# A Novel Three-Stage AI-Assisted Approach for Accurate Differential Diagnosis and classification of NIFTP and Thyroid Neoplasms

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The recent introduction of the term non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) marked a pivotal shift in the classification of encapsulated follicular variants of papillary thyroid carcinoma (EFVPTC) lacking invasive features. While its reclassification from the "malignant" to "low-risk neoplasm" category significantly reduced overtreatment, its histopathological diagnosis remains challenging due to overlapping features with other thyroid lesions and inter-observer variability. Artificial intelligence (AI) overcomes such key limitations of histopathological evaluation, ensuring a robust and efficient diagnostic process. While preliminary studies are promising, AI models capable of efficiently distinguishing NIFTP from other benign and malignant thyroid entities are yet to be developed. We devised an innovative AI-based three-stage hierarchical pipeline that systematically evaluates architectural patterns and nuclear features. The prioritized models were trained using 154,498 patches, derived from 134 sections prepared from 125 thyroid nodules, representing follicular nodular disease (FND), follicular adenoma, dominant nodule in FND, invasive EFVPTC (IEFVPTC), and classic and infiltrative follicular subtypes of PTC. External validation revealed good accuracy at the overall, patient-wise, and classwise levels. However, it showed limitations in the differential diagnosis of NIFTP from IEFVPTC—an expected challenge due to overlapping nuclear features and the absence of incorporating the assessment of the tumor capsule for invasive characteristics. While the novel approach and the algorithm show promise in transforming histopathological NIFTP diagnostics, further improvements and rigorous validations are necessary before considering its application in real-world clinical settings.