Park, J. H., Roxburgh, C. S.D., Edwards, J., Horgan, P. G. and McMillan, D. C. (2017) In reply to "Hynes S.O. et al. Back to the future: routine morphological assessment of the tumour microenvironment is prognostic in stage II/III colon cancer in a large population-based study". *Histopathology*, 71(2), pp. 326-327. (doi:10.1111/his.13195)

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Dear Editor,

In reply to "Hynes S.O. et al. Back to the future: routine morphological assessment of the tumour microenvironment is prognostic in stage II/III colon cancer in a large population-based study"

We read with interest the recent study by Hynes et al [1]. In this study of 445 patients undergoing surgical resection of stage II/III colon cancer, the presence of a conspicuous peritumoural inflammatory cell infiltrate, as measured by the Crohn's like reaction (CLR) and a modification of the Klintrup-Mäkinen grade (examining only the lymphoid cell population), was associated with improved prognosis. A high proportion of tumour-associated stroma, as measured by a 'global' assessment of the tumour stroma percentage (TSP) but not 'focal' assessment, was also associated with poorer survival. The CLR and global assessment of TSP demonstrated acceptable levels of inter- and intraobserver variability, whereas the peritumoural lymphoid infiltrate and focal TSP assessment did not. Identifying the complimentary prognostic value of both the inflammatory infiltrate and the TSP, the authors proposed a combined 'fibroinflammatory score', which stratified survival independent of stage, MSI status and chemotherapy use.

We however wish to raise a number of points for consideration. Acknowledging that it is the lymphoid population that holds most prognostic value within the inflammatory infiltrate, the proposed modification of the Klintrup-Mäkinen grade has not been validated as a reliable and reproducible measure. Although encompassing all inflammatory cell types, the original Klintrup-Mäkinen grade has been validated internationally as a reproducible, stage-independent characteristic in colorectal cancer [2, 3]. Therefore, it would be more readily

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applicable in routine clinical practice. Furthermore, given the high degree of interobserver variability of the modified Klintrup-Mäkinen grade, assessment of specific lymphoid populations may require immunohistochemical staining for immune cell subsets. The Immunoscore, reflective of $CD3^+$ and $CD8^+$ T-lymphocyte density, is one such example[4].

Hynes and colleagues employed semi-quantitative assessment of the CLR as described by Graham and Appelman, however it has recently been reported that more objective assessment of lymphoid follicle density or size increases not only reproducibility, but also prognostic value [5]. Similarly, although not associated with survival, it is of interest that the 'focal' assessment of TSP reflects a refinement of the previously described 'global' assessment, and again has previously been internationally validated in the context of retrospective analysis of clinical trial data [6, 7].

Finally, although the authors must be congratulated on further supporting the routine use of both the inflammatory infiltrate and stroma to inform prognosis of patients with colorectal cancer, the presently described 'fibroinflammatory score' is not the first tumour microenvironment score to consider combined assessment of both elements. Several groups have recognised the relative importance of both the inflammatory infiltrate and tumour-associated stroma; ranging from the Jass criteria described in 1986 [8], to the more recently described consensus molecular subtypes associated with distinctive tumour microenvironment phenotypes [9].

Recently, we have described a tumour microenvironment score based on combined assessment of the Klintrup-Mäkinen grade and TSP [10]. This score, termed the Glasgow Microenvironment Score (GMS), stratified survival independent of stage, mismatch repair status and chemotherapy use. The GMS also allows further insight into the evolution of the tumour microenvironment; a high TSP was rare and had no prognostic value in the presence of a high Klintrup-Mäkinen grade, only stratifying survival of those with a low density inflammatory infiltrate. These results were similarly observed when examining the combined prognostic value of the Immunoscore and TSP [11]. Taken together, we believe these results suggest that it is loss of the anti-tumour inflammatory infiltrate that promotes development of the tumour-associated stroma. Given the reliance of the GMS on validated, readily

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reproducible assessments, and its utilisation of routine pathological specimens, we would encourage the authors of the present study to adopt a similar approach to assessment of the tumour microenvironment in patients with colorectal cancer.

Yours sincerely,

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