Decision making in pharmacogenomic diagnosis: is there anything new under the sun?

'Selection or rejection of individual patients for specific treatments would revolutionize treatment outcomes'

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Diagnostic tests have long been an important component of drug discovery and drug use. Complex analytical measurements of new molecular entities are essential tools in the R&D process. These tests are most commonly used to assess drug metabolism, absorption and disposition – information that is applied in initial clinical studies to elucidate the pharmacokinetics for drug delivery and dosing.

The role of diagnostic devices in drug discovery and use

The concept of using diagnostic testing for drug selection is not new. Diagnostic testing has long been a cornerstone in the selection and dosing of antibiotic drugs. It also has an important role in determining optimal therapies in patients with breast cancer. Furthermore, diagnostic testing has often been of paramount importance in monitoring patients to determine the effectiveness of therapy or the presence of side effects, such as renal toxicity, hepatic toxicity and hematopoietic suppression.

Over the past ten years, growing knowledge in the area of pharmacogenomics has provided insight into the biology of disease and the likelihood of a pharmacological response to a drug [1–3]. Pharmacogenomics and the related discipline of proteomics enable unique measurements of the genetic constitutions and expression patterns of individuals, as well as dissecting and elucidating protein–protein interactions in disease process and drug response. The advent of microchip technology has led to the generation of huge, previously unattainable, sets of complex data on genetic constitution and expression. These data present unique challenges, requiring complex pattern analysis and new computational approaches, but also offer unique opportunities for decision making in both drug development on a generic level, and drug selection at the level of individual patient care decisions.

Issues with standardization

The scientific challenges in shaping this new technology have not dissuaded scientists, entrepreneurs and regulators from directing increased attention to this growing science. All are concerned with the tasks of ensuring that data are of high quality and are reproducible, of understanding the links between data and disease or drug response, and of addressing a complexity in signal that was previously unparalleled in diagnostic clinical medicine or pharmacological science. However, these tasks are plagued by the lack of standardization in this area, by the challenges of producing consistent data over time, and by the uncertainty in understanding signal reliability and the many possible biological and analytical interferences that can impede the use of microarray data.

In the field of drug development, the ability to define those populations that are most likely to benefit from, or be harmed by, a particular drug therapy is likely to revolutionize both scientific and business plans. 'Selection or rejection' of individual patients for specific treatments would revolutionize treatment outcomes, with positive impacts on health care quality and costs. The success of future studies in these areas will largely depend on the quality and success of the diagnostic tools used. It is, therefore, imperative that those developing studies to elicit pharmacogenomics diagnostic data ensure that the data mined is evaluated in a careful manner with clear study objectives.

1359-6446/03/$ – see front matter PII: S1359-6446(03)02715-6

For regulators, clinicians, researchers and patients, whatever the complexity of the information gathered from a new testing modality, the fundamental questions related to its use remain. These are best put in the simplest of terms: what is the purpose of testing and what is the ability of the test results to determine true versus false positive and negative response rates in an acceptable manner?

Diagnostic criteria

The questions at hand are not new and remain grounded in the decision-making constructs of Baysian statistics, first introduced into laboratory medicine by Galen and Gambino in 1976 [4]. The concept of diagnostic accuracy has been codified in well-defined laboratory standards [5] and is determined by the sensitivity and specificity of the new diagnostic tool in comparison with a 'gold standard' and by the prevalence of the condition in the test population.

Sensitivity is measured by the percentage of 'true positives' and specificity, by the percentage of 'true negatives'. The positive predictive value (PPV) of a test is the percentage of test positive patients; the negative predictive value (NPV) is the percentage of test negative patients. Although the sensitivity and specificity of a test are unaffected by the prevalence of disease, the PPV and NPV are dependent on prevalence; as prevalence increases, PPV will invariably rise and NPV will fall. Conversely, as prevalence decreases, NPV will rise and PPV will fall [4]. These expected changes in performance should be taken into account as new tests are introduced into drug development or clinical use.

Ensuring a standardized approach to data gathering has recently been strongly emphasized through the publication of a cautionary article arguing for a standardized approach toward the definition of accuracy for diagnostic tests via an initiative generated by the Standards for Reporting of Diagnostic Accuracy (STARD) steering committee [6].

Although developed in a different context than that of pharmacogenomic testing, the diagnostic criteria put forth by STARD can, with minor modifications, have full relevance to this new diagnostic area. Ultimately, without information on the sensitivity and specificity of a new testing procedure or the prevalence of the condition under investigation, and without estimates of the likely predictive values of positive and negative tests, pharmacogenomics information will not be of use to individual practising physicians.

The proactive path foward

The unnecessary costs would be too great if we do not proactively apply well-established methodologies to the evaluation of new diagnostic tools that have been developed over the past few years, and vested parties should be alert to this. As unique nuances of pharmacogenomic testing are encountered, we should not attempt to re-invent wheels that already provide the relevant information needed on new diagnostics. We should also not fail to ensure that, from the earliest inception of new clinical therapeutic studies, data are gathered properly to obtain clear answers about the efficacy of new diagnostics. Members of both the diagnostic and therapeutic regulatory groups at the Food and Drug Administration (http://www.fda.gov/) remain committed to working with companies early and continually in the development of new products, to ensure that the path to market is steady and sure.

References

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