European Journal of Cancer 82 (2017) 72–79

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Current Perspective

Universal Genomic Testing: The next step in oncological decision-making or a dead end street?

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Received 18 May 2017; accepted 18 May 2017
Available online 10 July 2017

KEYWORDS
Molecular tumour board;
Personalised medicine;
Personalised oncology;
Precision medicine;
Precision oncology;
Molecular targeted therapy;
Next-generation

Abstract The concept of 'personalised medicine' aims at allocating patients to different treatment options based on individual characteristics to optimise treatment benefit and side effects. In oncology, personalised treatments coupled to biomarkers have led to the approval of targeted agents with high anti-tumour activity. However, these therapies are often limited to narrow, molecularly defined subsets of patients with a specific morphomolecular tumour profile. Recently, it became obvious that the same molecular alteration might drive oncogenesis in many different tumours, and it might be beneficial to target the alteration in a histology informed but entity-overarching way. Consequently, Universal Genomic Testing (UGT) of tumours encompassing panel sequencing to whole-exome and transcriptome sequencing is propagated to revolutionise oncology. This article will describe the developments leading to

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http://dx.doi.org/10.1016/j.ejca.2017.05.034

sequencing;
Deep sequencing

identification and application of potential biomarkers using UGT. On this basis, it will review the clinical evidence of this approach and summarise recommendations for the ongoing evaluation of UGT as the next step in oncological decision-making.

1. Introduction

Tailoring treatment according to individual patient characteristics to maximise efficacy and avoid side effects is the major goal of personalised medicine. Regarding these characteristics, a wealth of evidence exists that individual molecular alterations drive cancers, which can be specifically targeted [1]. Some molecularly targeted agents (MTAs) yield unprecedented anti-tumour activity. Illustrative examples are imatinib against BCR-ABL gene rearranged chronic myelogenous leukaemia [2] or trastuzumab against HER2/NEU-overexpressing breast cancer [3]. However, approved personalised drugs are often limited to narrow, molecularly defined subsets of cancers [4].

As many molecular alterations exist across different tumour types [5], these cancers can be grouped on either genetic profile or histological appearance. Recently, this concept was tested via the inhibitory treatment of BRAF gene mutated tumours of different origins demonstrating clinical activity in some but not all tumour families in a basket trial [6]. This observation supported the concept of treating cancers with MTAs in a histology-informed but entity-overarching way if a targetable lesion is identified [4,7]. It became obvious that different cancers carrying the same molecular alteration might differ in their sensitivity to MTAs, necessitating an integration of morphological and molecular data before a potential treatment recommendation [6].

Today, due to technological advances and declining costs, large-scale parallel genomic or sub-genomic testing by next-generation sequencing constitutes the preferred approaches for comprehensive genetic analyses of tumours [8,9]. Both approaches to personalised oncology are often referred to as Universal Genomic Testing (UGT) [10]. Increasingly, the interdisciplinary discussions to match identified molecular alterations with potentially beneficial MTAs take place in emerging molecular tumour boards (MTBs). A subsequent treatment with a matched MTA can then be realised in a clinical trial or by off-label use.

UGT has created much hope to transform our current practice of cancer care into a world of personalised and 'precise' oncology, where insights into additional molecular targets and effective targeted therapies lead to major therapeutic achievements for cancer patients [7,9,10]. Here, we aim to describe the way to identify potential biomarkers using UGT and subsequently summarise the clinical evidence and potential pitfalls for UGT.

2. Identification of potential biomarkers

Fig. 1 illustrates the multi-step process of analysing and interpreting data generated by UGT. Efforts towards standardisation, validation and quality control in molecular cancer diagnostics should encompass not only individual steps but also the entire process [11,12].

The annotation and classification of sequence variants is challenging [13]. First, somatically acquired mutations must be differentiated from inherited germline polymorphisms. Analysis of matched 'normal' cells is the gold standard for somatic variant identification but increases costs and is not frequently used in targeted sequencing assays. Alternatively, putative somatic variants can be identified using databases of germline polymorphisms in healthy populations and of recurrent mutations in cancer (Table 1). These databases are valuable resources, yet they are not free from errors. In the end, such inaccuracies might lead to misinterpretation of the results.

In the second step, somatic variants are often classified into pathogenic driver mutations and functionally less significant passengers. Only a small minority of cancer-associated mutations has been studied functionally. The biological relevance of other variants can only be assessed indirectly based on factors including their predicted effects on protein structure and functional domains, the role of affected gene or through comparison with other, better-characterised mutations.

The final step is the assessment of therapeutic relevance or 'actionability' of variants deemed to be pathogenically relevant. The main promise of personalised cancer therapy is that genetic variants can serve as predictive biomarkers allowing selection of therapies with a high likelihood of success. However, only a limited number of biomarkers (e.g. HER2/NEU expression in breast cancer) have been shown to predict drug sensitivity or resistance in large, prospective randomised trials and are now included in drug labels. For other biomarkers, weaker evidence exists based on retrospective analyses or pre-clinical studies. When interpreting these data, uncertainty arises whether findings from one tumour type hold true in other cancers, or whether different mutations within the same gene have