

# Commentary

# Genomic advances and their impact on clinical trial design

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#### **Abstract**

Medical treatment for patients has historically been based on two primary elements: the expected outcome for the patient, and the ability of treatment to improve the expected outcome. The advance in genomic technologies has the potential to change this paradigm and add substantial value to current medical practice by providing an integrated approach to guide patient-specific treatment selection using the genetic make-up of the disease and the genotype of the patient. Specifically, genomic signatures can aid in patient stratification (risk assessment), treatment response identification (surrogate markers), and/or in differential diagnosis (identifying who is likely to respond to which drug(s)). Several critical issues, including scientific rationale, clinical trial design, marker assessment methods, cost and feasibility have to be carefully considered in the validation of biomarkers through clinical research before they can be routinely integrated into clinical practice. Here, we highlight the impact of genomic advances on various aspects of clinical trial design.

#### Introduction

Genomic signatures are being developed for various diseases to estimate disease-related patient trajectories (prognostic signatures) and to predict patient-specific outcome to different treatments (predictive tools) [1-14]. The ultimate clinical utility of a biomarker hinges on two fundamental questions: firstly, what is the added value of marker assessment in every patient in relation to the prevalence of the marker, specifically the incremental benefit of treatment selection based on the marker compared with the added costs and complexity induced by the measurement of such markers; and secondly, is the new treatment effective in all patients regardless of the marker status (the magnitude of benefit may differ within the marker-defined subgroups) or just in the markerdefined subgroup(s)? Critical components required for the validation of genomic biomarkers (either single markers or multi-marker signatures) include the choice of an appropriate clinical trial design, the choice of an adequate marker assessment method (immunohistochemistry, fluorescent in situ hybridization, real time PCR, highdimensional microarray- and proteomics-based classifiers, and so on), the reliability and reproducibility of the assay,

the logistics and feasibility of obtaining biospecimens, and the costs involved with assessing marker status. Here, we highlight the impact of genomic advances on various aspects of trial design.

## Marker validation strategies

Prognostic marker validation can be established using the marker and outcome data from a cohort of uniformly treated patients with adequate follow-up. The patients can be participants in a clinical trial, but a clinical trial is not necessarily required. Data from patients on the placebo arm or standard-of-care treatment arm of a trial (that is, the patients who are not given the drug being studied) can be used because a prognostic marker is associated with the disease or the patient and not with a specific therapy.

Designs for predictive marker validation are more complex and require, at a fundamental level, data from a randomized study. Such designs can be broadly classified into retrospective validation (using samples collected from a previously conducted randomized controlled trial (RCT)) and prospective validation (enrichment, all-comers, hybrid or adaptive analysis designs). Detailed discussions of these designs along with pertinent clinical examples have been published previously [15-23]. Data from an RCT and availability of specimens from a large number of patients are both essential for a sound retrospective validation, as otherwise it is impossible to isolate any causal effect of the marker on therapeutic efficacy from the multitude of other factors arising from a non-randomized design and/or selected samples [24,25]. An example of a well conducted, prospectively designed retrospective validation study that used previously collected samples is the colon cancer recurrence score based on a multi-gene real time PCR assay for predicting recurrence in stage II colon cancer [14].

# Using and incorporating genomic information in trial design

The strength of the preliminary evidence has a major role in the design of a prospective marker validation trial. One key issue is the hypothesized effectiveness of the new treatment: is it effective in all patients regardless of the

HER2, human epidermal growth factor receptor 2; RCT, randomized controlled trial.

marker status or only within certain marker-defined subgroups? For example, in the case of trastuzumab, an enrichment design strategy was used on the basis of strong preliminary data in which only human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients were eligible for two large randomized trials of trastuzumab in the adjuvant setting. These trials succeeded in identifying a subgroup of patients who received a significant benefit from trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide treatment [26]. However, subsequent analyses have raised the possibility of a beneficial effect of trastuzumab in a broader patient population than that defined in the two trials [27,28]. Therefore, unless there is compelling preliminary evidence that not all patients will benefit from the study treatment under consideration (such as there was for K-ras gene status in colorectal cancer [29,30]), it is prudent to include and collect specimens and follow-up from all patients (given that all patients are screened anyway) in the trial to allow future testing for other potential prognostic markers in this population, as well as for other marker assessment techniques. This paradigm of collecting specimens from all patients is currently being used in several large ongoing trials in lung cancer, colon cancer and breast cancer, where the primary aim is to validate a biomarker in either the entire population or only within a marker-defined subgroup [15,31-35].

Genomic advances not only continually influence the design of new trials, but also affect the (re)design of ongoing trials. Examples include (i) amending the design of ongoing clinical trials investigating panitumumab and cetuximab in colorectal cancer on the basis of the recent data that demonstrated that the benefit from these agents is restricted to patients with wild-type K-ras gene status [15], and (ii) informing the design of ongoing and planned trials for assessing the clinical efficacy of warfarin following the recently validated pharmacogeneticbased warfarin dosing algorithm [36]. Specifically, the ongoing US-based phase III trial testing cetuximab in addition to a combination of 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) as adjuvant therapy in stage III colon cancer (trial number No147) has now been amended to accrue only patients with K-ras wild-type tumors. The primary analysis will be conducted by looking for associations that are significant at the 0.05 level in the K-ras wild-type patients. Following a closed testing procedure, if this analysis is statistically significant at P = 0.05, the efficacy of the regimen in the entire population will also be tested at the 0.05 level, using the data from K-ras mutant tumors of approximately 800 patients who were previously enrolled on this trial before the amendment for including only the wild type K-ras patients.

# **Biomarker assessment**

Whether a local laboratory (an on-site laboratory where the patient is treated) or a central laboratory (where all testing is done in one central facility determined at the start of the study) is required for testing of a biomarker in a prospective clinical trial depends on many factors, with the intended ultimate clinical use of the biomarker and the assay methodology being the two key components. One example is the post-hoc central testing for *HER2* positivity in breast cancer, which showed a high degree of discordance with the local testing results [27,28]. This raises two important questions: (i) choice of using a central facility versus local laboratories for patient selection for therapeutic intervention trials, which in turn depends on the reliability and reproducibility of the assay and the complexity of the assay; and (ii) a potential need for a repeat assessment of the patient's marker status on a second sample, when feasible and ethically appropriate, if the first assessment deems the patient as having a 'normal' marker status and hence as ineligible for the trial in question.

#### **Conclusions**

In an era of individualized medicine, genomic signatures to capture the biological nature of the disease together with relevant patient-specific clinical and pathological information will be used to define the optimal therapeutic regimen for each patient. The clinical validation of biomarkers remains challenging given the multitude of marker assessment methods and the possibility that one drug can affect several molecular pathways. Two trials, I-SPY (investigation of serial studies to predict therapeutic response with imaging and molecular analysis) and BATTLE (biomarkerintegrated approaches of targeted therapy of lung cancer elimination trial), have attempted to address these issues by using diverse data types, in the case of I-SPY to identify biomarkers that predict the response to therapy, and in the case of BATTLE by randomizing patients to treatment choices on the basis of their multiple biomarker profiles [37-39].

The developmental pathway for genomic signatures and biomarker-directed therapies, from discovery to clinical practice, is complex. Two critical issues in the validation of genomic signatures are the choice of the clinical trial design according to the strength of the preliminary evidence, and questions surrounding the biomarker assays, such as the marker assessment methods, feasibility of obtaining the specimens, the reliability and reproducibility of the assay, and additional cost involved with assessing the marker status of every patient. Although genomic signatures theoretically provide an integrated approach to guide treatment selection and inform patient management, careful consideration of the issues outlined here are needed to determine the clinical utility of such biomarkers.

## **Competing interests**

DJS has received honoraria and/or consulting fees from Genomic Health, Exiqon, Precision Therapeutics, Genentech and Amgen.

#### **Authors' contributions**

SJM and DJS contributed to the conception, content and drafting of this commentary. Both authors have read and approved the final manuscript for publication.

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