

## Artificial Intelligence in cancer pathology—hope or hype?



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The Article by Kexin Ding and colleagues<sup>1</sup> uses artificial intelligence (AI) to infer somatic molecular changes (of both genome and proteome) from digital images of colorectal cancers. The authors made use of AI to initially segment (ie, separate out) tumour areas and then interrogate small areas (called tiles) within the tumour. The paper extends beyond other studies by interrogating the tiles and their spatial connections using a graph neural network (GNN). Since the tiles contain both cancer cells and non-malignant stromal cells (which comprises the tumour microenvironment), the GNN allows tumour heterogeneity to be analysed.

Using publicly available datasets, Ding and colleagues reached a similar level of accuracy to other studies that have used the same datasets but different algorithms.<sup>2-5</sup> The consistent results between differing studies affirms the notion that molecular data can be extracted from digital images. Analysis can start immediately on images becoming available, which is attractive as, theoretically, it will allow a workflow whereby histological and computational analyses are completed simultaneously. However, biomedical research history is replete with failed biomarker studies<sup>6</sup> and, although AI in cancer pathology is in its infancy, several obstacles are visible. Firstly, real-world data, in contrast to the curated images used in research, will contain a lot more noise. Tissues are fixed in formalin before sections are cut and variations in the fixation time can affect the molecular profile<sup>7</sup>—under-fixation might lead to tissue autolysis while over-fixation might alter the chemical properties of nucleic acids and proteins. In a large resection specimen, there will be variability in fixation; around five blocks of tumour are taken for colorectal cancers and currently there are no criteria for block selection nor data on how many blocks should be analysed. Most studies perform a pre-processing step on images to normalise the staining and exclude images that are out of focus.<sup>8</sup> However, technical artifacts can result in tissue folds, heterogeneity in stain uptake (even within small tissue fragments), or small patches within an image being out of focus.<sup>8</sup> In addition, where neoadjuvant therapy is being considered, decisions need to be made on biopsy specimens. These specimens might contain only small numbers of malignant cells—sufficient for diagnosis but possibly problematic for image analysis.

The most important consideration in the integration of AI into the clinical care pathway is accuracy. The highest AUC for gene mutation detection in the Article was 87.08 (95% CI 83.28–90.82). Although this result is excellent for research, clinicians might not deem this sufficiently accurate when deciding to administer or withhold chemotherapies. Even if algorithms become as accurate as genomic technologies (such as next-generation sequencing, NGS), it is unlikely that genomics will be replaced in the near future. Genomic technologies are becoming cheaper and quicker. Additionally, although AI algorithms can only inform on the biomarkers for which they have been trained, genomic technologies can provide pharmacogenomic data and inform on the generation of potentially targetable neoantigens. Although NGS can quantify mutations and inform on mutation-carrying tumour subclones, it is uncertain how AI algorithms will handle molecular heterogeneity where only a proportion of tumour tiles indicate actionable mutation. If both AI image analysis and genomic analysis are made use of for a tumour, a clinical (and potentially legal) quandary would arise if one form of analysis identified an actionable mutation and the other did not. In these cases, clinical decisions would probably be made on the genomic data.

What is the role of AI in cancer pathology if genomic data are considered superior (in the immediate future at least)? Computational image analysis can use pixel-level, object-level, and higher semantic-level data and can therefore extract huge amounts of information. The paucity of annotated images for use in training has hindered progress in AI algorithm development. However, weakly supervised algorithms<sup>2</sup> can obviate the need for annotation, although they require huge amounts of data. Diagnostic histopathology is undergoing digital transformation, which means that eventually every single tissue section will be scanned, and the resulting images used for primary diagnosis. Availability of data will therefore no longer be a limiting factor, which will enable AI algorithms to be developed for decision support in primary diagnosis (for both cancer and non-cancer diseases). Data availability will also allow digital algorithms to be trained on a variety of clinical features such as prognosis, cancer

For potentially targetable neoantigens see <https://clinicaltrials.gov/ct2/show/NCT04486378>

recurrence or metastasis, and responsiveness to therapy. In combination with genomic and other data, algorithms (such as those used by Ding and colleagues) could provide more precise information for patient management. The answer to the question in the title is, inevitably, that AI in cancer pathology has a lot of hope but we should be wary of the hype.

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