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Precision medicine in colorectal surgery: Coming to a hospital near you.

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In April 2003 the completion of the human genome project was a landmark event with subsequent explosion in the field of genomics. Despite the fanfare, sixteen years on genomics has failed to deliver the expected revolutions in cancer therapy, heralding a false dawn which has not materialised into clinical utility. In order to predict the next

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wave of technological advances The Royal College of Surgeons of England released 'The Future of Surgery' report. Areas identified to impact surgery over the next twenty years are minimally invasive techniques, imaging and virtual reality, specialised interventions and big data and genomics. Has genomics progressed the vision of precision medicine over the last two decades?

Precision medicine accounts for individual variability in genomic and environmental health-determinants, relying on prognostic and predictive information from individual patients and their tumours. Prognostic markers inform on the expected disease course in untreated individuals, while predictive markers pre-determine a patient's benefit from targeted therapy¹. Prognostic and predictive information can be gained from analysis of molecular abnormalities in colorectal cancer (CRC), which remains the second leading cause of cancer death in Australia, but current clinical utilisation of this information is limited. This is contrasted by the evolution of molecular classification systems in Melanoma. The Australian Melanoma genome project has categorised the mutational status of nearly 500 patients. Collaboration with The Cancer Genome Atlas Network has allowed these molecular subtypes to be classified into groups based on whether or not the mutations have clinically actionable alterations. This information is designed to guide patient therapy².

KRAS status is now routine for patients with metastatic CRC, determining whether Cetuximab³ will be effective as therapy. Further molecular advancements identified that MEK inhibition can rescue the response of KRAS mutant patients to EGFR therapy offering additional therapeutic options⁴. Success in models such as this led us to believe that identifying a mutation was equal to identifying a therapy target, however; this has not materialised. In rectal cancer a complete pathological response following neo-adjuvant chemoradiation therapy (NACRT) is a favourable prognostic sign with improved overall survival⁵. Genetic and molecular profiling of rectal tumours using microarray analysis has

identified gene profiles associated with poor response to NACRT⁶. Whilst initially promising, microarray analysis did not translate into the clinical field, and these profiles did not lead to treatment modifications.

An emerging alternative for obtaining molecular information involves blood analysis for circulating, cell-free tumour DNA (ctDNA). Utilising this method genetic abnormalities that underpin the emergence of clones resistant to therapy can be assessed over time⁷. As well as monitoring response, ctDNA is being pursued as a prognostic marker to identify those at risk for tumour recurrence in early-stage CRC⁸. The ability to pre-identify patients with early disease that will not be cured by surgery alone, has significant implications around eligibility for adjuvant therapy. It also assists in identifying patients with early disease that could benefit from neo-adjuvant therapy, which they would not otherwise receive. Post-operative detection of ctDNA can pre-empt radiological detection of recurrence and potentially act as a real-time marker of the impact of adjuvant therapy⁸.

Immunotherapy has been described as the fourth pillar of cancer therapy⁹, but its utilisation in CRC is limited to patients with a high mutational genomic load with microsatellite unstable tumours¹⁰. In this setting the profiling of tumour biopsies is now able to direct therapy, and underpinned FDA approval of pembrolizumab in this setting¹¹. A single biomarker alone is not sufficient to encapsulate the complexity of the tumour microenvironment and fails to address the mechanisms underlying resistance to therapy. Simple histopathology does not provide information about the spatial relationship of the immune cells within the tumours. Technology now exists that enables three-dimensional assessment of biopsies, acting as a surface plot to encapsulate intra-tumoural heterogeneity¹².

Genomics is starting to directly impact on patient care. Currently big-omics is driving targeted treatment toward multi-layered, multi-drug approaches¹³, with more than 2000 novel biomarkers and immun-oncology agents under assessment in numerous clinical trials around the world¹⁴. The mutational load of tumours may become an important component of classification, with molecular pathology becoming as essential as histopathology. Deeper exploration of the underlying genomic structure of tumours may actually develop the long desired specific prognostic and predictive markers of care, directly assisting surgeons in the complex decision-making processes involved around patient management and allow the delivery of truly personalised therapy. After a long wait with high expectations, the genomic revolution and personalised medicine may be coming.

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