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SKIE: An Automated Approach to Quantitation of Ki-67 Index from Human Gastrointestinal Neuroendocrine Tumor

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BACKGROUND: Ki-67 index is an established diagnostic factor in gastrointestinal neuroendocrine tumors (GI-NETs). Automated assessment of this index is challenging due to the difficulty in computationally distinguishing tumor from non-tumor regions in standard histopathological images. We propose an integrated approach, termed SKIE (Synaptophyin-Ki-67 index estimator), combining whole slide image (WSI) analysis with double immunohistochemical staining for Ki-67 and synaptophysin (stains tumor regions).

METHODS: SKIE detects the tumor regions, extracts five hot-spots based on the Ki-67 positive cell density within the tumor regions, and computes the average index. The index for 50 WSIs of human GI-NETs were compared with four pathologists' assessment based on Ki-67 staining alone and the gold standard obtained via exhaustive counting by a fifth pathologist based on double stained images. The performance of SKIE was also compared to the current most widely used automated immunostain quantification tool, ImmunoRatio.

RESULTS: Among 50 WSIs, all five pathologists unanimously graded 32, wherein, SKIE achieved 96.87% accuracy. The one discordant case was attributed to staining inconsistencies. The remaining 18 WSIs had discordant grades. Thus, the gold standard was chosen for comparison. 15 WSIs matched with the gold standard, one was assigned a lower, and two were assigned a higher grade by SKIE. Moreover, SKIE outperformed ImmunoRatio by ~3 fold. Also, SKIE displayed 0.80 ± 0.96% index error rate (significant linear weighted Cohen's

kappa, κ = 0.669, while being ~9K times faster in computing the index from a hot-spot. In contrast, the average index among the four pathologists had a moderate Cohen's kappa, κ = 0.47, which SKIE outperforms. SKIE-estimated hot-spots, when re-graded by the fifth pathologist resulted in the revision of five cases to higher grades than previously anticipated, demonstrating SKIE's better hot-spot selection capability and ability to improve clinical workflow.

CONCLUSION: The proposed method is faster, robust and more accurate than existing automated and manual methods.