MSI TESTING
IHC STAINING VERSUS MOLECULAR PCR TESTING



idylla
by BIOCARTIS

THINK IDYLLA™
BECAUSE TIME MATTERS

IDYLLA™ CDx MSI TEST ENSURES OPTIMAL DIAGNOSTIC RESULTS

The standardized, fully automated Idylla™ CDx MSI Test overcomes the barriers of traditional PCR and IHC testing.

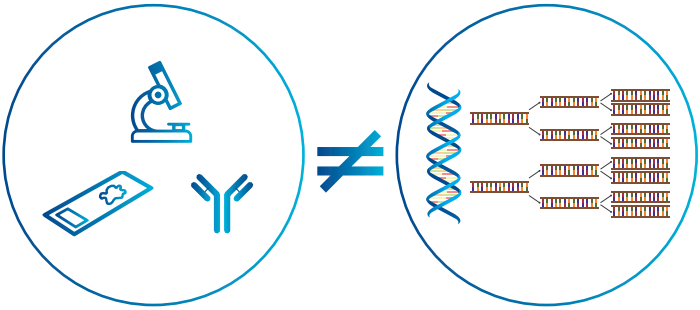
Features	IHC	Traditional PCR*	Idylla™ CDx MSI
Identification of defective protein	✓	-	-
Detection of genomic instability	-	✓	✓
Results within 2.5 hours	✓	-	✓
Limited hands-on time	-	-	✓
No batching needed	✓	-	✓
MSI testing in any laboratory setting	✓	-	✓
Standardized	-	-	✓
IVD from tissue to result	-	-	✓
IVDR-compliant (CDx)	✓	-	✓
Only 1 FFPE tissue section needed**	-	-	✓
No need for paired normal tissue sample	✓	-	✓
No need for external controls	-	-	✓
Fully automated sample-to-result	-	-	✓
Contamination control	-	-	✓
Objective result interpretation	-	-	✓

*PCR-based fragment-sizing test

**≥ 33% neoplastic cells and tissue area 25-300 mm^2 (10 µm)



IHC STAINING VERSUS MOLECULAR PCR TESTING



MMR by IHC

MSI by PCR

MSI testing by PCR and MMR assessment by IHC provide fundamentally different insights into tumor samples.

Immunohistochemistry (IHC) evaluates the presence or absence of mismatch repair (MMR) protein expression; however, detectable protein expression does not necessarily indicate intact MMR function. Approximately 5–10% of tumors with impaired MMR function retain MMR protein expression, potentially leading to false-negative dMMR results.

Microsatellite instability (MSI) testing by PCR detects DNA changes caused by defective mismatch repair. Unlike IHC, MSI provides a functional assessment of MMR activity, identifying deficiencies even when the proteins stain positive but are non-functional.[1]

MSI TESTING IS RECOMMENDED FOR VARIOUS APPLICATIONS

GUIDELINES ON MSI TESTING FOR LYNCH

In international guidelines **both MMR by IHC and/or MSI by PCR are recommended** methods for pre-screening.[2]

The **decision** about which screening method to be used depends primarily on the **availability of resources** and **expertise of the lab.**

ESMO RECOMMENDATION FOR CO-TESTING IN METASTATIC COLORECTAL CANCER FOR IMMUNOTHERAPY INDICATION

ESMO recommends combining both tests to assess the eligibility to treatment with immune checkpoint inhibitors of mCRC and other cancers of the lynch syndrome spectrum.[3,4]

IHC LACKS STANDARDIZATION WITH POTENTIAL IMPACT ON PERFORMANCE

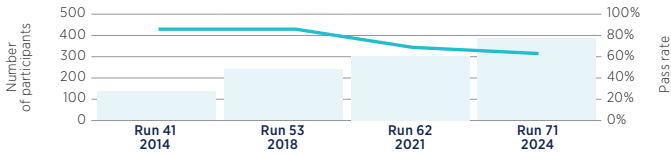
IHC REPORTING CHALLENGES

- Subjective interpretation[5,6]
- Molecular confirmation needed for equivocal cases
- No consensus on staining cut-off[7] criteria
- MMR gene mutations may result in impaired functional activity without absence of MMR protein staining[8]

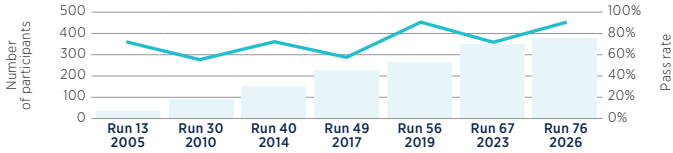
IHC WORKFLOW CHALLENGES

- Wide variability of antibody performance[9]

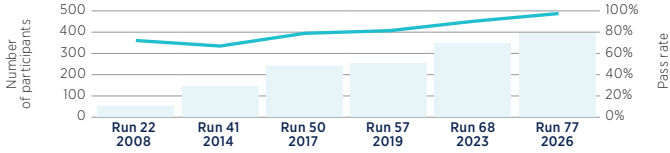
Proportion of sufficient results for PMS2 in the four NordiQC runs performed[10]



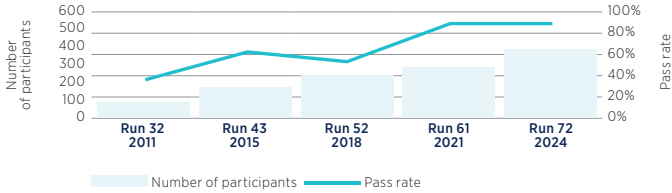
Proportion of sufficient results for MLH1 in the six NordiQC runs performed[11]



Proportion of sufficient results for MSH2 in the five NordiQC runs performed[12]



Proportion of sufficient results for MSH6 in the five NordiQC runs performed[13]



- The recommendation to use four MMR antibodies is not yet widely adopted
- Wide variation in protocol parameters (e.g., antibody dilution and incubation times)
- The use of less sensitive detection systems[12]

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(2) Stjepanovic, N. et al. (2019). Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of oncology: official journal of the European Society for Medical Oncology, 30*(10), 1558–1571. https://doi.org/10.1093/annonc/mdz233

(3) Luchini, C. (2019). ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. *Annals of oncology: official journal of the European Society for Medical Oncology, 30*(8), 1232–1243. https://doi.org/10.1093/annonc/mdz116

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(5) André, T. et al. (2024). Nivolumab plus Ipilimumab in Microsatellite-Instability-High Metastatic Colorectal Cancer. *The New England journal of medicine, 391*(21), 2014–2026. https://doi.org/10.1056/NEJMoa2402141

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(7) Li, X. et al. (2023). Heterogeneous expression of mismatch repair proteins and interpretation of immunohistochemical results in colorectal cancer and endometrial cancer. *Pathology, research and practice, 248*, 154647. https://doi.org/10.1016/j.prp.2023.154647

(8) McCarthy, A. J. et al. (2019). Heterogenous loss of mismatch repair (MMR) protein expression: a challenge for immunohistochemical interpretation and microsatellite instability (MSI) evaluation. *The journal of pathology. Clinical research, 5*(2), 115–129. https://doi.org/10.1002/cjp2.120

(9) NordiQC Assessment Run 52 2018 Mismatch Repair Protein MSH6: https://www.nordiqc.org/downloads/assessments/101_83.pdf

(10) NordicQC Assessment Run 71 2024 – Mismatch Repair Protein PMS2 (PMS2): https://www.nordiqc.org/downloads/assessments/188_84.pdf

(11) NordicQC Assessment Run 76 2026 – Mismatch Repair Protein MLH1 (MLH1): https://www.nordiqc.org/downloads/assessments/214_81.pdf

(12) NordicQC Assessment Run 77 2026 – Mismatch Repair Protein MSH2 (MSH2): https://www.nordiqc.org/downloads/assessments/217_82.pdf

(13) NordicQC Assessment Run 72 2024 – Mismatch Repair Protein MSH6 (MSH6): https://www.nordiqc.org/downloads/assessments/189_83.pdf

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