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Il significato della medicina di precisione

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There are numerous challenges that need to be overcome to successfully implement precision medicine in cancer care. These include biological challenges such as tumour heterogeneity and genomic evolution, technical challenges such as limitations of molecular tests, pharmacological challenges such lack of effective drugs, and regulatory and reimbursement challenges. 1) Tumour heterogeneity. During tumour progression, subclones frequently arise resulting in differences in the proportion and pattern of specific aberrations between the primary tumour and metastases or tumour recurrences. Strikingly, metastases are not necessarily more complex than the primary tumour from which they originated, but can actually lose aberrations that are present in the primary lesion. 2) Genomic evolution and resistance. The array of clones with particular aberrations can change under both the selective pressure of a targeted therapy and as a result of the mutagenic activity of radiation and chemotherapy. There are two general conceptual approaches to deal with intratumoural heterogeneity and emergence of resistance: in-depth characterization of tumours and recurrence to identify rare and dominant clones, and low-depth sequential characterization of tumours to identify driver clones. Repeated biopsies at progression can assist in determining whether emergent aberrations could be treatable by specific means. As obtaining multiple biopsies is costly and associated with potential morbidity, surrogates such as molecular imaging or analysis of circulating tumour cells or circulating free DNA, are also being pursued in ongoing studies. 3) Undruggable targets. The role of in-depth molecular analysis is to identify molecular aberrations that can be targeted with existing therapeutic strategies. However, many proteins are currently 'undruggable', and loss-of-function mutations of tumour suppressor genes, such as TP53, are currently not actionable. However, our drug toolkit is rapidly evolving and emerging technologies that interrupt protein-protein and DNA-protein interactions, and approaches such as siRNA might achive the potentially render previously undruggable targets druggable. 4) Technical challenges. The identification and validation of markers of sensitivity and resistance is a key step necessary for the implementation of personalized cancer therapy. In early clinical trials generally carried out in heavily pretreated patients with advanced-stage or metastatic disease patients

occasionally demonstrate unexpected responses. In-depth characterization of these 'unusual responders' may help to identify important biomarkers of sensitivity, within personalized cancer therapy programmes. Comprehensive analysis of not only alterations in the genome but also the epigenome, transcriptome, proteome, and gene–gene, protein–protein and genome–environment interactions is likely to have important clinical implications in biomarker development. 5) Need for new trial designs. Novel clinical trial designs are being developed to identify and validate biomarkers and targeted therapeutics. Independent of the design, access to tissue molecular tumor characterization is a prerequisite for conducting such studies which often is a limiting factor for patient accrual. Biomarker discovery and validation must be integrated into all aspects of drug development, from discovery through to clinical trials. 6) Pharmacological challenges. Although multiple targeted therapies are currently entering clinical trials, it is not yet clear whether these agents have the appropriate specificity, pharmacology and pharmacodynamics to inhibit their therapeutic targets. There is a real risk of abandoning outstanding targets due to studies of therapeutic agents with poor or variable bioavailability, short half lifes or off-target toxicity delivered with inappropriate dosing. Indeed, with very few exceptions, it is not yet known what degree and duration of target inhibition is necessary to develop optimal outcomes. Patient selection, rational combination therapies, surrogate markers identification and tumor tissue banking have become key areas of research. Research efforts should be directed at generating the level of evidence required to make comprehensive testing reimbursable. Until that time, partnerships between academia and industry as well as significant philanthropic support is needed to facilitate comprehensive molecular characterization to demonstrate that it benefits patients.