From pharmacogenomics to integrated personal omics profiling: a gap in implementation into healthcare

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Pharmacogenomics, one of the cornerstones of personalized medicine, was primarily developed to stratify hyperresponders and hyporesponders in drug therapy based on genetic polymorphisms. Current high-throughput technology developments enable not only genotyping and whole-genome sequencing, but also the assessment of the far more complex dynamic changes of the epigenome and its functional consequences measured on the level of changes in mRNA, protein and metabolites. The integrated personal omics profiling of one human individual demonstrated what is technically possible. This example has initiated further studies that are similar in their concepts. The gap between the potential of today’s technologies and their implementation into healthcare is based on several factors, with the important ones being a lack of clear-cut clinical guidelines and education in the field.

Pharmacogenetics is the study of genetic factors influencing responses to drug therapy. The availability of high-throughput genotyping technologies has led pharmacogenetics evolving into pharmacogenomics [1]. The study of genomic variations and their effects on interindividual differences in drug response is the origin of personalized medicine, which is often also referred to as precision or individualized medicine [2]. However, neither pharmacogenomics screening for the assurance of efficacy or avoidance of major side effects nor genotyping for human individuals’ susceptibility to common diseases are yet part of common medical practice. This is despite the fact that the example of the integrated personal omics profiling (iPOP) of one human subject [3] has demonstrated how truly individual we are on the level of the epigenome, transcriptome, proteome and metabolome of our cells. In this article, we will discuss how these very individual data can and should be used for both improved medical treatment and optimized strategies in order to preserve a healthy status.

Genome-wide association studies & pharmacogenomics

The genome-wide association studies (GWASs) catalog [4] summarizes the results of published studies on single-nucleotide polymorphism (SNP)–trait associations that include at least 100,000 SNPs and report a p-value below 10^{-5} [5]. The more than 14,000 listed SNP–trait associations provide an overview of the complex genetic basis of common diseases. For those individuals who have accumulated a number of risk variants in their genome, a high susceptibility for one or another disease can be predicted. However, most of these SNPs show odds ratios of below 1.15 (i.e., on their own, they have only a very small effect on the respective trait or disease). Therefore, despite a continuously growing list of SNP–trait associations, the genetic basis of most diseases is still largely unsolved.

Interestingly, most GWASs in pharmacogenomics result in far higher odds ratios (i.e., when studying the relation between gene variants and drug response, only rather small numbers of controls and cases are needed) [6]. This implies that it
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is far easier to predict an individual’s response to a marketed drug than his/her susceptibility to a common disease. One explanation for this discrepancy is that there is a relatively small list of genes that are involved in the response to synthetic drugs. The best examples are polymorphisms in genes encoding the diverse group of drug-metabolizing enzymes, most notably the CYP450 enzymes. Genetic variants in these enzymes may lead to increased or decreased: clearance of the parent drug and/or its pharmacologically active metabolites; production of active metabolites from the respective prodrugs; or formation of toxic metabolites, potentially leading to adverse drug reactions [7].

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Two antithrombotic drugs, clopidogrel and warfarin, are often-used examples for demonstrating the complicated road of pharmacogenomics from bench to bedside. Clopidogrel is an antiplatelet drug that reduces cardiovascular events in patients with coronary heart disease. Because CYP2C19 plays a major role in the metabolism of clopidogrel to its active metabolite, personalizing its use via the identification of associations between genetic variations of CYP2C19 and clopidogrel effects is an attractive therapeutic strategy. However, there are highly variable conclusions about the association between carriage of a CYP2C19 loss-of-function allele and the risk of adverse cardiovascular events in individuals using clopidogrel [8]. Warfarin is an anticoagulant that is highly efficacious in preventing thromboembolic events in specific patient groups, but its narrow therapeutic window and highly variable dose responses between individuals make it difficult to achieve the desired effects [9]. Although the pharmacogenomics of warfarin offers real patient benefits in clinical practice, its widespread adoption may still require several years of work [10].

Clopidogrel and warfarin belong to a list of more than 120 drugs for which the US FDA recommends genotyping before their use [11]. Such labeling was introduced in order to provide dosing instructions or warnings, particularly for drugs to be taken by patients who are at higher risk for toxicity or therapeutic failure because of metabolism by polymorphic enzymes, which is analogous to what is done to avoid drug–drug interactions. Moreover, the FDA uses the labeling in order to inform prescribers about serious safety issues, including drugs that have been in use for decades [12]. However, at present, with the exception of modern oncology, pharmacogenomic testing is rarely performed in clinical practice [6]. Although the costs of a genomic analysis are often taken as an argument, the main point may still be a lack of education of physicians in genomic counseling [13].

Personal component of common diseases
Cancer is the first common disease for which it was realized that there is a very individual origin of disease for every patient. Cancer genomics studies, such as those performed by the consortia of the The Cancer Genome Atlas [14] and the Cancer Genome Project [15], made significant progress in characterizing the principal driver mutations and biologic pathways behind individual cases of cancer. Therefore, it is no surprise that, at present, modern oncology takes great advantage from pharmacogenomics and other high-throughput technologies [16]. Since cancer chemotherapeutics often display more severe toxicities than other drugs, it is important to identify patients who are at risk for these toxicities. In addition, many types of cancer are often characterized by the overexpression or increased activity of signaling proteins, such as membrane receptors, kinases and transcription factors. A classical example is HER2, which is overexpressed in approximately 30% of breast cancers, leading to a reduced response to standard therapies. By contrast, specific inhibition of HER2 by the monoclonal antibody drug Herceptin® (Genentech, CA, USA; trastuzumab) significantly improves the survival rate. Since Herceptin therapy is very costly and only HER2+ breast cancer patients respond to it, molecular testing for HER2 expression levels is often used as a reference for how personalized medicine can be cost efficient. New insights from cancer genomics projects provide hints for the development of new ‘personalized’ drugs that target a specific mutation for cancer, some 20 of which have already obtained FDA approval [17].

Following the example of cancer, physicians started to understand that most other common diseases, such as Type 2 diabetes and dementia, occur in many different forms (i.e., they are far more individual than previously assumed). This suggests that a new molecular taxonomy should be defined for all diseases [2]. Thus, patients should not only be stratified by pharmacogenomic methods, but also the molecular features of their disease subtype, such as the underlying mechanisms, should be taken into account for a truly personalized treatment.

Dynamics of health & disease
Every one of the approximately 250 tissues and cell types that form a human individual’s body carry the same genome, which, with the exception of cancer,
stays stable during the person’s life. Classical pharmacogenomics addresses the most important of the average of 3.5 million variations of each individual’s genome compared with the reference genome, but as outlined above, pharmacogenomics cannot explain all of the inherited aspects of common diseases. In contrast to the genome, the epigenome varies not only from cell type to cell type, but also significantly over time and in response to perturbations, such as drug treatment or dietary changes. Cancer can be considered to be largely an epigenome disease, but also many other diseases are affected by epigenomic dynamics, such as complications of diabetes, rheumatoid arthritis or hypertension. The human epigenome is being investigated by large research consortia, such as the Encyclopedia of DNA Elements (ENCODE) [18], the Roadmap Epigenomics Project [19], the Human Epigenome Consortium [20] and the Functional Annotation of the Mammalian Genome (FANTOM) [21].

The fast progress in high-throughput technology initiated a shift from nucleic acid hybridization-based assays, such as those used in GWAS ‘chips’, to direct sequencing-based technology, such as ChIP-seq, MeDIP-seq, FAIRE-seq and others [22]. These methods enable the monitoring of transcription factor binding to chromatin, methylation of genomic DNA or accessibility of chromatin. For capturing the dynamics of the epigenome within a selected tissue or cell type, a time series analysis needs to be performed (i.e., new samples have to be taken repeatedly after a few hours, days or weeks). The same principles apply to investigations of functional consequences of the dynamic epigenome, such as up- or down-regulated mRNA expression followed by altered protein expression and metabolite concentration changes.

In summary, this implies that the status of a person in health as well as in disease cannot be reliably deduced from a single genotyping experiment, as has been suggested by classical pharmacogenomics, but rather needs to be profiled on the level of the epigenome, transcriptome, proteome or metabolome over a longer time period.

Panoramic views on human individuals

The ‘proof of principle’ for the amount of data today’s high-throughput technologies can collect for one human individual has been provided by the team of Michael Snyder [3]. Via many samples taken over nearly 2 years, a most complete picture of the molecular profile of one individual (Snyder himself) was determined on the level of the genome, the epigenome (DNA methylation, histone modifications and transcription factor binding), the transcriptome, the proteome, the metabolome, the antibodyome and the microbiome. The investigated samples had been obtained from easily accessible material, such as white blood cells, serum and feces. This iPOP allowed, for example, linking a viral infection to elevated glucose levels, which could be restored by lifestyle changes. This panoramic view on the physiology of a human individual can be compared with what Google Maps provides for the whole earth [2]. This analogy also defines an important goal of personalized medicine: the complexity of an individual human should be understood as easily and intuitively as nearly everyone understands and uses Google Maps.

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The iPOP study has initiated a number of comparable studies, such as the currently running molecular monitoring of 100 healthy individuals over 9 months, the Hundred Person Wellness Project, at the Institute of Systems Biology (ISB) in Seattle [23]. The estimated costs of US$10,000 per individual may be more than worth the disease-preventing insights that could be obtained from this study. The n = 1 iPOP study as well as the n = 100 Hundred Person Wellness Project clearly differ from standard clinical trials: they lack a control group and do not use blinding and randomization. Moreover, the number of investigated individuals is several magnitudes lower than what is used today in GWASs. This may cause some scepticism about the power of these studies. However, when we accept how individual we are on all molecular levels, the concept of average levels and their statistics becomes largely obsolete. For example, in the field of vitamin D, there is a huge debate on whether the recommended serum concentration of 25-hydroxyvitamin D should be 50 or 75 nM, or even higher, in order to prevent a number of disorders, ranging from bone fractures to autoimmune diseases [24]. In view of personalized medicine, a possible answer to this discussion could be that everyone will have an individual optimal 25-hydroxyvitamin D level, which should be achieved by appropriately dosed supplementation, diet or lifestyle changes, and there are some initial indications that this may be the case [25].

Incorporating pharmacogenomics into routine clinical practice

The translation of research findings in pharmacogenomics into clinical practice has been slow. Even well-defined pharmacogenomic data have not found their
way into everyday patient care, because it is only rarely useful for clinicians. A major reason to this is the complexity of the interplay between genomics and clinical outcomes. The clinical consequences of observed variability in drug exposure due to genetic variants depend on: the magnitude of drug exposure caused by the polymorphism; the relationship between pharmacokinetic and pharmacodynamic properties of the drug; the relationship between drug dose and clinical effect/adverse drug reactions; and the severity of possible adverse drug reactions and/or clinical consequences of reduced efficacy [26].

One major barrier to clinical implementation is the lack of clear, curated, peer-reviewed pharmacogenomic guidelines. Clearly, pharmacogenomics has reached a point at which rigorously created, evidence-based clinical practice guidelines are needed in order to move towards appropriate clinical implementation. Such guidelines are being developed by, for example, the Pharmacogenomics Knowledge Base (PharmGKB) [27], the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Pharmacogenomics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (both highlighted on [27]), the GAPP Knowledge Base [28] and the Pharmacogenomics Research Network [29]. Even with the increasing availability of clinical guidelines for specific gene–drug pairs that clearly indicate how prescribing should be modified based on test results, the actual implementation of dose modifications remains a challenge [30].

An additional issue involves the appropriate regulation of genotyping, as indicated by the recent publicity surrounding the interactions between the FDA and the genomics company 23andMe (CA, USA). In October 2013, the FDA ordered 23andMe to cease marketing its flagship Personal Genome Service (PGS). The potential effect of inaccurate results obtained using the PGS was magnified by its direct availability to consumers. The FDA was concerned that, for example, patients taking warfarin might adjust their dose independently from consulting a physician, leading to higher rates of thrombotic or bleeding events, on the basis of information regarding warfarin metabolism provided by the PGS [17].

Taken together, clinical pharmacogenomics guidelines represent a critical step in enabling the translation of clinical genetic test results into practical prescribing decisions. In order to prepare for the inclusion of clinical pharmacogenomics tests as a medical standard of care, medical and related professionals need to expand the availability and scope of pharmacogenomics education. Thus, education at medical schools needs to be reassessed [13].

Conclusion
Pharmacogenomics is a cornerstone of personalized medicine and has demonstrated its potential to change the way healthcare is offered by stratifying patients into various categories, such as responders, nonresponders or individuals who may experience adverse drug reactions. This should allow physicians to classify and treat diseases by their molecular profiles rather than by their ‘classical’ diagnosis. Physicians have to learn to use appropriate databases for the interpretation of the patient’s genomic information. Even with the help of tailored computer programs, this will yield far more information than a physician may interpret from a typical 15-min visit. Therefore, this clearly suggests a participatory model of healthcare, where the healthy individual and, if possible, the patient also takes enough time to conduct the primary interpretation of his/her data. The latter demands more health literacy (i.e., better education of the average citizen relating to common diseases) [31].

Future perspective
At present, it can only be speculated as to whether acquiring iPOP-type profiles will ever become standard in human life surveys. However, some 13 years ago, when the first human genome was sequenced with the investment of more than $100 million, nobody could reliably predict that, today, close to 100,000 humans had been sequenced and soon 1 million others will follow. Even if the price of iPOP-type omic measurements drastically drops to potentially less than $1000, should we measure everyone simply because we can do it? It may be expected that a meta-analysis of hundreds of iPOP-type investigations will result in the conclusion that a few thousand, not millions of parameters should be measured. However, this will still be some 100-times more data than is presently measured in a standard blood test. Nevertheless, careful following of individuals’ profiles over time will become more important in order to monitor the dynamic components of health and disease.

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