

Genomics and biomarker research in drug development: Overrated, or a revolution to come?

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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 toward 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 might 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 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, in a study 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 might 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 these 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 might 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.¹² The European Medicines Agency (EMA) has adopted a similar formalized approach to biomarker qualification, but there currently exists no formal process in Canada 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 in Canada as in other jurisdictions. The impact that this might have on the scope of biomarker utilization in Canada remains to be seen, as the legal and regulatory requirements might 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 the extent to which 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 antineoplastic drugs, including the Cancer Cell Line Encyclopedia and the US National Cancer Institute (NCI-60) panel, among others.¹⁶ In certain cases, the use of pharmacogenomic biomarker information has undoubtedly led 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 on incorporation 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) might 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

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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 might be incorporated into patient care decisions.

With the establishment of large–scale research initiatives such as the Precision Medicine Initiative from the National Institutes of Health (NIH), it is anticipated that PheWAS with sample sizes of one million or more participants might soon become a reality.¹⁸ When considering how genetic information from large pools of volunteers might 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 might begin to appreciate the true pleiotropy of many genetic variants, which might be associated with diverse and unexpected phenotypic outcomes.¹⁹ As an example, early phenome–wide association 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 might shift toward one of drug repositioning.¹⁹ Through this strategy, drugs that were originally developed to target one molecular pathway might find novel uses in other clinical situations as we begin to uncover the pleiotropic effects of many genetic biomarkers and the roles they might play in multiple disease processes. As an example, cyclin–dependent kinase 4 (CDK4) inhibitors, originally marketed as antineoplastic drugs, have also been found to be beneficial treatment agents in rheumatoid arthritis due to the shared molecular pathways between the disease and certain forms of cancer.²⁰ As the realm of PheWAS continues to expand, it is inevitable that many more such similarities will be elucidated, and the discovery of novel uses for existing drugs might 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 genome–wide association studies became feasible and the FDA launched its “Critical Path Initiative”, one might pose the question of whether genomic and biomarker research is living up to its potential. 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 too simplistic, failing to capture the true reality of complex pathophysiological processes, to be clinically useful? To cast a definitive verdict might be premature. It must be remembered that genomic and biomarker research remains in its infancy, and new research paradigms such as phenome–wide association studies 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.

References

- Collins F. Has the revolution arrived? *Nature*. 2010 Apr 1;464(7289):674–675.
- World Health Organization. Biomarkers in risk assessment: validity and validation. 2001; *Environmental Health Criteria* 222.
- Visscher PM, Brown MA, McCarthy MI, Yang J. Five years of GWAS discovery. *Am J Hum Genet*. 2012 Jan 13;90(1):7–24.
- Roden DM. Phenome–wide association studies: a new method for functional genomics in humans. *J Physiol*. 2017 Feb 23;595(12):4109–4115.
- Daly AK. Genome–wide association studies in pharmacogenomics. *Nat Rev Genet*. 2010 Apr;11(4):241–246.
- Strimbu K, Tavel JA. What are biomarkers? *Curr Opin HIV AIDS*. 2010 Nov;5(6):463–466.
- Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med*. 1996 Oct 1;125(7):605–613.
- Tutton R. Pharmacogenomic biomarkers in drug labels: what do they tell us? *Pharmacogenomics*. 2014 Feb;15(3):297–304.
- Tremblay J, Hamet P. Role of genomics on the path to personalized medicine. *Metabolism*. 2013 Jan;62 Suppl 1:S2–5.
- Food and Drug Administration. Innovation or stagnation: challenge and opportunity on the critical path to new medical products [Internet]. 2004 March 16, 2004;1. Available from: <https://www.fda.gov/downloads/scienceresearch/specialtopics/criticalpathinitiative/criticalpathopportunitiesreports/ucm113411.pdf>
- Food and Drug Administration. Guidance for industry: pharmacogenomic data submissions [Internet]. 2005 March, 2005;1. Available from: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079849.pdf>
- Amur S, Frueh FW, Lesko IJ, Huang SM. Integration and use of biomarkers in drug development, regulation and clinical practice: a US regulatory perspective. *Biomark Med*. 2008 Jun;2(3):305–311.
- Food and Drug Administration. List of qualified biomarkers [Internet]. 2017; Available from: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm>.
- Canadian Association for Population Therapeutics Annual Conference. Regulatory perspective on biomarkers and surrogate endpoints; May 6, 2012; Toronto: Canadian Association for Population Therapeutics; 2012.
- Health Canada. Guidance document: submission of pharmacogenomic information [Internet]. 2008 August 13, 2008;1. Available from: <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/submission-pharmacogenomic-information.html>
- Reinhold WC, Varma S, Rajapakse VN, Luna A, Sousa FG, Kohn KW, et al. Using drug response data to identify molecular effectors, and molecular "omic" data to identify candidate drugs in cancer. *Hum Genet*. 2015 Jan;134(1):3–11.
- Food and Drug Administration. Table of pharmacogenic biomarkers in drug labeling [Internet]. 2016; Available from: <https://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>.
- Precision Medicine Initiative. 2017; Available from: <https://allofus.nih.gov/about>.
- Bush WS, Oetjens MT, Crawford DC. Unravelling the human genome–phenome relationship using phenome–wide association studies. *Nat Rev Genet*. 2016 Mar;17(3):129–145.
- Rastegar–Mojarad M, Ye Z, Kolesar JM, Hebbbring SJ, Lin SM. Opportunities for drug repositioning from phenome–wide association studies. *Nat Biotechnol*. 2015 Apr;33(4):342–345.