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Editorial

A Call for Pharmacogenovigilance and Rapid Falsification in the Age of Big Data: Why not First Road Test Your Biomarker?

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''*It Don't Mean a Thing If It Ain't Got That Swing*''
Duke Ellington (1931)

Smart Decision Tools for Drugs and Health Products

The conventional drug development paradigm can test new drug candidates only in a limited number of patients and healthy volunteers, typically in the order of a few thousand at most. While the common adverse drug reactions (ADRs) are discerned prior to clinical use, less common or rare ADRs and population-wide efficacy of new drugs are often delineated in greater granularity after regulatory approval in clinical practice. In some cases, serious ADRs may be discovered as long as 36 years after a drug receives regulatory approval (Ladewski et al., 2003). Surveillance of drug safety and efficacy after regulatory approval, pharmacovigilance, is therefore a centerpiece concept in clinical pharmacology and population health.

Since the 1970s, governments around the world have established institutions for regulatory science and pharmacovigilance, although they remain cursory in many parts of the developing world. Early signal detection and mechanistic evaluation of ADRs and drug efficacy, not to mention extrapolation of pharmacovigilance data from population-to-population (i.e., population bridging), are areas of active research in rational therapeutics and postgenomics medicine. Health technology assessment (HTA), for example, has led to development of smart decision tools and foresight methods that inform postmarketing surveillance, and are relevant for other health products such as vaccines and nutritional supplements as well.

Put in other words, pharmacovigilance aims to understand the epidemiology and mechanisms of vast heterogeneity in drug-related outcomes, be they ADRs or therapeutic outcomes, at an individual and population scale. *Pharmacogenomics*, another field of 21st century integrative biology, aims to explain the genomics basis individual differences in drug safety and efficacy.

The new term *pharmacogenovigilance*, coined first by Şardaş in 2010, is defined as ''pharmacovigilance activities informed and guided by accompanying pharmacogenomics analyses.'' (Şardaş, 2010). Because both pharmacovigilance and pharmacogenomics share the objective of explaining person-to-person and between-population heterogeneity in drug pharmacokinetics and pharmacodynamics, pharmacogenovigilance buttresses the current efforts for rational and mechanistically informed monitoring of drugs.

The integration of pharmacovigilance and pharmacogenomics activities under the rubric of the new field of pharmacogenovigilance offers much conceptual and practical advances, and are described in detail elsewhere (Şardaş, 2010). For our purposes in this editorial, we wish to emphasize, however, that pharmacogenovigilance by virtue of its incorporation of pharmacogenomics biomarkers, is more *mechanistic* in its approach to surveillance than traditional pharmacovigilance. Such mechanistic orientation enables

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more than basic academic insights. It permits, for example, extrapolation of early signals on drug-related events from one population to another when the worldwide distribution of pharmacogenomics biomarkers linked to a given drug safety or efficacy event is known. It also helps to understand the pharmacokinetic and pharmacodynamic performance of drugs in population extremes such as in poor and ultrarapid metabolizers, and thus brings about a population scale overview in the course of postmarketing surveillance (Warnich et al., 2011). The above is also of crucial importance to efficiently address the increasing demands for HTA in different populations.

Road Testing Biomarkers in Naturalistic Real-Life Contexts

The emergence of Big Data

As we have analyzed recently, the Big Data systems

> ''…gather data from seemingly unconnected sources, be they weather forecasts, stock market data, population migration patterns, biosensors, household good and foodstuff manufacturers, and social media. By combining large volumes of data across hitherto discontinuous silos, big data advocates hope to create knowledge that is otherwise impossible to decipher.'' (Dereli et al. 2014).

Hence, there is now further reason, with the arrival of Big Data research and development (R&D) in particular, to invest in pharmacogenovigilance as part of the biomarker development activities in the pursuit of personalized healthcare, be they with drugs, vaccines, or nutrition. The same is also true with the advent of next-generation sequencing (NGS) technologies and their applications in pharmacogenomics, which led to the identification of novel unique variants affecting pharmacogenes' function (Mizzi et al., 2014). Per definition provided by the U.S. National Institutes of Health expert working group, a biological marker (biomarker) is ''a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention'' (Biomarkers Working Group, 2001).

It is not uncommon that a biomarker discovered in the course of drug discovery or Phase 1 to 3 clinical trials, and one initially deemed to be informative to forecast drug pharmacokinetics and pharmacodynamics, performs poorly or less informatively afterwards when it hits the clinic and public health practice in real-life contexts where a greater range of environmental factors might lessen the overall informational value provided by a biomarker of interest.

The issue of false positives in biomarker development deserves even greater consideration in the current age of Big Data that brings an even larger volume of biomarker claims. The traditional Phase 1 to Phase 4 biomarker developmental axis is in need of strategies for ''*rapid falsification,*'' (i.e., rapid removal of biomarker candidates from further development that are unlikely to survive the complexity of real-life settings in clinical use or public health practice). Evaluating the biomarker candidates under conditions where environmental contributions are maximized (e.g., in public health or hospital practice) to reflect the real-life contexts, combined with the so-called ''early cycle HTA'' (IJzerman and Steuten, 2011; Steuten and Ramsey, 2014), might be one way forward before investing fully in an otherwise promising biomarker candidate.

There are a number of drug development contexts that will lend well to testing biomarkers in the course of pharmacogenovigilance activities under the above ''road testing'' vision. One such case is generic drugs in current clinical use without companion biomarkers where new basic discovery research suggests novel pharmacogenomics biomarkers. Road testing biomarkers in a real-life setting with the principles of pharmacogenovigilance would then offer insights on how well the biomarker performs in situations where genomic components might be reduced due to greater environmental contributions. In the event a pharmacogenomics biomarker retains its informational predictive value under such strenuous real-life conditions, that could very well represent a worthy biomarker candidate for triaging and further R&D investment. While Big Data continues to provide an incoming flux of biomarker claims, pharmacogenovigilance might indeed be one new strategy to best harness Big Data and rational decision-making for biomarker selections in drug development and personalized medicine R&D.

Concluding Remarks

Drug and health product surveillance is in need of anticipatory systems that can detect early signals of safety and efficacy as new drugs and health interventions transition from a limited clinical trial sample to population scale applications. Additionally, Big Data R&D combined with HTA are offering enormous promises, as well as challenges for not only how best to sort out the biomarkers that will perform exceptionally well in real-life complexity and in the presence of environmental contributions (Özdemir et al., 2014), but also with the identification of novel functional variants leading to rare drug outcomes (Kampourakis et al., 2014). Old linear models of biomarker development are unlikely to weed out the biomarkers that will fail in the clinic until it is too late. Pharmacogenovigilance combined with Big Data and electronic health records offer new ways to rethink biomarker development strategies and biomarker triaging so that only the biomarkers that survive testing in real-life contexts are further invested in. Looking further, pharmacogenovigilance might catalyze the emergence of allied decision tools in other omics fields such as *nutrigenovigilance*, *vaccigenovigilance*, and so on. The reader is referred to the *Journal's* special issue on vaccinomics published in September 2011 (http://online.liebertpub.com/toc/omi/15/9).

Rapid falsification for biomarker triaging in the era of Big Data driven R&D might as well emerge as a veritable trend and practice. Pharmacogenovigilance is also here to stay with us as with Big Data. We would not be surprised if they prove to be excellent companions, both conceptually and in practice.

Duke Ellington (1899–1974), the legendary American composer and jazz orchestra bandleader, wrote the ''It Don't Mean a Thing (If It Ain't Got That Swing)'' in 1931 during intermissions at Chicago's Lincoln Tavern. Perhaps if Ellington were with us today in the era of Big Data, he might have agreed. A road test for system level real-life biomarker relevance is a valuable decision tool for 21st century integrative biology and related fields of scholarship such as personalized medicine (Kalow et al., 1999; Özdemir and Lerer, 2005). A biomarker has ''the swing'' if passes the hard test of pharmacogenovigilance and rapid falsification.

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