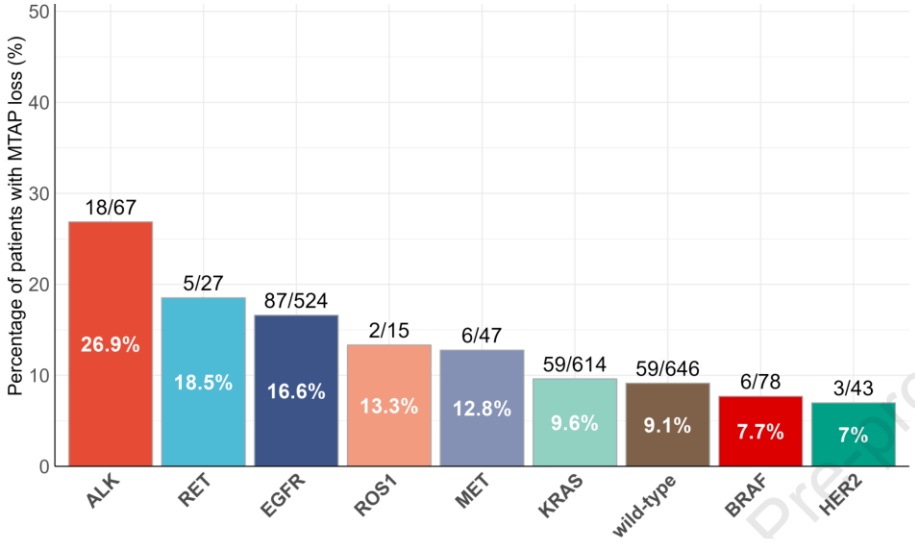
There is significant overlap with other relevant alterations: pan-tumor

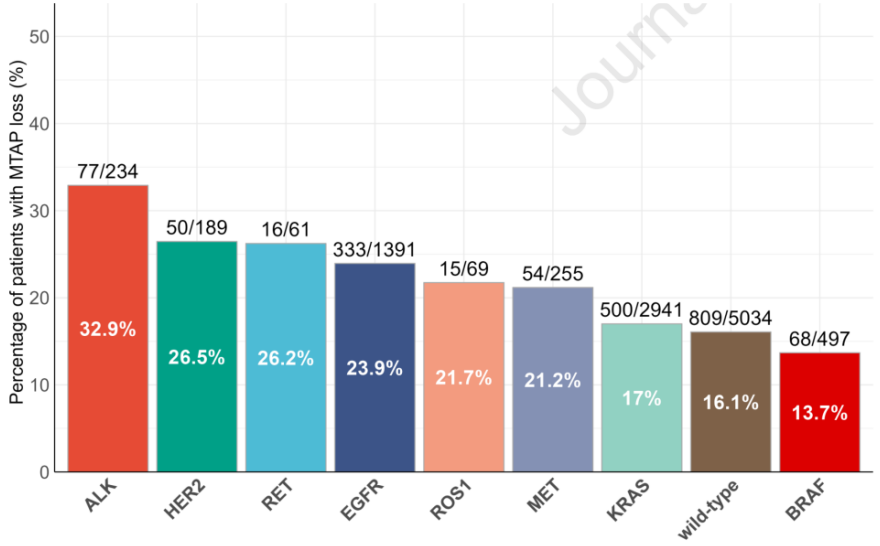


Pavlick DC, *et al*. JCO Precis Oncol 2025

Molecular context

There is significant overlap with other relevant alterations: NSCLC





Aldea M, *et al*. Ann Oncol 2026

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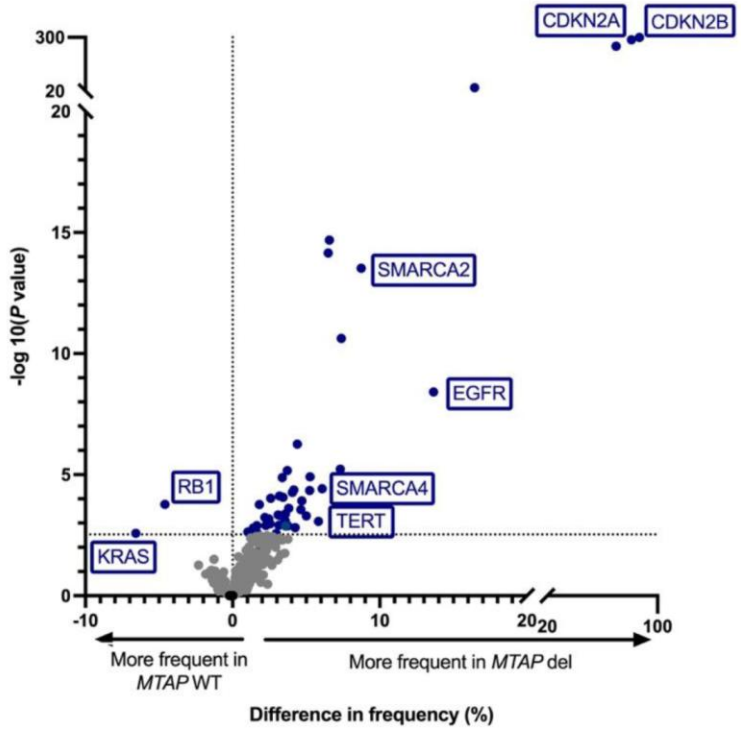

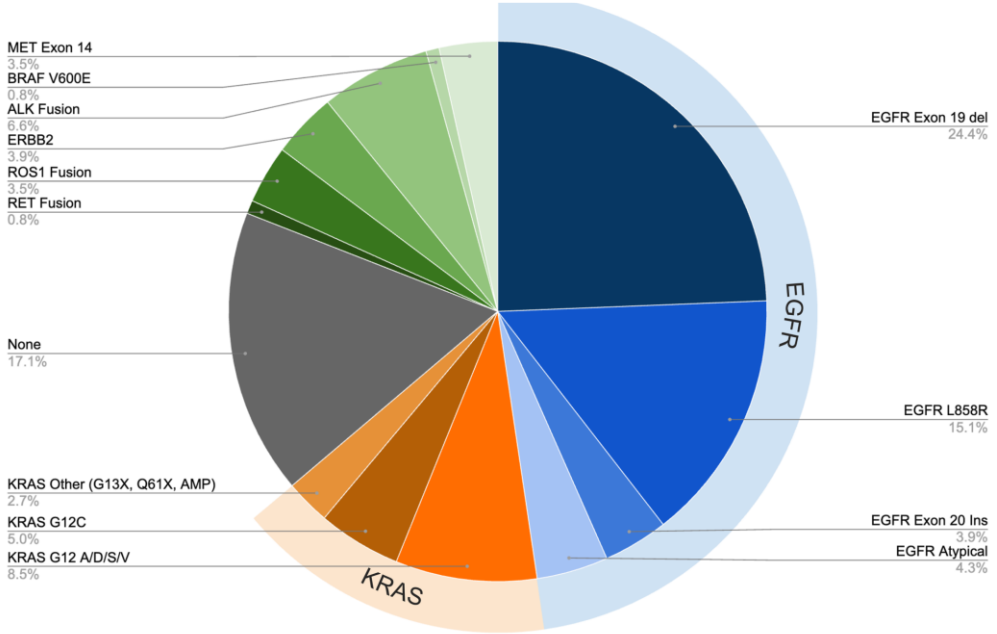

Ross JS, *et al*. J Thorac Oncol 2026

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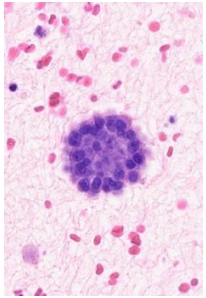
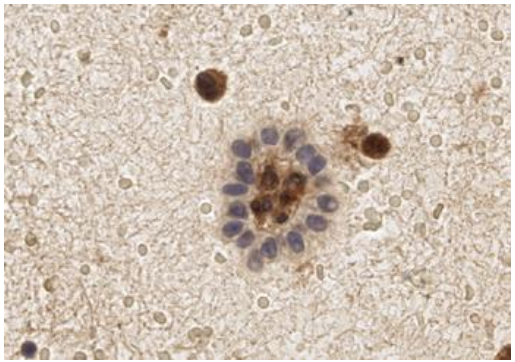
Detection methods: immunohistochemistry (IHC)

Interpretation criteria

- **Clone selection**
  - Lack of standardization, mAb1813 is a good choice
- **Staining pattern**
  - Granular cytoplasmic staining
  - Expression in lymphocytes/stroma (internal control)
- **Definition of loss**
  - Complete absence of cytoplasmic staining in tumor cells with retained positive internal control
- **Heterogeneous / partial cases**
  - FISH/NGS correlation recommended
- **Preanalytical requirements**
  - Adequate FFPE fixation; validated external controls

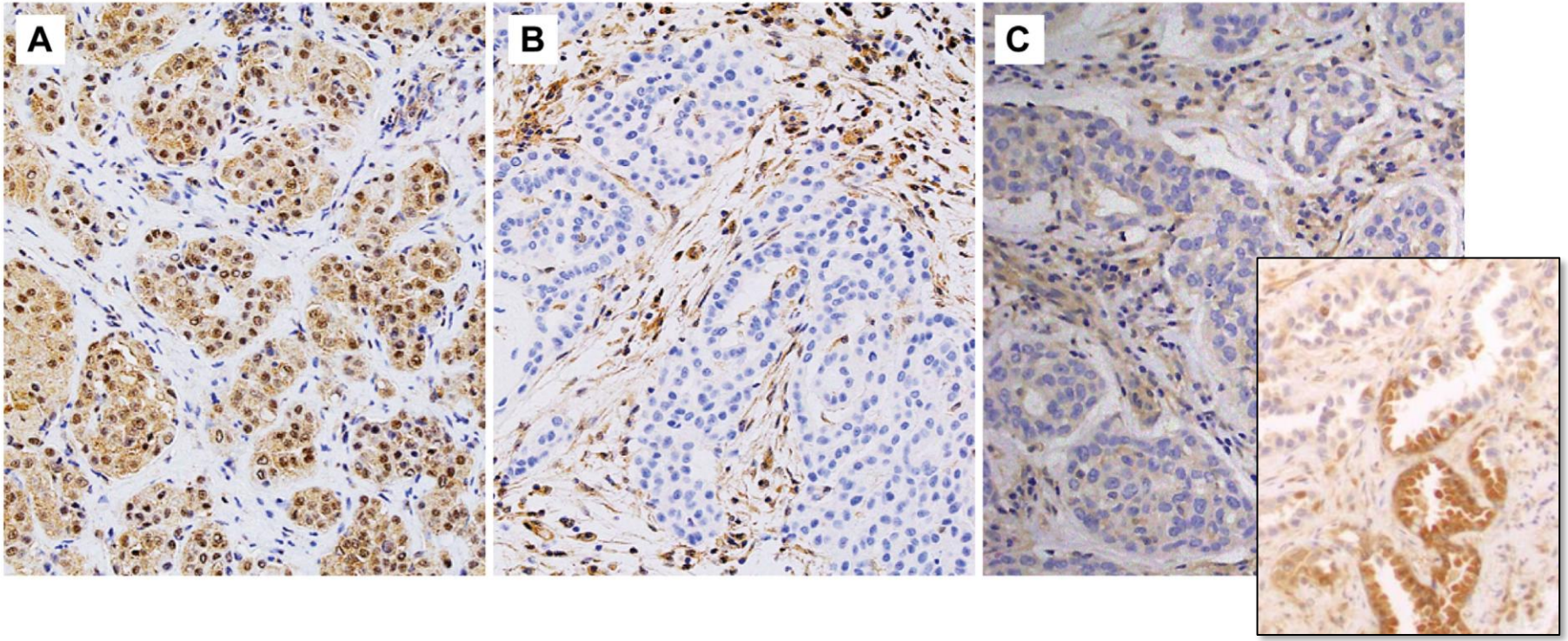




Adapted from Febres-Aldana CA*, et al*. Mod Pathol 2024

Detection methods: immunohistochemistry (IHC)

Scoring: retained, loss and equivocal (faint/heterogeneous)

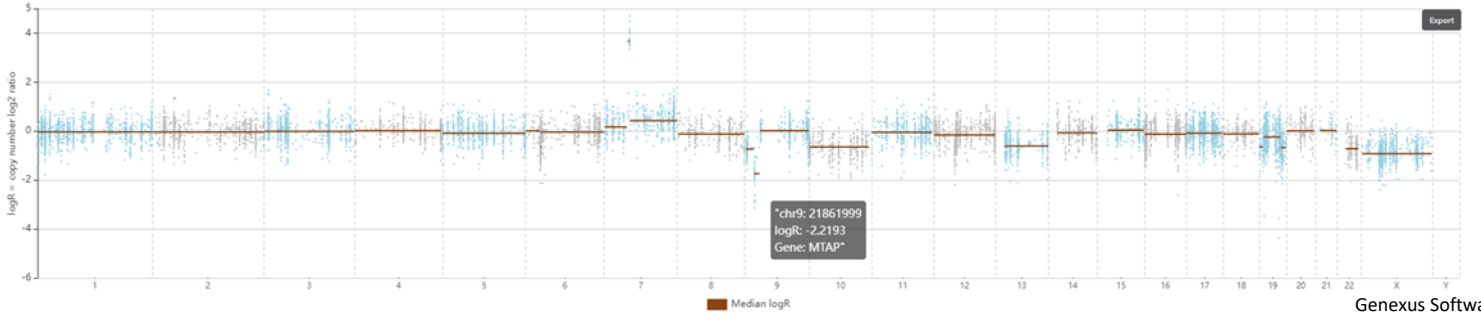


Adapted from Febres-Aldana CA*, et al*. Mod Pathol 2024; Sakai T, *et al*. bioRxiv [Preprint] 2026.

Detection methods: next-generation sequencing (NGS)

Practical tips

- **Diagnostic sensitivity (width)**
  - *MTAP* not covered in many small panels
  - *CDKN2A* as a surrogate?
- **CNV calling criteria**
  - Influenced by tumor purity
  - Be careful with automated criteria
  - Use FISH in discordant IHC-NGS cases?



Genexus Software 6.8.4.0

Febres-Aldana CA 2024; Aldea M, *et al*. J Thorac Oncol 2026; Ross JS, *et al*. J Thorac Oncol 2026

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Conclusions

- ***MTAP*** maps to 9p21.3 and is frequently co-deleted with *CDKN2A*; ~10 of NSCLC, enriched in *EGFR*-mutant tumors
- *MTAP* loss is **prognostic** (shorter OS), **therapeutic** and an **acquired resistance mechanism** after TKI therapy
- **IHC**: sensitive, inexpensive and feasible on scant samples
- **NGS**: requires high tumor content and dedicated *MTAP* coverage; adds molecular context

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2108 Vol. 9, 2108–2113, June 2003 Clinical Cancer Research

Homozygous Deletion of *CDKN2A* and Codeletion of the Methylthioadenosine Phosphorylase Gene in the Majority of Pleural Mesotheliomas

Peter B. Illei,[1] Valerie W. Rusch, Maureen F. Zakowski, and Marc Ladanyi[2]

Departments of Pathology [P. B. I., M. F. Z., M. L.] and Surgery [V. W. R.], Memorial Sloan-Kettering Cancer Center, New York, New York, 10021

UTOPIA Project