[15:50 – 16:30]

Pharmacogenetics (PGx) – GlaxoSmithKline experience

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Introduction

PGx is a tool that can be used to identify genetic markers or patterns that may help predict how patients will respond to medicines. The results of this research could potentially help us to readily and accurately identify which patients are likely to respond well and/or to experience an Adverse Drug Reaction (ADR) following administration of a particular drug; in short, getting the right medicine to the right patient at the right dose.

As part of this effort, GSK is routinely collecting blood samples for potential DNA analysis in its Phase I, II and III drug development trials (with appropriate ethics committee review/ approval and informed consent). The intent is that these study-specific collections will facilitate timely access to samples for DNA analysis if a specific need / medicine response were to be identified. Thus, the overall goal is that PGx data will provide valuable information to help us make better decisions during the drug development process, and we expect this will have a positive impact on pipeline attrition, clinical trial design and conduct, and the efficiency of the entire research and development (R&D) process.

Applying PGx in Drug Development

Typically, during the development of a compound, responders and non-responders to a drug molecule are identified. "Responders" can be described as individuals that show a benefit from using a particular medicine, and "non-responders" as individuals who do not show benefit from the medicine. PGx can be used to help explain why some of these patients respond and others do not.

The goal of efficacy PGx is to differentiate these groups early in development and where appropriate to prospectively select responders for subsequent clinical trials, thereby only developing the medicine for the patient population that has the greatest probability of gaining health care benefit. With this strategy, prospective efficacy PGx may also offer the possibility of reducing the size and length of clinical trials and focusing valuable R&D resources.

Uncommon and serious ADRs often are difficult to detect during clinical development. Thus, it may be only that once a drug is on the market and the population using the drug increases, that less common serious ADRs become evident. However, even a low incidence of a serious ADR may quickly result in access to a medicine being limited or withdrawn. PGx may provide a post-marketing opportunity to identify prospectively those patients at risk of experiencing such ADRs so that the medicine can remain on the market and continue to benefit the majority of patients who can take it safely.

Efficacy and Safety Profiles

For PGx to be fully incorporated into regulatory decision making, a distinction needs to be made between the different roles that PGx can play. It should be stressed that there are very different implications depending on whether efficacy and/or safety is the focus and the impact of PGx on the risk:benefit ratio of the medicine. A diagnostic test for identifying those who are at higher risk of ADRs vs. determining and utilizing efficacy profiles (e.g. patient enrichment and stratification) may have different requirements and specifications to meet. For example, if a PGx marker set were being used to identify patients susceptible to a serious ADR, it would need to be highly sensitive. A PGx marker set used to predict efficacy in a non-life-threatening condition where the response rate is 30% in the general patient population might exhibit a lower sensitivity and still have considerable value. It should be noted that both sensitivity and specificity must be relatively high for a marker set to be clinically useful.

It also needs to be remembered that the safety profile of any medicine is assessed against its potential benefits. For example, it may be acceptable for an effective drug for an aggressive cancer to be associated with severe headaches, whereas that ADR may not be acceptable for a treatment for a more benign condition.

GSK applies PGx and genomics across the pipeline to help deliver new and existing medicines to the patient populations most likely to benefit and least likely to experience an ADR. In the presentation to be made, actual examples will be provided where PGx has been utilized in GSK.

Summary: PGx as an Evolutionary Process for its application and utilization

Pharmacogenetic science is still developing. As one might expect for an area undergoing evolution, many elements of the pharmacogenetic debate are based on a scientific rationale, and supported by preliminary evidence that the goal of improving some aspects of healthcare is achievable. However, much research has yet to be done. To this end, it is vital to recognize that the applications of pharmacogenetics to medicine will evolve over time rather than there being a rapid revolution in medicinal practice. Some aspects of pharmacogenetics will inevitably cause us to reassess our current predictions and models for research, drug development and clinical practice, whilst others will align with the current framework for healthcare delivery.

The scope of the application of pharmacogenetics will necessitate case-by-case basis evaluation i.e. there will be no single model for pharmacogenetics integration. It is clear though that PGx "success stories" will continue thereby moving towards fulfilling the promise for better, targeted medicines and healthcare outcomes as well as improved drug development.