Translational genomics in breast cancer

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The six biological characteristics acquired by cells during the multistep development of human cancers are well defined (sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis) and result from the accumulation of mutations [1]. To this "cell autonomous"-centric view of cancers the tumour microenvironment, modulated by the host genome, is increasingly recognised as much more than a bystander, since it contributes to the biological properties of the tumour [1]. Under this conceptual framework the complete characterisation of the germline and tumour genomes should provide us with all the information for better managing cancer patients [2]. Until this goal is reached much more research is needed to demonstrate that this will be clinically useful. To date most of this research in breast cancer (and other cancers) has used technology that falls short of providing a true whole genome view and has relied on microarrays for characterisation of tumour DNA/RNA, targeted mutational analysis, or tissue-based characterisation of proteins or nucleic acids [3,4]. Sequencing technology has progressed rapidly, allowing the characterisation at single nucleotide resolution of tumour DNA and RNA, with the first example in breast cancer showing enormous complexity and evolution between primary tumour and distant metastasis [5]. A large international effort is underway, characterising thousands of cancer genomes, including (eventually) around 2000 breast cancers, which will represent a gigantic step in understanding the extent of the complexity and how it will affect plans for its application in the clinical setting [6]. Even with continually improving sequencing technology and decreasing costs it will take years and large investment before we have evidence that the sequencing information (germline polymorphisms and somatic mutations) will result in knowledge that will then translate into improved screening, diagnosis, prognostication, prediction, targeted treatments and response monitoring. All the early evidence we have would suggest that this will be the case, and, for example, drugs and treatment strategies are increasingly being developed based on the molecular characterisation of tumours [7]. There is also increasing evidence that better classifiers and improved prognostication can be derived from combined analysis that profile both tumour DNA and RNA [8–10]. The validation of "first-generation" prognostic signatures, usually based exclusively on gene expression profiling, has proven particularly challenging [11]. It has been even more difficult to identify and validate predictors of response to non-targeted therapies (radiotherapy and chemotherapy), although analysis of large sample sets from clinical trials have already provided preliminary evidence of novel markers [12]. Neoadjuvant therapy trials hold great promise as the right framework to identify these predictive biomarkers for chemotherapy (and targeted therapies) response. ER and Her2 are predictors of a lack of benefit from targeted therapies (hormone therapy and anti-Her2-targeted agents) when the cancers do not express the markers (i.e. have excellent negative predictive value), but fail to identify tumours that despite expressing the biomarkers still fail to respond to the targeted therapies. Again there is early evidence that fully characterising the cancers will provide us with the mutations that underlie the mechanisms of resistance to these targeted therapies [13]. The next couple of years will see the reporting of results from several studies that will provide us with glimpses of where the field is going. These include a large study of array-based profiling of tumour DNA and RNA from an Anglo-Canadian consortium (METABRIC), the complete genomic characterisation of a few hundreds of breast cancers by groups in Europe, Canada and the USA, and the profiling of tumours in the context of neoadjuvant studies. In future all breast cancer clinical trials should include genomic profiling of patient samples, since this is the pre-requisite for determining the clinical utility of biomarkers and ultimately the strategy to improve patient management by delivering personalised cancer medicine.

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Conflict of interest statement

The author has no conflicts of interest associated with this article to declare.

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