



Limitations of CDKN2A loss identification as a surrogate for MTAP loss in non-small cell lung cancer.

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Background

- S-methyl-5'-thioadenosine phosphorylase (MTAP) loss is a potential biomarker for response to MTA-cooperative PRMT5 inhibitors.^{1,2}
- Cyclin-dependent kinase inhibitor 2A (CDKN2A)* loss by next-generation sequencing (NGS) is often regarded as a surrogate for MTAP loss, but its diagnostic accuracy has not been fully evaluated.³

1. Smith CR, et al. *Cancer Discov.* 2025;15(1):139–161.
2. Brune MM, et al. *Lung Cancer.* 2024;197:107963.
3. Brune MM, et al. *J Thorac Oncol.* 2026;21(1):112–123.

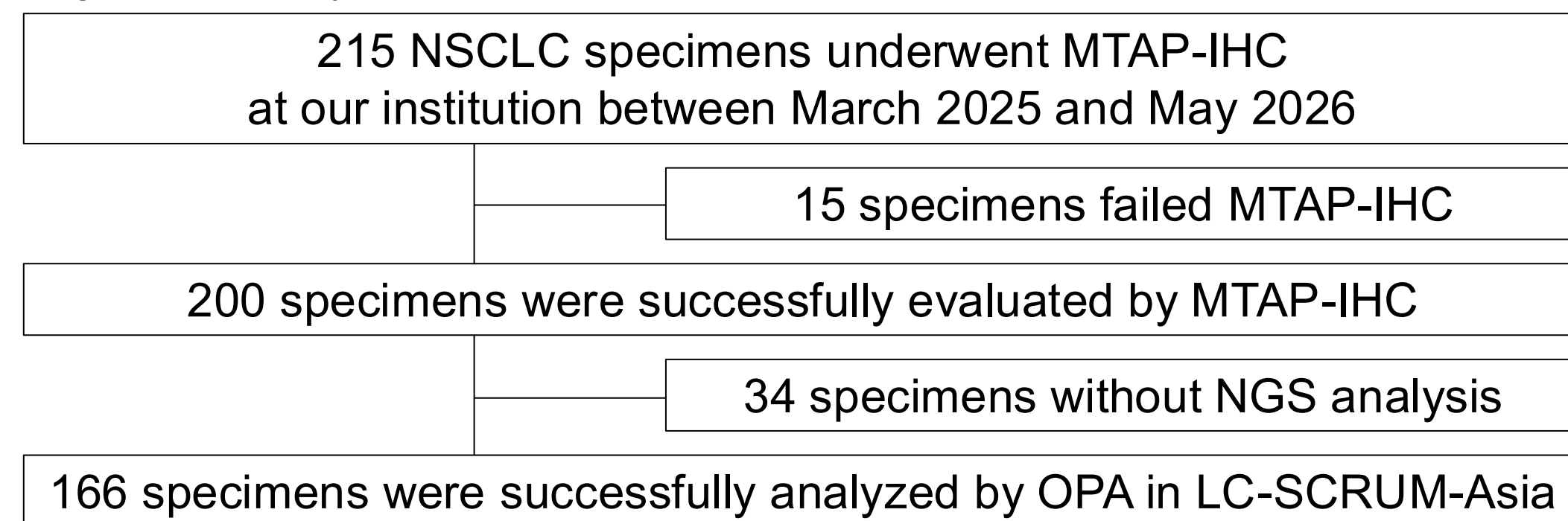
Objective

- To assess the accuracy of NGS-detected *CDKN2A* loss as a surrogate for MTAP loss.

Methods

- Patients with non-small cell lung cancer (NSCLC) who underwent MTAP immunohistochemistry (IHC) at our institution between March 2025 and May 2026 and had evaluable *CDKN2A* status by NGS were included.

Figure 1. Study flow



- MTAP status was evaluated by IHC using the 2G4 antibody. Based on the findings of our previous study, MTAP status determined by IHC was used as the reference standard.⁴

Table 1. Concordance between MTAP IHC and fluorescence in situ hybridization (FISH) (Ref.4, updated)

		MTAP FISH		
		Intact	Hemizygous loss /monosomy	Homozygous loss
MTAP IHC	Retained	10	-	-
	Loss	-	1	21

4. Hirata T, et al. *J Clin Oncol.* 2026;44(16_suppl):8025.

- CDKN2A loss was assessed using the OncoPrint Precision Assay (OPA), an NGS panel that does not cover MTAP, within LC-SCRUM-Asia, a multi-institutional lung cancer genomic screening project in Asia.
- MTAP FISH was performed on samples with MTAP loss by IHC and CDKN2A retained by NGS to confirm the MTAP status determined by IHC.
- Tumor cellularity, defined as the percentage of tumor cells in the specimen, was assessed by pathologists.
- The maximum variant allele frequency (Max VAF) was defined as the highest VAF among all mutations detected by OPA.

Table 2. Patient characteristics

		N = 166 (%)
Age, year-old	Median [range]	69 [28-87]
Sex	Male	103 (62)
ECOG PS	0 – 1	162 (99)
Stage at diagnosis	III - IV	149 (90)
	Recurrence	17 (10)
Smoking status	Ever	115 (69)
Histology	Adenocarcinoma	130 (78)
	Squamous cell carcinoma	23 (14)
	NSCLC-NOS/Large	11 (7)
	Others	2 (1)
Number of prior systemic therapies	0	140 (85)
	1	14 (8)
	2 or more	12 (7)
Type of prior systemic therapies	Platinum-based	16 (10)
	ICIs	6 (4)
	Tyrosine kinase inhibitors	18 (11)
Genomic alterations	<i>EGFR</i> mutations	52 (31)
	<i>KRAS</i> mutations	24 (14)
	<i>ALK</i> fusions	10 (6)
	<i>BRAF</i> mutations	7 (4)
	<i>ERBB2</i> mutations	5 (3)
	<i>MET</i> exon14 skipplings	4 (2)
	<i>RET</i> fusions	3 (2)
	<i>ROS1</i> fusions	2 (1)

PS: performance status, NSCLC-NOS: non-small cell lung cancer, not otherwise specified, ICIs: Immune checkpoint inhibitors

Table 3. Characteristics of samples

		N = 166 (%)
Sampling methods	EBUS-TBNA/MFB	81 (49)
	TBB	44 (27)
	Needle biopsy	20 (12)
	Cell blocks from Effusion	13 (8)
	Surgical biopsy/resection	8 (5)
Sampling sites	Mediastinal lymph node	80 (48)
	Lung	65 (39)
	Pleural effusion	13 (8)
	Liver	3 (2)
	Axillary lymph node	2 (1)
	Pleura	1 (1)
	Bone	1 (1)
	Skin	1 (1)

Longest diameter, mm Median (range) 2.5 (0.5-25.5)

Tumor cellularity, % Median (range) 30 (5-80)

EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration, MFB: mini-forceps biopsy, TBB: transbronchial biopsy, VAF: variant allele frequency

Results

Table 4. Concordance between MTAP status by IHC and CDKN2A status by NGS

		MTAP status by IHC as reference standard		PPA	PPV
		Loss	Retained		
		n = 48	n = 118		
CDKN2A status by NGS	Loss	10	2	21%	83%
	Retained	38*	116	(10/48)	(10/12)

PPA: positive percent agreement, PPV: positive predictive value

* FISH was performed in 12 of 38 specimens.

Figure 2. Confirmation of MTAP status by FISH in specimens with MTAP loss by IHC and CDKN2A retained by NGS

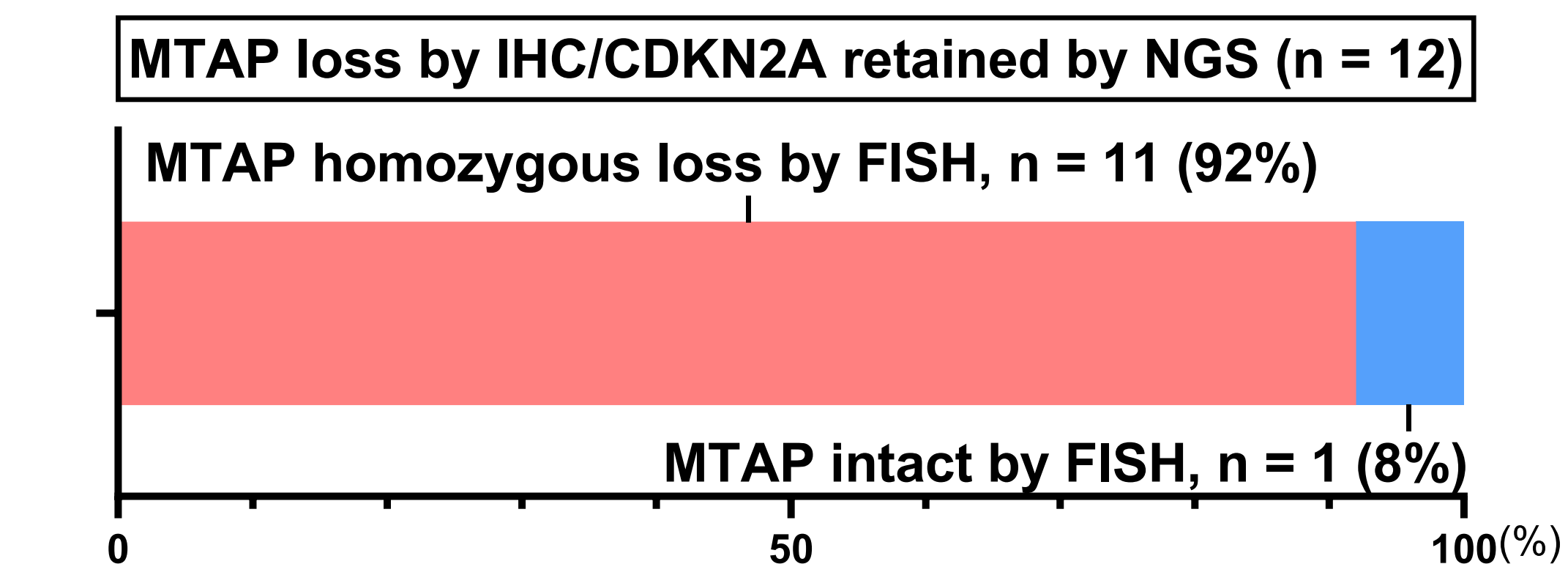


Table 5. Association between tumor cellularity and CDKN2A status by NGS in samples with MTAP loss by IHC

Tumor cellularity	MTAP loss by IHC	CDKN2A status by NGS	
	n = 48	Loss	Retained
Less than 10%	2	-	2 (100)
10%	3	-	3 (100)
20%	9	-	9 (100)
30%	9	2 (22)	7 (78)
40%	7	1 (14)	6 (86)
50%	4	1 (25)	3 (75)
60%	5	2 (40)	3 (60)
70% or more	4	1 (25)	3 (75)
Not evaluable	5	3 (60)	2 (40)

Figure 3. Concordance between NGS-detected CDKN2A loss and MTAP loss by IHC according to tumor cellularity (cutoff, 30%) among specimens with MTAP loss by IHC

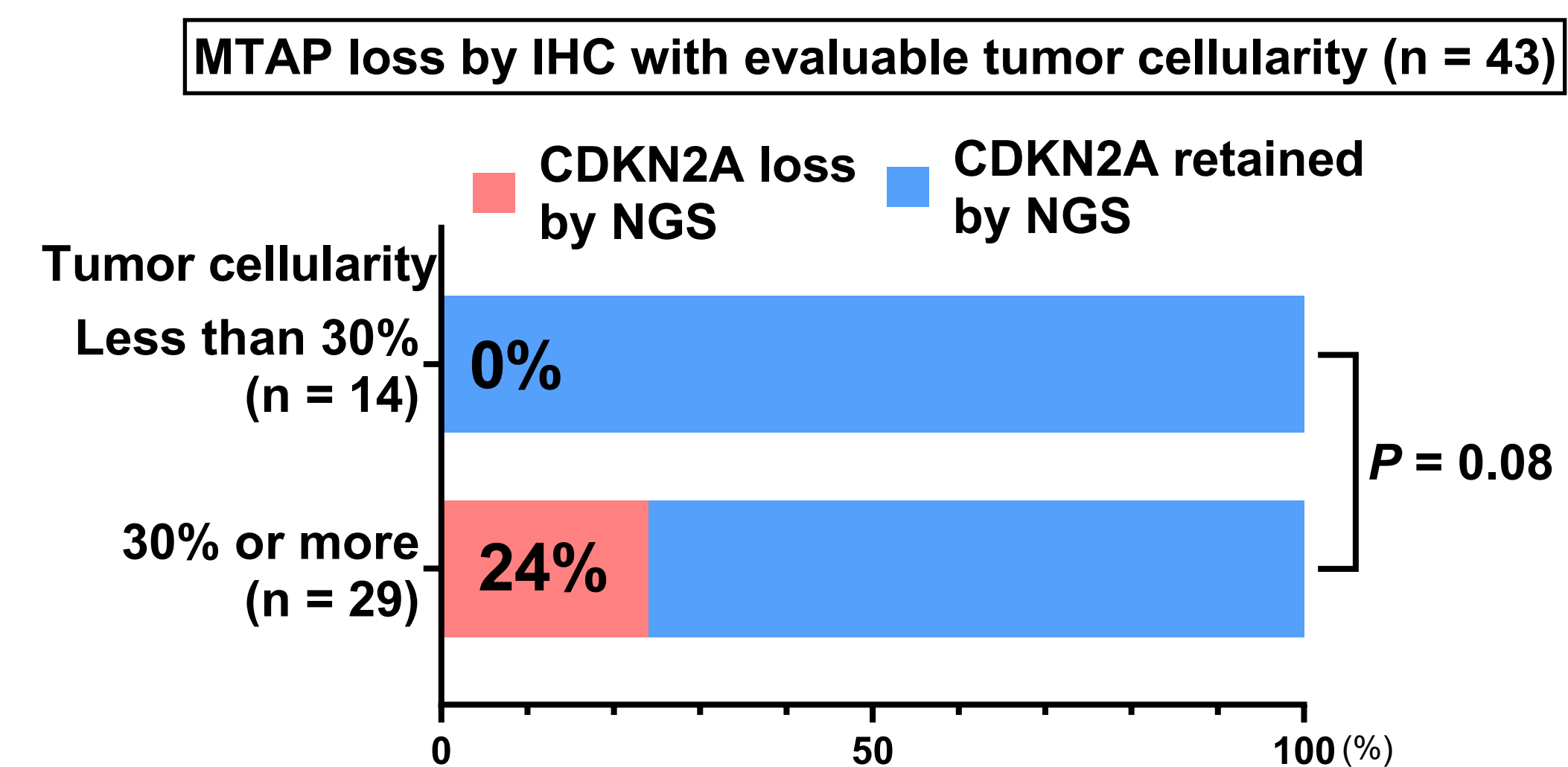
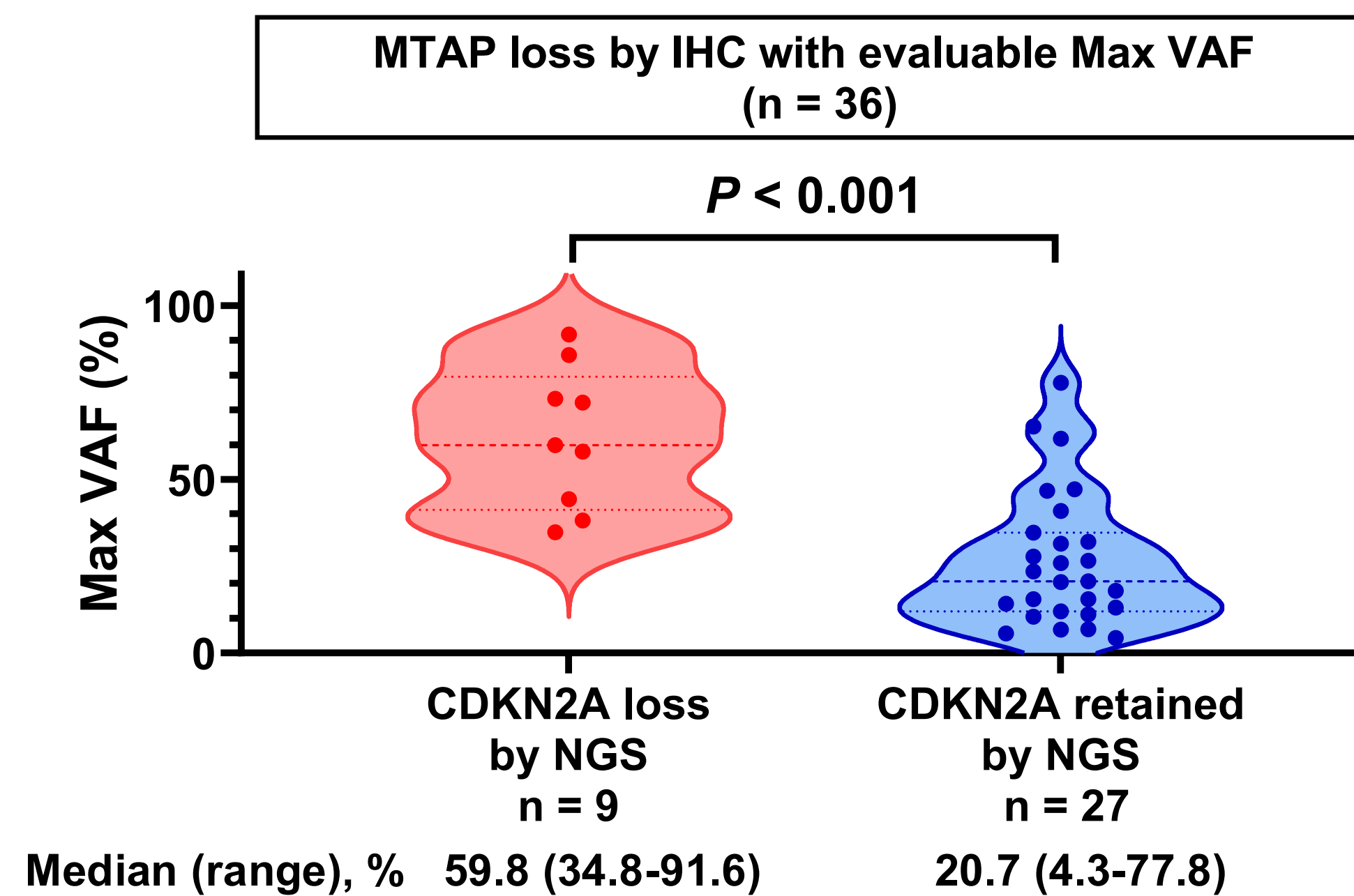


Figure 4. Association between Max VAF and CDKN2A status by NGS in samples with MTAP loss by IHC



Summary

- Among 166 specimens, MTAP IHC identified 48 specimens with MTAP loss (29%), whereas NGS identified 12 specimens with CDKN2A loss (7%).
- The positive percent agreement and positive predictive value of NGS-detected CDKN2A loss for MTAP loss by IHC were 21% and 83%, respectively.
- Among 12 specimens with MTAP loss by IHC but without CDKN2A loss detected by NGS, 11 (92%) showed MTAP loss by FISH.
- Among specimens with MTAP loss by IHC and tumor cellularity of less than 30%, no CDKN2A loss was detected by NGS.
- The Max VAF was significantly higher in specimens with concurrent MTAP and CDKN2A loss than in those with MTAP loss alone (median, 59.8% vs 20.7%; $P < 0.001$).

Conclusions

- CDKN2A loss was not detected by NGS in a substantial proportion of NSCLC specimens with MTAP loss, suggesting that CDKN2A loss have limited utility as a surrogate marker for MTAP loss.
- In specimens with low tumor cellularity, admixture with non-tumor cells may reduce the sensitivity of NGS for detecting CDKN2A loss, whereas IHC may be a more suitable method for identifying MTAP loss.

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