**Genomics and Biomarker Research in Drug Development: Overrated, or a Revolution to Come?**

As our understanding of physiology and pathophysiology continues to evolve, the domains of pharmacological research and drug development are seeing parallel increases in the sophistication of their methodology. Such expanding knowledge is expected to form the foundation of many future medical advances, slated to propel us towards a veritable era of *personalized medicine* in which treatments are tailored to unique patient subgroups at a molecular and genetic level (1). Although the prospect of monumental advances in medical treatment may well be looming on the horizon, the current climate of genomic and biomarker research in drug development reveals a picture of mixed success. To truly usher in an era of personalized medicine, the utility and drawbacks of biomarker research must be understood, regulatory requirements must become consistent at national governing levels, and the information that is gained from such research must have a clinically meaningful impact to foster advances in treatment.

A *biomarker* has been defined broadly by the World Health Organization as “any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease” (2). The use of biomarkers in medical research is certainly not new, although with the more recent advent of human genome-wide association studies (GWAS) (3), novel biomarkers have found increasing use within the field of genomics and pharmacogenomics. A typical GWAS evaluates potential correlations between genetic variants, usually single nucleotide polymorphisms (SNPs), and certain phenotypic outcomes, such as the occurrence of disease or the response to a pharmacological agent (4,5). In the context of a GWAS, a SNP could be considered a genetic biomarker, although biomarkers can take many other forms, including serving as surrogate endpoints in clinical trials (6). The use of biomarkers, such as LDL cholesterol, as surrogate endpoints for more meaningful clinical outcomes, such as death from cardiovascular disease, is often a convenient and cost-effective alternative in research settings (6). However, biomarkers must be used cautiously as they can be misleading. For instance, using rhythm-control as a surrogate endpoint for decreased cardiovascular morbidity in arrhythmia patients, a select group of anti-arrhythmia agents was approved that was subsequently shown to increase mortality among certain patient subgroups (7). Moreover, the utility of genetic biomarkers such as SNPs may be called into question, as they are often associated with relatively small effect sizes for the phenotypic trait of interest (8,9). Despite their potential to make research more targeted and efficient, it must therefore be remembered that biomarkers are contributing but one piece to the ever-complicated puzzle of biological pathways.

Recognizing a progressive decline in new drug development, in 2004 the United States Food and Drug Administration (FDA) launched its “Critical Path Initiative”, a series of proposals to increase the development of novel pharmaceutical agents (10). Chief among those included the integration of biomarkers into pharmacological research (10). To encourage collaboration among government, academia, and industry, the FDA also introduced formal guidelines and a regulated approach to biomarker qualification for drug research (11,12). These initiatives have spurred the creation of a list of qualified biomarkers that may be used in various stages of drug development, including pre-clinical and clinical trials (13). As an example, the Predictive Safety Testing Consortium (PSTC) has submitted a series of early-stage nephrotoxicity biomarkers that can serve as alternatives to traditional later-stage markers, such as creatinine and glomerular filtration rate (GFR) (12). The European Medicines Agency (EMA) has adopted a similar formalized approach to biomarker qualification, although in Canada, there currently exists no formal process for biomarker recognition (14). For its part, Health Canada has published a guidance document in which it encourages the submission of biomarker information for the purposes of pharmacogenomics research and drug development (15), however, the actual qualification and recognition of such biomarkers has not been regulated as thoroughly as it has in other jurisdictions. What impact this may have on the scope of biomarker utilization in Canada remains to be seen, as the legal and regulatory requirements may have difficulty keeping pace with the technological advancements that are made in genomics and biomarker research.

The utility of biomarkers, particularly in the realm of drug development, ultimately depends upon to what extent they are able to influence meaningful clinical outcomes, including patient morbidity and mortality. At present, the use of biomarkers in pharmacogenomics research has been largely concentrated in the field of oncology (8). For example, there exist several large databases of cancer cell line information correlated with pharmacological profiles of various anti-neoplastic drugs, including the Cancer Cell Line Encyclopedia (CCLE) and the US National Cancer Institute (NCI-60) panel, among others (16). In certain cases, the use of pharmacogenomic biomarker information has undoubtedly lead to improved clinical outcomes, as with the FDA approval of trastuzumab (Herceptin) for HER2 receptor positive breast cancer patients, with accompanying guidelines that HER2 status must be established prior to treatment initiation (8). In many other cases, however, the clinical implications of published drug-biomarker interactions remain uncertain. The FDA maintains a list of drug-biomarker interactions that are currently included in official drug labels (17), although it has been reported that the majority of these interactions are of questionable significance as they are not supported with guidelines as to how they should be incorporated into clinical decision-making (8). Due to the uncertain clinical significance surrounding many genetic biomarkers, some researchers have proposed that a paradigm shift towards phenome-wide association studies (PheWAS) may be beneficial (4). Through PheWAS, starting from the standpoint of genetic variants and searching for all correlated phenotypic outcomes, a better appreciation of the pleiotropic effects of many previously discovered genetic biomarkers might be obtained. (4). It is foreseeable that such complementary approaches of GWAS and PheWAS could serve to make biomarkers more robust clinical tools, capable of contributing to better guidelines on how drug-biomarker interactions may be incorporated into patient care decisions.

With the establishment of large-scale research initiatives such as the *Precision Medicine Initiative* (PMI) from the National Institutes of Health (NIH), it is anticipated that PheWAS with sample sizes of one million or more participants may soon become a reality (18). When considering how genetic information from large pools of volunteers may be combined with the vast data sets contained within electronic medical records (EMRs), the exciting potential of PheWAS becomes apparent. For instance, utilizing such information as EMR billing codes and past medical history as markers for phenotypic traits, we may begin to appreciate the true pleiotropy of many genetic variants, which may be associated with diverse and unexpected phenotypic outcomes (19). As an example, early PheWAS studies found that genetic variants such as the HLA-B27 and CTLA4 genes were associated with numerous diverse autoimmune diseases, suggesting a potential common underlying biological pathway among seemingly distinct pathophysiological processes (18). As similarities among diverse disease entities are discovered, it is possible that the process of drug development may shift towards one of *drug repositioning* (19). Through this strategy, drugs that were originally developed to target one molecular pathway may find novel uses in other clinical situations as we begin to uncover the pleiotropic effects of many genetic biomarkers and the role they may play in multiple disease processes. As an example, cyclin-dependent kinase 4 (CDK4) inhibitors, originally marketed as anti-neoplastic drugs, have also been found to be beneficial treatment agents in rheumatoid arthritis, due to the shared molecular pathways that exist between the disease and certain forms of cancer (20). As PheWAS continues to expand, it is inevitable that many more such similarities will be elucidated, and the discovery of novel uses for existing drugs may perhaps become just as important as the development of completely new agents.

Looking back on the previous two decades of the twenty-first century, during which time human GWAS became feasible and the FDA launched its “Critical Path Initiative”, the question of whether genomic and biomarker research is living up to its potential may be posed. Are more revolutionary drug-biomarker interactions akin to the classic trastuzumab-HER2 receptor interaction waiting to be discovered, whether through new drug development or drug repositioning? Or is the genetic biomarker approach simply too simplistic, failing to capture the true reality of complex pathophysiological processes, to be clinically useful? To cast a definitive verdict may be premature. It must be remembered that genomic and biomarker research remains in its infancy, and new research paradigms such as PheWAS present intriguing possibilities for shedding light on the current shadows of our knowledge, offering promise that the revolution we have been awaiting is still to come.

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