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Beyond CRC: AI-powered MSI Status Detection Across Gastric, Endometrial and Biliary Tract Cancers— Robust Validation Across 11 International Cohorts and Novel Cross-Indication Insights

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Background

- MSI-H/dMMR is a key biomarker for guiding immune checkpoint inhibitor therapy in solid tumors [1].
- Reflex testing is recommended for Gastric (GC), Endometrial (EC), and Biliary Tract Cancers (BTC) [2].
- The low prevalence of MSI-H (especially in BTC) means broad testing yields few positive results, leading to high resource utilization and underdiagnosis due to assay variability.
- We previously developed MSIntuit CRC for the pre-screening of MSI-H patients with colorectal cancer with a deep learning model directly on H&E whole slide images (WSI).

Objectives

Develop and validate three new AI models to accurately predict MSI-H status directly from standard H&E-stained slides in GC, EC, and BTC.

Establish a pre-screening workflow to safely rule-out negative patients, significantly reducing the need for costly and time-consuming molecular testing.

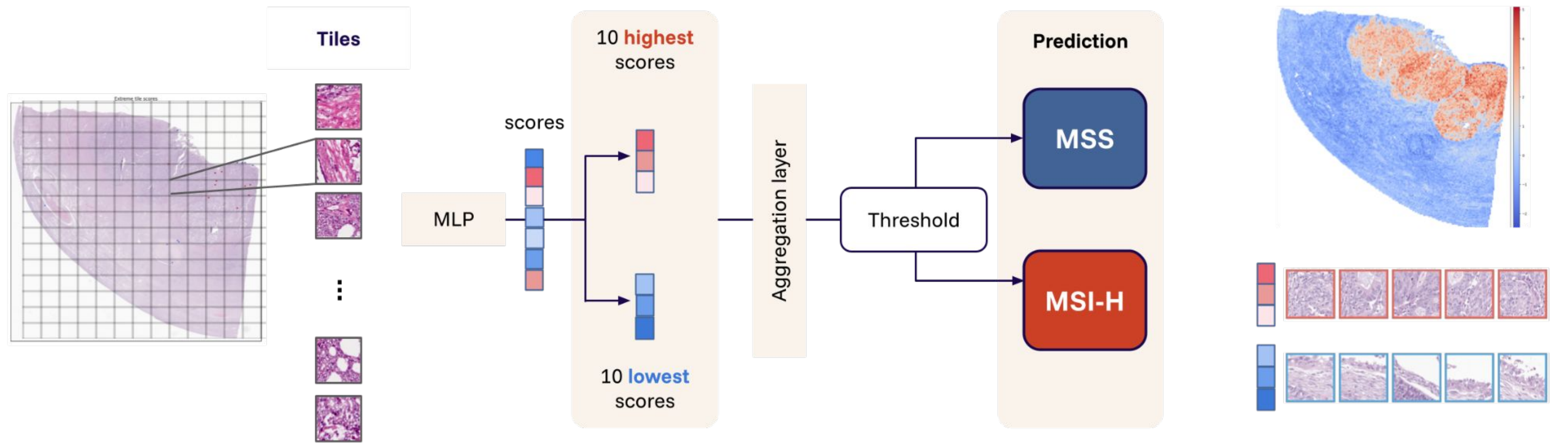
Data

GC	**Training** 2 centers N = 317	**Training** TCGA-STAD N = 373	**External validation** 2 centers N = 270
EC	**Training** 2 centers N = 239	**Training** TCGA-UCEC N = 478	**External validation** 2 centers N = 267
BTC	**Training** 2 centers N = 219		**External validation** 1 center N = 282

Method

- **Input**: Digitized H&E-stained whole slide images, with known MSI/MMR status.
- **Architecture**: Foundation models (H-optimus-0) combined with Multiple Instance Learning (MIL).
- **Preprocessing**: Automated tumor segmentation applied during training (for EC only) and at inference time (GC, EC, and BTC).
- **Evaluation Metrics**: Sensitivity, Specificity, NPV, PPV, and morphological pattern analysis.

Feature Extraction with Foundation Models → **Classification with Multiple Instance Learning model** → **Interpretability**



Model Overview. All three models rely on the same architecture: an H&E slide is tessellated in small tiles and encoded through a foundation model. A score is attributed to each encoded tiles, extreme scores are aggregated into a probability. Final prediction for the slide is obtained after thresholding of the probability. Scores attributed to each tiles can be later used to interpret predictive regions on the slide.

Results

Models were optimized to prioritize high sensitivity (comparable to standard testing methods).

Based on natural prevalence (p_{MSI}), a significant portion of patients can bypass further molecular testing:

- **MSIGC** 63% ruled out (p_{MSI} = 0.10)
- **MSIEC** 36% ruled out (p_{MSI} = 0.25)
- **MSIBTC** 71% ruled out (p_{MSI} = 0.04)

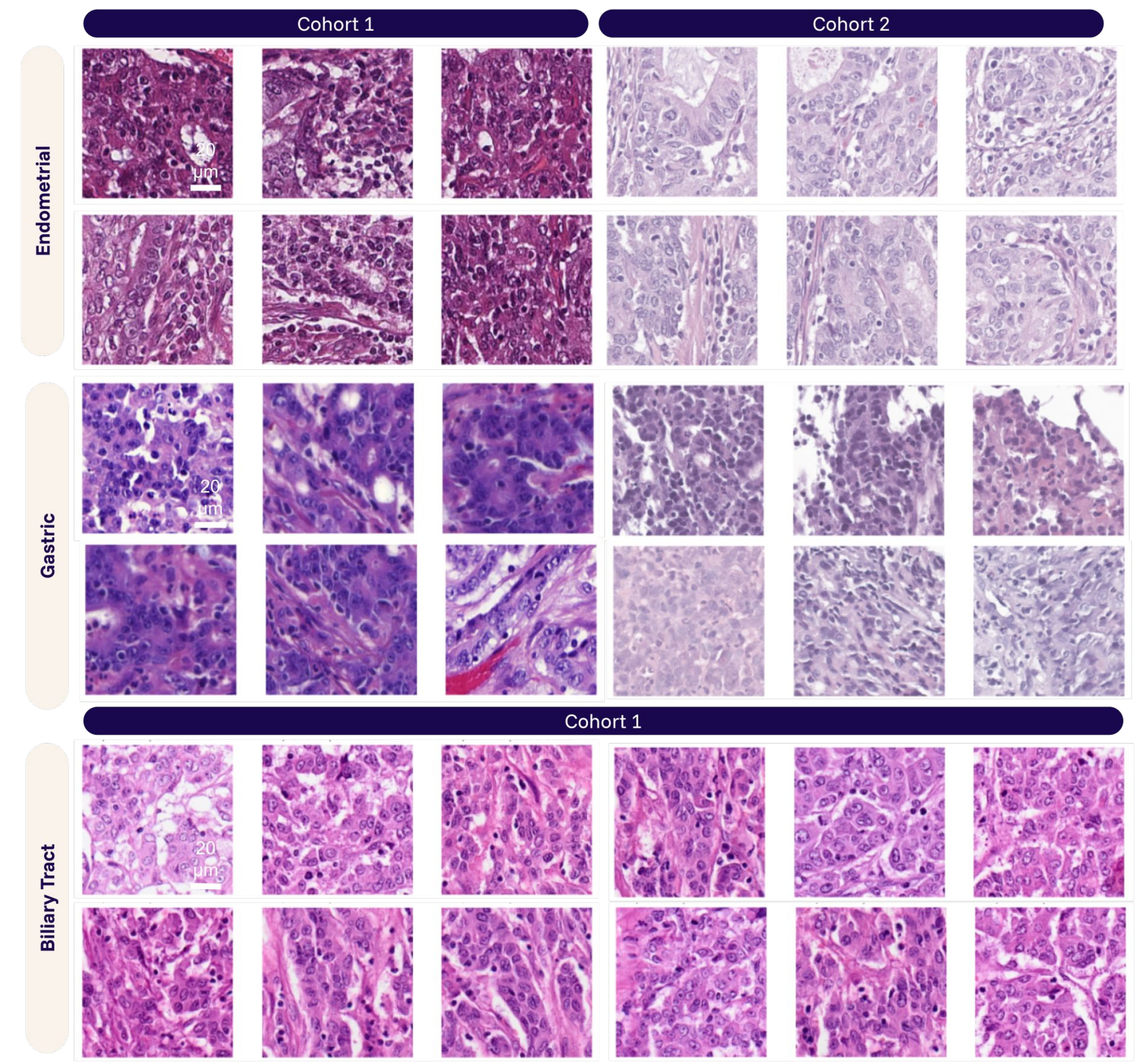
Model	n_{TOTAL}	n_{MSI} (%)	Sensitivity [95% CI]	Specificity [95% CI]	NPV [95% CI]	PPV [95% CI]
MSI GC model	270	66 (24%)	**0.92** [0.73 – 1.00]	**0.69** [0.50 – 0.84]	**0.99** [0.96 – 1.00]	**0.29** [0.20 – 0.4]
MSI EC model	267	85 (32%)	**0.90** [0.65 – 1.00]	**0.44** [0.23 – 0.76]	**0.95** [0.89 – 1.00]	**0.29** [0.24 – 0.42]
MSI BTC model	282	13 (4.6%)	**0.77** [0.61 – 0.96]	**0.73** [0.67 – 0.78]	**0.99** [0.96 – 1.00]	**0.10** [0.00 – 0.15]

Results

Shared Morphological Features for MSI-H

Cross-indication meta analysis

Abundant tumor-infiltrating lymphocytes (TILs) | Solid Tumor Growth | Mild to moderate pleomorphism



Cross-indication predictive regions. For each indication (EC, GC, BTC), tiles most predictive of MSI-H class across each external validation cohorts are represented. Common histological features are observed. Specifically, abundant tumor-infiltrating lymphocytes, merged tumor glands or solid tumor growth with mild to moderate pleomorphism are correlated with a MSI-H prediction.

Conclusions

- Robust external validation achieved on an unprecedented scale across independent, international cohorts for three distinct indications.
- Revealed shared, cross-indication histological patterns predictive of MSI-H, advancing our morphological understanding of the MSI-H tumor microenvironment.
- Across the different tumor types, 36% EC, 63% GC and 71% BTC cases could forgo standard MSI/MMR testing and allow a more targeted resource allocation.

References & acknowledgements

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