

ORIGINAL PAPER

PAN-TRK EXPRESSION IN MISMATCH REPAIR-DEFICIENT COLORECTAL ADENOCARCINOMA: PREVALENCE AND CLINICOPATHOLOGICAL CORRELATES IN A VIETNAMESE COHORT

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Deficient mismatch repair/high microsatellite instability (dMMR/MSI-H) colorectal cancer (CRC) represents a distinct molecular subgroup with therapeutic implications, particularly in the context of immunotherapy and emerging targeted treatments. *NTRK* rearrangements are enriched in dMMR colorectal adenocarcinoma compared to pMMR tumors, creating a critical opportunity for targeted therapy with TRK-inhibitors. Our study aimed to evaluate the frequency of pan-TRK expression in dMMR colorectal adenocarcinoma.

We conducted a retrospective cross-sectional study of 211 patients with histologically confirmed dMMR CRC who underwent surgical resection at two tertiary centers in Ho Chi Minh City between 2020 and 2024. Mismatch repair status was determined by immunohistochemistry (IHC) using MLH1, PMS2, MSH2, and MSH6 antibodies. Tissue microarrays were constructed, and pan-TRK expression was assessed using IHC (clone EPR17341).

Among the 211 analyzed cases, we identified 15 tumors (7.1%) with positive pan-TRK expression, including 12 cases that exhibited membranous staining, whereas 3 cases demonstrated cytoplasmic pattern. We did not observe nuclear staining in any tumor. Most of positive tumors (93%) exhibited a diffuse staining pattern. We observed a higher frequency of pan-TRK expression in tumors exhibiting specific clinicopathological features, including proximal colon location, mucinous histology, high-grade morphology, and lymphovascular invasion. Additionally, most positive cases exhibited concurrent MLH1/PMS2 loss. However, these associations did not reach statistical significance.

To our knowledge, this study represents the first comprehensive analysis of pan-TRK expression in Vietnamese patients with dMMR CRC. Our findings highlight its potential clinical relevance and provide a basis for future molecular studies, with possible implications for targeted therapeutic strategies.

Key words: pan-TRK, *NTRK*, colorectal cancer, microsatellite instability, deficient mismatch repair.

Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide. According to GLOBOCAN

2022, colorectal cancer ranks as the third most frequently diagnosed cancer in both sexes, accounting for approximately 9.6% of all new cancer cases, with nearly two million new diagnoses annually. It is also the second

leading cause of cancer-related mortality globally [1]. Although the incidence and mortality rates of CRC have declined in many developed countries, an increasing trend has been observed in several Asian regions. In Vietnam, CRC ranks fourth among the most common cancers and remains one of the five leading causes of cancer-related death [2]. Moreover, the burden of CRC in Vietnam is projected to double in both incidence and mortality over the next two decades [3].

The management of CRC requires a multimodal approach, with surgical resection remaining the cornerstone of treatment. Despite advances in systemic therapies, the prognosis of metastatic CRC remains poor, with a 5-year overall survival rate of less than 15%. Notably, more than 80% of CRC patients in Vietnam are diagnosed at advanced stages (stage III or IV) [4], underscoring the urgent need for more effective and personalized therapeutic strategies. Among patients with metastatic CRC, approximately 5–15% harbor deficient mismatch repair or high levels of microsatellite instability (dMMR/MSI-H). These tumors demonstrate limited benefit from chemotherapy but show increased sensitivity to immune checkpoint inhibitors [5, 6]. Consequently, universal testing for dMMR/MSI-H is recommended by the National Comprehensive Cancer Network guidelines for colon cancer (version 3.2024) [7]. Nevertheless, up to 30% of patients with dMMR/MSI-H metastatic CRC show primary resistance to immunotherapy [8–10]. This highlights the need for additional predictive biomarkers.

In advanced or metastatic CRC, comprehensive molecular profiling, including *RAS*, *BRAF*, *HER2* and *NTRK* alterations, is increasingly recommended to guide targeted therapies and enrollment [11]. *NTRK* fusions are rare oncogenic events in CRC, with an overall prevalence of approximately 0.2–1%, but are enriched in dMMR/MSI-H tumors with frequencies approaching 5% [12–15]. Microsatellite instability is commonly found in fusion-driven tumors in general, with reported rates of approximately 57%, and is more frequent in *NTRK*-rearranged tumors, ranging from 62% to 88% [14, 16, 17]. These findings support the rationale for prioritizing *NTRK* fusion screening in patients with dMMR/MSI-H CRC [18]. Importantly, metastatic CRCs harboring *NTRK* fusions have been reported to follow a more aggressive clinical course [16]. TRK inhibitors represent a promising therapy, particularly for patients refractory to immunotherapy. Recently, TRK inhibitors, such as larotrectinib and entrectinib, have demonstrated high response rates exceeding 75% across tumor types and have received Food and Drug Administration approval for tumor-agnostic indications [19]. Current international guidelines recommend a two-step testing strategy, in which pan-TRK immunohistochemistry (IHC) is used as an initial screening tool, followed by confirmatory next-generation sequencing (NGS) [20, 21].

Understanding TRK protein expression in dMMR/MSI-H CRC has crucial biological and clinical implication. However, data from Vietnam remain limited. This study aimed to determine the frequency of pan-TRK expression in dMMR colorectal adenocarcinoma and its association with clinicopathological features.

Material and methods

Tissue samples

We employed a retrospective cross-sectional design to evaluate pan-TRK in dMMR CRCs. Among 1,855 CRC patients who underwent colorectal resection at the Oncology Hospital, Ho Chi Minh City, and University Medical Center between 2020 and 2024 and were screened with MMR IHC, 211 cases with dMMR status meeting the inclusion criteria were selected. Histological confirmation of dMMR CRCs was established *via* IHC assessment using a four-antibody panel: anti-MLH1 (clone M1; Cat. No. 760-5091), anti-MSH2 (clone G219-1129; Cat. No. 760-5093), anti-MSH6 (clone SP93; Cat. No. 760-5092), and anti-PMS2 (clone A16-4; Cat. No. 760-5094). In accordance with CAP guidelines, dMMR was defined as the complete loss of nuclear expression in at least one of these four proteins in tumor cells, while internal controls (e.g., lymphocytes or stromal cells) remained positive (Figure Supplementary S1) [22, 23]. Exclusion criteria included patients with multiple primary malignancies or those who had received neoadjuvant chemotherapy and/or radiotherapy.

Tissue microarray construction

We constructed tissue microarrays (TMAs) using a manual TMA instrument, extracting duplicate 3 mm tissue cores from representative tumor areas of each formalin-fixed, paraffin-embedded block. Subsequent 4 µm hematoxylin-eosin stained sections were reviewed to verify histological adequacy and representativeness.

Immunohistochemical staining

Immunohistochemical staining was performed on TMA sections using a commercially available VENTANA pan-TRK antibody (clone EPR17341, Cat. No. 790-7026; Roche/Ventana, USA), a rabbit monoclonal primary antibody directed against the C-terminal region of TRK A, B and C proteins. Staining was carried out on the BenchMark ULTRA automated staining platform (Ventana Medical Systems) using the iVIEW DAB Detection Kit (Ventana Medical Systems). Cerebellar tissue was used as a positive control which showed weak to moderate pan-TRK staining intensity [24, 25]. Pan-TRK expression was independently evaluated by two pathologists, Quoc Thang Pham, Quoc Dat Ngo and classified according to staining localization and intensity. Pan-TRK positivity was defined

as any degree of specific staining (cytoplasmic, membranous, nuclear or mixed) in $\geq 1\%$ of tumor cells. The intensity was graded as weak (1+), moderate (2+), or strong (3+) relative to the intensity observed in control tissues [24, 25].

Statistical analysis

Statistical analyses were performed using Stata 17.0. Continuous variables were summarized as mean $\pm$ standard deviation or median (interquartile range), as appropriate, while categorical variables were presented as frequencies and percentages. Associations between pan-TRK expression and clinicopathological variables were analyzed using the χ^2 test or Fisher's exact test. A p -value < 0.05 was considered statistically significant.

RESULTS

Clinicopathological characteristics and the expression of pan-TRK of deficient mismatch repair colorectal cancers

The study cohort comprised 211 patients diagnosed with dMMR CRC. The mean age at diagnosis was 52.5 years (range, 17–92 years), with a slight male predominance of 61.1%. Regarding tumor location, we most frequently observed tumors in the right colon (52.5%), followed by the left colon (36.5%) and rectum (10.9%). In terms of gross morphology, we most commonly identified an exophytic growth pattern, accounting for 61.1% of tumors. Histologically, conventional adenocarcinoma remained the predominant subtype, representing 128 of 211 cases (60.7%). Other relatively common histological subtypes included mucinous adenocarcinoma and serrated adeno-

carcinoma (Supplementary Table SI). Less common variants comprised signet-ring cell adenocarcinoma (4.7%), medullary carcinoma (1.4%), adenoma-like carcinoma (1.4%), undifferentiated carcinoma (0.5%), and micropapillary carcinoma (0.5%). Overall, we identified high-grade morphology in 26.5% of tumors. Concurrent loss of MLH1 and PMS2 represented the most common mismatch repair deficiency pattern (49.3%), followed by concurrent loss of MSH2 and MSH6 (24.2%) (Supplementary Table SI).

We next investigated the expression of pan-TRK in dMMR CRC patients. We identified 15 cases of positive pan-TRK immunohistochemical expression, representing a prevalence of 7.1%. Analysis of the staining patterns revealed diverse subcellular localizations: concurrent membranous and cytoplasmic staining was the most frequent, observed in 12 (80%) cases with intensities ranging from weak to strong. Cytoplasmic pattern was noted in three cases (20%), with focal nuclear positivity. Notably, most of these positive cases (93%, $n = 15$) exhibited a diffuse staining pattern (Figure 1). This distribution is similar to that reported by Lasota *et al.* [26], in which membranous-cytoplasmic staining accounted for 11 of 15 cases, with the remaining cases showing cytoplasmic pattern (4 cases).

Correlation between pan-TRK expression and histopathological features of deficient mismatch repair colorectal cancer

We further analyzed the relationship between pan-TRK expression and various clinicopathological parameters to identify potential clinical predictors of *NTRK* alterations (Table I). Within our dMMR cohort, tumors located in the proximal colon demonstrated

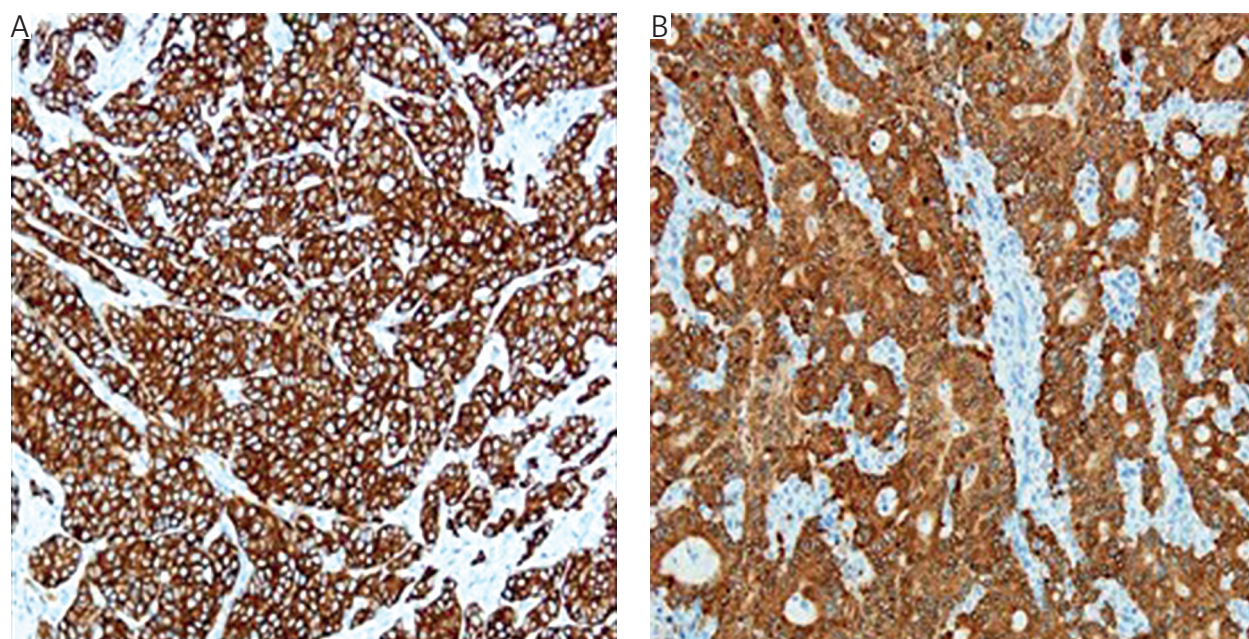


Figure 1. Pan-TRK-positive immunohistochemistry in deficient mismatch repair colorectal adenocarcinoma. A) Strong, diffuse membranous and cytoplasmic staining pattern. B) Strong cytoplasmic staining with focal nuclear staining

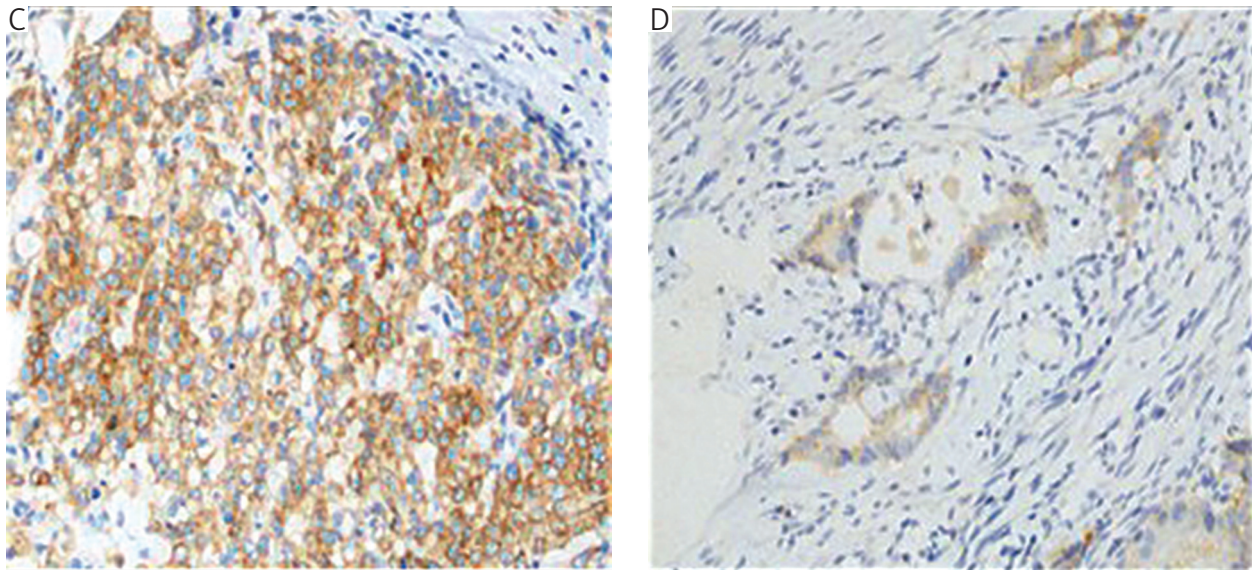


Figure 1. C, D) Membranous and cytoplasmic staining with moderate and weak intensity, respectively (200 $\times$ magnification, tissue microarray core)

Table I. Correlation between pan-TRK expression and clinicopathological features

CHARACTERISTICS (<i>N</i> = 211)	PAN-TRK EXPRESSION, <i>N</i> (%)		<i>P</i> -VALUE
	NEGATIVE	POSITIVE	
Age group [years]			
< 50	84 (95.5)	4 (4.5)	0.222
$\geq$ 50	112 (91.1)	11 (8.9)	(*)
Gender			
Male	119 (92.3)	10 (7.7)	0.649
Female	77 (93.9)	5 (6.1)	(*)
Tumor location			
Right colon	100 (90.1)	11 (9.9)	0.113
Left colon and rectum	96 (96)	4 (4)	(**)
Histologic subtype			
Conventional adenocarcinoma	119 (93)	9 (7)	0.805
Mucinous adenocarcinoma	38 (90.5)	4 (9.5)	(**)
Other	39 (95.1)	2 (4.9)	
Tumor grade			
Low grade	145 (93.5)	10 (6.5)	0.536
High grade	51 (91.7)	5 (8.9)	(*)
Tumor necrosis			
Present	54 (96.4)	2 (3.6)	0.363
Absent	142 (91.6)	13 (8.4)	(**)
TILs			
Low	85 (94.4)	5 (5.6)	0.449
High	111 (91.7)	10 (8.3)	(*)
pT			
T1–T2	18 (90)	2 (10)	0.640
T3–T4	178 (93.2)	13 (6.8)	(**)
pN			
N0	179 (92.7)	14 (7.3)	1.000
N1–N2	17 (95)	1 (5)	(**)

Table I. Cont.

CHARACTERISTICS (N = 211)	PAN-TRK EXPRESSION, N (%)		P-VALUE
	NEGATIVE	POSITIVE	
cM			
M0	193 (92.9)	15 (7.1)	1.000
M1	3 (100)	0 (0)	(**)
Staging			
I	17 (89.5)	2 (10.5)	0.631
II–IV	179 (93.2)	13 (6.8)	(**)
Lymphovascular invasion			
Present	37 (86)	6 (14)	0.088
Absent	159 (94.7)	9 (5.3)	(*)
dMMR			
Concurrent loss of MLH1/PMS2	96 (92.3)	8 (7.7)	
Concurrent loss of MSH2/MSH6	45 (88.2)	6 (11.8)	0.208
Isolated loss of PMS2	40 (100)	0 (0)	(**)
Isolated loss of MSH6	15 (93.7)	1 (6.3)	

** χ^2 test

* Fisher's exact test

a higher frequency of pan-TRK expression compared to those in the distal colon and rectum. Among the histologic subtypes, we observed that mucinous adenocarcinoma had the highest proportion of pan-TRK-positive tumors (9.5%). Notably, we found higher frequency of pan-TRK expression in tumors with aggressive pathological features, including high-grade morphology and lymphovascular invasion. Additionally, tumors with high levels of tumor-infiltrating lymphocytes (TILs) demonstrated a frequency one and a half times higher than the frequency of pan-TRK expression compared to those with low TILs. However, none of these associations reached statistical significance (Table I).

Furthermore, pan-TRK positivity tumors presented with specific MMR protein loss patterns. Tumors demonstrating pan-TRK positivity frequently exhibited combined MLH1 and PMS2 deficiency, accounting for over half of the cases ($p = 0.208$). In contrast, we found no statistically significant correlation between pan-TRK status and other variables, including gender ($p = 0.649$), pTNM staging ($p = 0.631$), and tumor necrosis ($p = 0.363$). These findings suggest that within the dMMR population, pan-TRK expression – and by extension, potential *NTRK* fusions – is preferentially enriched in right-sided CRC with MLH1/PMS2 deficiency. Collectively, these results indicate that while pan-TRK expression is uncommon in dMMR colorectal adenocarcinoma, its presence is selectively associated with distinct histopathological features.

DISCUSSION

In this study, we evaluated pan-TRK expression in a cohort of dMMR CRCs and demonstrated that

pan-TRK positivity was present in a small but distinct subset of tumors. Importantly, pan-TRK expression showed a non-random distribution and appeared to be enriched in tumors with clinicopathological features classically associated with mismatch repair deficiency, including right-sided location, mucinous differentiation, and some aggressive pathological characteristics.

The overall frequency of pan-TRK expression observed in this cohort was relatively low, which is in line with the established understanding that *NTRK* alterations are uncommon in colorectal adenocarcinoma. Previous studies reported that prevalence of pan-TRK expression in colorectal cancer has varied widely, ranging from approximately 2.7% to 6.2% [1, 25, 27]. The frequency identified in our study is comparable to that presented by Schraa *et al.* [25] and Zhang *et al.* [27], at 6.0% and 6.2%, respectively. However, Svrcek *et al.* [1] showed the frequency of pan-TRK expression rate of 2.0% based on IHC testing. In the same cohort, fluorescence *in situ* hybridization identified a higher proportion of *NTRK* alterations (5.3%). Furthermore, several cases that were negative by IHC were subsequently found to harbor specific *NTRK* rearrangements, such as *ETV6-NTRK3* which have been reported to exhibit low detectability by immunohistochemical screening.

Moreover, several studies employing NGS, which is widely regarded as the reference standard for detecting *NTRK* alterations, have reported prevalence rates of *NTRK* alterations in dMMR CRC ranging from approximately 5.2% to 7.0% [14, 27, 28]. Taken together, these findings are in keeping with a method-dependent detection spectrum, in which IHC serves as a practical screening approach, while fluorescence *in situ* hybridization and NGS are recommended as confirmatory

or reference methods for *NTRK* fusion detection. From a diagnostic pathology perspective, this concordance with NGS-based data lends further support to the interpretation of our immunohistochemical findings, while underscoring the need for cautious evaluation of negative results in selected clinicopathological contexts.

The reported subcellular localization of pan-TRK expression has shown considerable variability across studies. Although cytoplasmic staining is most commonly observed in tumors harboring *NTRK* rearrangements, the localization pattern may vary substantially depending on the fusion partner and its native cellular compartment [29]. In tumors with a low prevalence of *NTRK* fusions (such as lung, thyroid, and colorectal carcinomas), fusion partners are often diverse and lack tumor-specific predominance [14]. This molecular heterogeneity may, at least in part, account for the variability in pan-TRK staining patterns reported in colorectal carcinoma across different studies.

Pan-TRK expression was more frequently observed in right-sided tumors and in cases with mucinous differentiation. These features are well-recognized hallmarks of mismatch repair-deficient colorectal carcinoma. In the present study, right-sided colorectal tumors accounted for 11 of the 15 pan-TRK positive cases, representing 73.3% of all positive tumors. This finding is consistent with reports from multiple geographic regions, in which right-sided tumors similarly predominated, with proportions ranging from approximately 75% to 86.7% [1, 25, 27, 30].

The higher frequency of pan-TRK expression observed in right-sided CRCs may be related to the distinct molecular landscape of tumors arising in this anatomical location. Compared with left-sided tumors, right-sided CRCs are known to exhibit greater molecular heterogeneity and a broader spectrum of genetic alterations beyond common driver mutations such as *APC* and *TP53*. Notably, Hu *et al.* [31] reported that the number of private somatic mutations in right-sided CRC was approximately eightfold higher than that in left-sided tumors. In addition, higher rates of microsatellite instability contribute to an increased mutational burden and may facilitate chromosomal rearrangements. Epigenetic alterations, including increased levels of promoter hypermethylation, are also more frequently observed in right-sided tumors and may further disrupt regulatory pathways. Together, these molecular features may provide a permissive genetic and epigenetic background for the emergence of rare rearrangements, including *NTRK* fusions. Nevertheless, this association remains speculative and warrants validation in larger cohorts with integrated molecular analyses. Although the number of pan-TRK positive cases was limited, a higher proportion of expression was observed in tumors with high-grade morphology and lymphovascular invasion. This trend raises the possibility that TRK pathway activation may

be associated with more aggressive pathological behavior in a subset of mismatch repair-deficient colorectal carcinomas.

Among pan-TRK positive tumors, loss of MLH1 and PMS2 represented the most common mismatch repair deficiency pattern. This finding may suggest a closer association between pan-TRK expression and tumors arising through the MLH1-related pathway, which is frequently linked to distinct molecular alterations in colorectal carcinogenesis. Notably, however, the proportion of pan-TRK-positive tumors exhibiting MSH2/MSH6 loss in our study was higher than that reported by Svrcek *et al.* (40% vs. approximately 10%) [1]. Although MSH2/MSH6-deficient tumors have generally been considered less frequently associated with pan-TRK expression, this discrepancy may reflect differences in the distribution of mismatch repair deficiency patterns across populations. In particular, the proportion of MSH2/MSH6 loss has been reported to range from approximately 10.8% to 26.5%, with studies from Asian populations showing a tendency toward higher frequencies, potentially increasing the likelihood of detecting pan-TRK positivity in this subgroup [32–34]. Notably, no cases with isolated loss of PMS2 showed pan-TRK positivity, which is consistent with the findings of Svrcek *et al.* [1]; however, given the very small number of positive cases, further studies with larger sample sizes are needed to determine whether this observation is statistically significant.

Several limitations of this study should be acknowledged. First, molecular confirmation of *NTRK* rearrangements was not performed in this study; therefore, direct correlation between pan-TRK immunohistochemical expression and underlying genetic alterations could not be established. Second, the relatively small number of pan-TRK-positive cases limited the statistical power to detect significant associations. Third, mismatch repair deficiency was determined solely by IHC without parallel molecular MSI testing, and potential discordance cannot be excluded.

Conclusions

Pan-TRK expression identifies a small but distinct subset of dMMR CRCs with characteristic clinicopathological features. Our findings provide baseline data on pan-TRK expression in a Vietnamese dMMR cohort. These results highlight the potential value of pan-TRK IHC as a practical screening approach and may contribute to future molecular investigations and optimized diagnostic strategies for identifying *NTRK*-altered tumors.

Disclosures

1. Institutional review board statement: This study was approved by the Ethics Committee of the Univer-

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4. Conflicts of interest: None.

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