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Immunoscore for (colorectal) cancer precision medicine

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Immunotherapies targeting immune checkpoints such as *CTLA4*, *PDCD1* (programmed cell death 1, PD-1), and *CD274* (*PDCD1* ligand 1, PD-L1) have revolutionised oncology.[1] High-level microsatellite instability (MSI-high) caused by mismatch repair deficiency is routinely used as a biomarker to predict response to immune checkpoint blockade.[2] In colorectal carcinoma, MSI-high status correlates with tumour neoantigen loads, which in turn correlate with immune response.[3] Combined analysis of tumoural and immune factors [e.g., so-called TIME (Tumour Immunity in the MicroEnvironment) classification] can be a new cancer classification system. However, immune response measurements have not been used as robust pathologic biomarkers in clinical practice. Along with the inherent complexity of the immune system, difficulty in reproducibly assessing immune cells remains a major cause of this gap.

In an ardent attempt to address the gap, the international immunoscore project [4] was initiated to standardise immune measurements, resulting in the study by Pagès et al.[5] in this week's issue of Lancet. Pagès et al.[5] assessed the reproducibility and prognostic role of the immunoscore assay that measured *CD3*$^+$-cell and *CD8*$^+$-cell densities in the tumour centre and invasive margin, using over 2,600 patients (51.5% male; a median age of 69 years, ranging 19-101) with stage I-III colon cancer across 13 countries. Standardised protocols for

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Use of standardised official symbols: We use Human Genome Organisation (HUGO)-approved official symbols (or root symbols) for genes and gene products, including CD3, CD8, CD274, CTLA4, and PDCD1; all of which are described at www.genenames.org. The official symbols are italicised, to differentiate from non-italicised colloquial names that are used along with the official symbols. This format enables readers to familiarise the official symbols for genes and gene products together with common colloquial names.

immunohistochemistry and digital image analysis generated highly reproducible results across institutions and operators (R > 0.96). The prognostication of the immunoscore was shown in both training and validation sets, and in time-to-recurrence (TTR, the primary endpoint), disease-free survival, and overall survival analyses. Using all cohorts, multivariable-adjusted hazard ratios (95% CI) in the TTR analysis were 0.65 (0.53-0.79) for intermediate (vs. low) immunoscores and 0.40 (0.30-0.54) for high (vs. low) immunoscores. Importantly, the immunoscore demonstrated a larger relative prognostic value than pT-stage, pN-stage, lymphovascular invasion, tumour differentiation, and MSI status. The prognostication by the tumour-node-metastasis (TNM) staging was improved with the addition of the immunoscore (TNM+I). Regarding a study limitation, approximately 10% of cases failed to satisfy specimen quality criteria, implying that immunoscore tests may not yield satisfactory results for some patients though recent evidence suggests a lower drop rate with the pre-defined standardised procedure.

The study by Pagès et al. [5] provides evidence for the immunoscore as a prognostic biomarker in colon cancer that can be standardised across pathology laboratories. The prognostic value of the immunoscore in colon cancer has been shown by an independent study.[6] So what is next? There remain outstanding issues to resolve. Whether the immunoscore can serve as an actionable predictive biomarker for response to therapy remains to be investigated. Costs, benefits, and feasibility in pathology laboratory workflow need to be examined before implementing the immunoscore as a pathology test. In addition, T cells encompass very heterogenous cell populations, and other immune cells such as NK cells, dendritic cells, and macrophages are also important in determining behaviour of cancer cells. Technological advances including single cell transcriptome analysis (RNA-sequencing), multiplex immunofluorescence assays, and in vivo pathology technologies will allow better characterisation of tumour-immune interactions. There is still much to learn about the tumour-immune interactions and clinical utility of various existing and emerging immune biomarkers.

Factors other than tumour and immune cells must also be considered. Accumulating evidence points to the role of exposures (the exposome) in modulating tumour-immune interactions.[7, 8] The microbiome is one such factor. Among all human organs, the colorectum has by far the most abundant amount of microorganisms. The gut and intratumor microbiota have been shown to affect responsiveness to chemotherapy and immunotherapy in gastrointestinal and other cancers.[9] Recent molecular pathological epidemiology (MPE) research has provided evidence for influences of fibre-rich diets on the microbiota and carcinogenic process,[10] and influences of omega-3 polyunsaturated fatty acids (PUFA) on tumour-immune interactions.[11] Robust immune cell assays such as the immunoscore test can drive advancements of integrative immunology-MPE research, which can provide novel evidence for immunomodulatory roles of nutritional, lifestyle, and pharmacological factors including omega-3 PUFA, vitamin D, physical activity, and aspirin.[8] Transdisciplinary science of immunology-MPE can also open opportunities to investigate the role of immune biomarkers in selecting patients for interventional use of an immunomodulatory factor.[8] Although lagging behind immunotherapeutic advances, the development of cancer immunopreventive strategies is on the horizon.[12, 13] Implementing immunomodulatory diets and lifestyle may be cost-effective cancer prevention strategies at the societal level.[8]

In summary, the study by Pagès et al.[5] represents a great step toward standardised immune response measurements for solid tumours. After clinical utility and cost effectiveness are proven, the immunoscore assay can be implemented in clinical settings. The advancement of robust immune assays will upgrade population-scale cancer immunology research. Integrative analyses of exogenous and endogenous factors (including the microbiome) and tumour-immune interactions will enable even more personalised characterisation of cancer toward precision medicine. Widespread use of high-quality tumour-immune interaction analyses will transform clinical and population studies worldwide, which can eventually contribute to global cancer prevention and control.

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Abbreviations

MPE	molecular pathological epidemiology

MSI	microsatellite instability
PD-1	programmed cell death 1
PUFA	polyunsaturated fatty acid
TIME	Tumor Immunity in the MicroEnvironment
TNM	tumour-node-metastasis