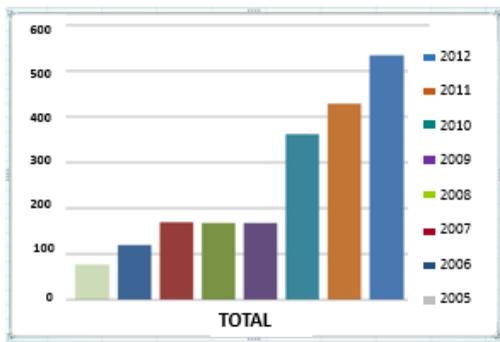


## Pharmacogenovigilance: Roadmap your biomarkers

One of the main aims of **Pharmacovigilance** (PV) is basically to understand the epidemiology and mechanisms of vast heterogeneity in drug-related outcomes, both Adverse Drug Reactions and therapeutic outcomes, at an individual and population scale. Meanwhile, another field of the 21st century integrative biology, **Pharmacogenomics (PGx)**, aims to explain **how variability of gene expression at an individual level leads to differences** regarding **susceptibility to disease, as well as**, drug safety and efficacy. PGx, also, aims to optimise the use of medicines, by targeting medicines to patient's individual genes. This is known as '**Personalised Medicine**'. The potential of PGx has been recognized by many pharmaceutical companies that are now integrating PGx into their development strategies for medicines. Evidently, the number of PGx requests in recent years is increasing.

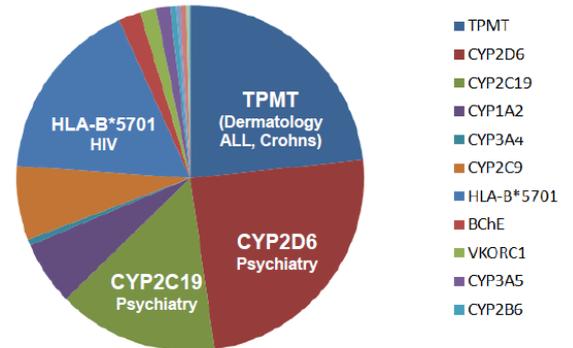


**Figure 1: Pharmacogenomics testing from 2005-2012**

(Adapted from EMA, Ron van Schaik presentation, 08-09 Oct. 2012)

Due to the fact that both PV and PGx share the objective of explaining person-to-person and between-population heterogeneity in drug pharmacokinetics and pharmacodynamics, the advantages of the integration of these activities was realized and implemented under the rubric of the new field of **Pharmacogenovigilance**. Pharmacogenovigilance, defined as PV activities informed and guided by accompanying PGx analyses, buttresses the current efforts for rational and mechanistically-informed drug design and monitoring and offers much conceptual and practical advances. To begin with, tailor-made therapeutics and cost-effective disease management will only become possible when inter-individual variability is addressed. By 2012, the therapeutic areas with the greatest number of Pharmacogenovigilance requests are shown in the diagram below:

PGx requests 2012 (n=536)



**Figure 2: Pharmacogenomics requests in 2012 for genetic variants of specific genes. The corresponding therapeutic areas are, also, indicated**

(Adapted from EMA, Ron van Schaik presentation, 08-09 Oct. 2012)

Pharmacogenovigilance is expected to affect all aspects of a drug's life cycle: clinical trial development, authorization-related (regulatory) aspects and post-marketing surveillance/development.

### Big Data pool and Pharmacogenovigilance

Pharmacogenovigilance combined with Big Data and electronic health records offers new ways to rethink biomarker development strategies and biomarker triaging for drugs, vaccines etc., so that only the biomarkers that survive testing in real-life contexts, under conditions where environmental contributions are maximized (e.g., in public health or hospital practice), are further invested in for personalized healthcare. It is not uncommon that a biomarker discovered in the course of drug discovery or Phase I to III clinical trials, and one initially deemed to be informative to forecast drug pharmacokinetics and pharmacodynamics, performs poorly or less informatively afterwards, when it becomes available in clinical 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 cost-effectiveness of such rapid falsification strategies for the removal of biomarker candidates that are unlikely to survive the complexity of real-life settings from further development is obvious for pharmaceutical companies. The prerequisite is the availability of DNA testing sequencing technologies that will allow the identification of novel unique variants affecting pharmacogenes function.

## Post-marketing surveillance impact

Regarding post-marketing surveillance, Pharmacogenovigilance, by virtue of its incorporation of PGx biomarkers, is more mechanistic in its approach than traditional PV. It permits, for example, extrapolation of early signals on drug-related events from one population to another, assuming that the worldwide distribution of PGx 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 can, thus, address dosing regimes, lack of drug efficacy and medication adherence (continuation/discontinuation) from a population scale overview. Such information, if available, would contribute to medicinal products' reference safety information (e.g. SmPC), as well as, in Periodic Safety Update Reports and Risk Management Plans. In fact, the Department of Genetics at Stanford University maintains a **PGx knowledge resource** called PharmaGKB, which includes clinical information, such as dosing guidelines, published information on medicines, associations between genes and medicines and relationships between genotypes and phenotypes. Part of this resource lists the European Union (EU)-authorised medicines approved by the EMA that contain **pharmacogenetic information** in their SmPC. The clinical implementation of Pharmacogenovigilance over a 7-year period (up to 2012) has revealed genetic variants that affect response to a great variety of drugs, such as clopidogrel, tamoxifen, warfarin, efavirenz etc. and can determine the progression/management of the underlying disease.

## What does the future hold?

Looking further into the future, Pharmacogenovigilance is expected to amend the drug development/licensing paradigm into "Re-learn" and Re/De-licence". It is, also, expected to catalyze the emergence of allied decision tools in other omics fields such as nutrigenovigilance, vaccigenovigilance etc. Addressing the interplay of genomic and environmental influences (diet, lifestyle, polypharmacy, toxins, and gut microbiome) is expected to be the future challenge for Pharmacogenovigilance. The new field that will emerge, "Pharmacometabolomics-aided PGx" will offer great intervention opportunities for testing hypotheses with regard to disease heterogeneity or mechanisms for variation in drug response under real-life conditions.

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