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PHARMACOGENOMICS BIOMARKERS FOR IMPROVED DRUG THERAPY RECENT PROGRESS AND FUTURE DEVELOPMENT

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ABSTRACT

Pharmacogenomic research sheds light on how people react to existing and novel medicines, and pharmacogenomic biomarkers hold considerable promise for predicting drug response and guiding drug selection and dosage. Rapid technological advancements in genetic analysis demonstrate that the number of genetic variants important for medication action is significantly more than previously anticipated, and that truly tailored drug response prediction necessitates attention to millions of uncommon mutations. We examine the evolutionary history of genetic variants in drug-metabolizing enzymes, highlight some key examples of current pharmacogenomic biomarker applications, and provide an update on germline and somatic genome biomarkers in drug development and clinical practise. We also go through current technology developments with a focus on complicated genetic loci, current attempts for pharmacogenomic biomarker validation, and future scenarios that include rare genetic variants for truly individualised genetically guided drug prescription.

KEYWORDS:

INTRODUCTION

Differential response to pharmacological treatment constitutes a major source of patient morbidity and mortality. Between 5 and 13% of in- and outpatient experience adverse drug-related events, mostly adverse drug reactions (ADRs) and sub-therapeutic effects of drug therapy.[1] Various patient-specific factors, including age, polypharmacy, concomitant diseases, and diet as well as heritable factors contribute to these inter-individual differences

with genetic polymorphisms explaining around 20–30% of the inter-individual variability in drug response.[2]

The liver as the central organ of drug metabolism is involved in the clearance of around 70% of drugs. Enzymes encoded by the cytochrome P450 (CYP) superfamily of genes are responsible for > 75% of phase 1 drug metabolism and thus constitute major modulators of drug response. Importantly, CYP genes are highly polymorphic between individuals and across populations, which can have important implications for the bioactivation and/or detoxification of medications.[3]

Pharmacogenomic biomarkers that can predict drug response have been attributed great promise for the improvement of molecular diagnostics in routine clinical care. It is helpful to distinguish between (i) germline biomarkers, which can influence systemic drug pharmacokinetics and pharmacodynamics and (ii) biomarkers in the somatic cancer genome, which modulate how cancer cells respond to drugs. Besides genetic factors, epigenetic modifications of DNA or histones have been linked to differences in drug response. In oncology, epigenetic alterations in cancer cells have been linked to increased expression of drug efflux transporters, mediating resistance to chemotherapy. Detection of epigenetically modified DNA in the blood stream can be used for tumor stratification and presents an emerging tool for monitoring treatment efficacy as well as development of drug resistance.[4] Moreover, pharmacological modulators of the epigenetic machinery have been successfully used in oncological treatment, mostly as adjuvants to sensitize tumors to standard-of-care chemotherapy. For a comprehensive update of this field, we refer to recent reviews.[5]

Discovery of genomic biomarkers

Cancer cells often contain multiple genomic alterations that together are responsible for deregulated growth. Cancer cells often depend on the continued presence of these genomic alternations and sudden inhibition of the signals that emanate from these genomic alterations frequently results in death of the cancer cells, a phenomenon coined ‘oncogene addiction’.[6] The presence of specific changes in the genomes of cancer cells can therefore have strong predictive value for responsiveness to therapies that target these mutations. The rapid development of new genomic technologies over the past decade has greatly expedited the detailed analysis of cancer genomes at multiple levels. DNA microarray analysis has made possible genome-wide analyses of gene expression, whereas innovations in large-scale DNA sequence analysis (‘next-generation sequencing’) have made it possible to compile a detailed

inventory of mutations in cancer genomes. Moreover, comparative genomic hybridization (CGH) technologies have allowed the genome-scale identification of copy number gains and losses in cancer. More recently, technologies for high-throughput measurement of protein biomarkers have been developed, including tissue microarrays and reverse-phase protein lysate arrays. Finally, large-scale functional genetic screens in mammalian cells have made possible the functional identification of genes that act in cancer--relevant signaling pathways and genes.

Gene expression biomarkers

As cellular behavior is controlled by gene activity, it seemed logical to assume that differences in aggressiveness of tumor cells could be inferred from differences in gene expression. Hence, initial microarray gene expression studies focused on the identification of prognostic biomarkers in cancer. The sequence of events that leads to the development of a clinically useful gene expression profile is depicted. Several multigene biomarkers (‘gene signatures’) are already in clinical use for prognosis of early stage breast cancer, including the 70-gene MammaPrint signature and the 16-gene OncotypeDX test.[7] Clinical use of additional gene signatures for prognosis in other cancer types will probably follow soon. The introduction of next-generation sequencing technology has also made it possible to use high-throughput transcript sequencing to quantify gene expression as an alternative to microarray analysis. RNA sequencing provides a more sensitive platform for detecting gene expression differences and also allows researchers to detect additional transcripts, including diverse small RNAs. Furthermore, it enables researchers to see altered patterns of RNA splicing or transcript editing that may contribute to disease.[8]

Pharmacogenomic germline biomarkers

Differences in the response to exogenous substances have already been described more than two millennia ago by the Greek philosopher Pythagoras who noticed in the sixth century before Christ that individuals responded very differently to the ingestion of fava beans with some experiencing severe hemolytic anemia.[9]

Excitingly, only in the last decades, technological advances have shed light on the molecular bases underlying these differences and discovered the responsible genetic polymorphisms (in the case of hemolytic responses to fava beans, genetic variants in G6PD were found to be responsible for the inter-individual differences in toxicity). By now a whole arsenal of genetic

variants has been identified that mechanistically link alterations in structure or functionality of the gene product to differences in drug response or toxicity.

Pharmacogenomic biomarkers are mostly located in genes encoding drug-metabolizing enzymes, transporters, drug targets, or HLA alleles and predict drug efficacy or inform about the risk to develop ADRs. Furthermore, genetic biomarkers have revolutionized the therapy of cystic fibrosis (CF) and we refer the interested readers to some of the recent excellent reviews that cover the field of genetically guided, targeted CF therapy.[10]

Clinically important examples of associations between genetic variants and drug response or toxicity

The Effect of CYP2D6 Genotype on Codeine Efficacy and Toxicity

Codeine, an analgesic and antitussive opium alkaloid, is Odemethylated by CYP2D6 to its active metabolite morphine and CYP2D6 activity constitutes the determining factor for codeine pharmacokinetics. Patients homozygous for loss-of-function haplotypes in CYP2D6, including the *4, *5, and *6 alleles, experience drastically reduced morphine formation and lack of analgesia. Consequently, in such poor metabolizers (PM), alternative medications that are not metabolized by CYP2D6 should be considered, such as buprenorphine, morphine, fentanyl, methadone, or non-opioid analgesics. In contrast, in ultrarapid metabolizers (UM), in which the active CYP2D6 gene is duplicated, morphine formation is increased and standard codeine doses can result in serum morphine levels that substantially exceed the therapeutic range, resulting in severe toxicity. The risk is highest in pediatric patients who receive codeine following adenotonsillectomy and multiple cases of lifethreatening respiratory depression or death due to codeine therapy have been reported.[11]

Warfarin Pharmacogenetics

Warfarin is the most commonly used oral anticoagulant for the treatment and prevention of thromboembolic events. However, a narrow therapeutic window combined with substantial inter-individual variation in warfarin pharmacokinetics and pharmacodynamics poses severe clinical challenges. Warfarin inhibits the VKORC1 subunit of epoxide reductase, thereby disrupting the formation of the vitamin K-dependent clotting factors. Warfarin is a racemic mixture of R- and S-enantiomers with the latter being around 5 times more potent. S-warfarin is inactivated by CYP2C9 and eliminated predominantly via the urine.

Likely reasons for the mixed outcomes include differences in reference (usual care in EUPACT vs. dosing algorithm guided by clinical variables in COAG), the use of loading dose (loading dose given in EUPACT vs. no loading dose in COAG) or the diversity of the trial population (homogeneous European population in EUPACT vs. 27% Africans and 6% Hispanics in COAG). Thus, while all trials suggest numerical, but not necessarily significant, benefits of genotype-guided dosing, the clinical utility of preemptive warfarin genotyping appears limited. The Role of HLA-Alleles in Hypersensitivity to Abacavir The antiretroviral guanoside analogue abacavir is commonly used for the treatment of HIV infections in adults and pediatric patients older than 3 months. While the drug is generally well tolerated, around 4% of patients experience hypersensitivity syndrome (HSS) that manifest as fever and gastrointestinal and respiratory problems as well as dermatological symptoms that range from rashes to Stevens-Johnson syndrome or toxic epidermal necrolysis.[12]

This non-covalent binding is highly specific and can be abrogated by a single point mutation of the S116 residue, which results in a lack of T cell activation.[13]

Following identification and clinical implementation of this pharmacogenomic biomarker, abacavir prescriptions drastically increased and indeed this biomarker might be one of the best examples where genotyping for one mutation can completely prevent the occurrence of compound toxicity. Prior to initiating abacavir therapy, screening for the HLAB*5701 allele is recommended by the FDA, the Clinical Pharmacogenetics Implementation Consortium (CPIC), and the Dutch Pharmacogenetics Working Group (DPWG) and in case the allele is detected, alternative therapy is mandated.[14]

Associations Between TPMT Genotype and Thiopurine Toxicity

The thiopurine mercaptopurine (6-MP) and its prodrug azathioprine (AZA) are used for the treatment of acute lymphoblastic leukemia (ALL) and are also widely prescribed off-label for their immunosuppressive effects in the treatment of Crohn’s disease and ulcerative colitis. AZA is rapidly metabolized into 6-MP in the liver, which is further either bioactivated by hypoxanthine-guanine-phosphoribosyltransferase (HPRT) to form thioguanine nucleotides or inactivated by either thiopurine-S-methyltransferase (TPMT) or xanthine oxidase (XO) to 6-methylmercaptopurine or thiouric acid, respectively.

Myelosuppression is the most common adverse reaction to thiopurine therapy and patients with reduced TPMT activity are at substantially increased risk. Importantly, TPMT genotype

is a strong predictor for TPMT activity and even patients heterozygous for the TPMT loss-of-function alleles *2A or *3 showed significantly higher incidences of dose reductions due to toxicity. Due to the substantial body of evidence that links TPMT genotype to thiopurine treatment outcomes and adverse events, TPMT genotyping is already widely applied in clinical practice. The costeffectiveness of preemptive TPMT genotyping remains however inconclusive[15] and data from randomized controlled trials is currently lacking.

The Role of SLCO1B1 Variants in Simvastatin-Induced Myopathy

Severe toxicity has been observed in patients receiving the blockbuster drug simvastatin for treatment of dyslipidemia, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of cholesterol biosynthesis. Importantly, the SNP rs4149056 located in SLCO1B1 (SLCO1B1*5), the gene encoding the hepatic simvastatin transporter OATP1B1, causes impaired hepatic import of the drug which prevents the interaction with its hepatic target HMG-CoA reductase and results in increased plasma concentration due to impaired hepatic clearance. Patients are at 2.6- or 4.5-fold increased risk per variant allele of developing myopathy when taking normal (40 mg daily) or high doses (80 mg daily) of simvastatin, respectively. Due to these risks, particularly in the high dose group, the FDA issued a warning that high dose regimens of simvastatin should only be used in patients who have already received high doses for more than 12 months without musclerelated adverse effects.[16]

DPYD Variants and Fluoropyrimidine Toxicity

Combinatorial therapies that include fluorouracil, such as the chemotherapeutic regimens FOLFOX and FOLFIRI represent the first-line treatment for various solid tumors. Fluorouracil (5FU) and other fluoropyrimidines, such as capecitabine, tegafur, and floxuridine, inhibit thymidylate synthase, which catalyzes the rate-limiting step in deoxythymidine triphosphate (dTTP) biosynthesis, thereby inhibiting DNA replication.[17]

Importantly, a recent study in 2038 patients demonstrated that 5FU dosing guided by prospective genotyping for the reduced functionality allele DPYD*2A resulted in significantly lower incidences of severe toxicities (73% in historic controls vs. 28% in genotype-guided cohort) and appeared to reduce costs for the health care system.[18] Thus, implementation of DPYD genotyping for 5FU therapy in routine clinical care might be a promising next step in reducing patient morbidity while at the same time allocating health care resources more efficiently.

Rare genetic variants and population specificity

Genetic variants can be classified as common (> 1% allele frequency, also called genetic polymorphisms) or rare (< 1% frequency) depending on their prevalence in the overall population. Recent twin studies indicated that the contribution of genetic factors to drug response differs drastically between medications. While genetic factors contributed only to a minor extent to differences in talinolol pharmacokinetics, heritable factors were responsible for 80– 90% of the differences in the pharmacokinetics of metoprolol and torsemide; importantly, however, the analyzed common genetic polymorphisms only explained around 40% of this variability.[19] These results indicate that additional factors, such as rare genetic variants can be important modulators of drug pharmacokinetics. Indeed, recent population-scale sequencing projects revealed that ADME genes harbor vast numbers of rare genetic variants that are not assessed by conventional genotyping arrays. Rare variants are more likely to have deleterious effects with an estimated odds ratio of 4.2 compared to variants with MAF > 0.5% and combined are estimated to account for 30– 40% of the functional variability in ADME genes.[20]

Importantly, variant and haplotype frequencies differ majorly between populations. Thus, while a variant may be rare globally, frequencies of a minor allele might be substantial in specific populations. One such example is the prevalence of the reduced functionality allele CYP2C8*2, which is not found in individuals of European or East Asian ancestry but is common in Africans (MAF = 15.9%). Similarly, the loss-of-function CYP3A4*20 allele causing increased risk of adverse reactions to, e.g., paclitaxel, was not found in Asian, African, South American, and most European populations but reached frequencies of 3.8% in specific regions of Spain. Combined, these findings suggest that ethnic origin is an important parameter in pharmacogenomic research and understanding of the geographical distribution of genetic variability builds the fundament for precision public health approaches.

The treatment with antiretrovirals in Zimbabwe provides an impressive case for the benefit of such approaches: When the national ministry of health implemented a WHO recommendation to change the first-line treatment of HIV to efavirenz, unexpectedly many Zimbabweans experienced ADRs associated with efavirenz overdose. Importantly, in Zimbabwe, 20% of the population are homozygous for the reduced functionality allele CYP2B6*6 which entails that efavirenz plasma concentrations exceed the recommended therapeutic levels, resulting in the local failure of a globally established dosing regimen. Thus, in order to prevent such

public health crises, selection of first-line treatment should be evaluated for each population separately, considering the specific genetic landscapes in the geographic region of interest.[21]

Rare variants and precision medicine

With decreasing sequencing times and costs, it is envisioned that precision medicine will increasingly utilize NGS technologies to derive predictions of drug response. Such analyses should be tailored to the drug in question and encompass genes likely to affect its kinetics, response, or risk of adverse reactions. In this concept, a pre-defined panel of genes is sequenced using NGS and genetic variants in the patient of interest are identified. Analysis of the sequencing results will yield (i) non-sense mutations, such as frameshift, stop-gain, or start-lost variants; (ii) silent (also called synonymous) mutations; and (iii) missense mutations that result in amino acid exchanges. While exceptions from the rule exist, synonymous variants rarely have a functional effect, whereas the vast majority of non-sense variants result in a loss-of-function of the gene product. Missense variants however are more heterogenous: while some variants result in reduced functionality alleles, others do not have any functional effects. Overall, around 70% of genetic variants within coding sequences have no pronounced effect on the functionality of the gene product, whereas 30% of the mutations unveiled by exome sequencing result in reduced function or loss-of-function alleles.

Due to the vast number of rare genetic variants, it is not feasible to experimentally characterize the functional effects of all such mutations, thus posing a significant challenge for the clinical interpretation of genetic variability and hampering the translation of genomic data into actionable advice.

Current computational tools have been trained on disease-causing genetic variants and use evolutionary constraints as the main parameter to predict functional effects ofthe mutations in question. Such an approach poses problems for the assessment of pharmacogenetic variants as ADME genes are often only poorly conserved. Consequently, while computational tools correctly classify disease-causing variants with accuracies between 70 and 90%[22], a comprehensive assessment of their performance for ADME missense variants revealed only much lower predictive accuracies. ADME-specific optimization of computational prediction models is thus necessary, which will provide an important step forward to allow the rapid translation of exome sequencing data into a compendium of functionally altered genes of relevance for the specific drug therapy in question for each patient, adding relevant information for pharmacogenetically guided drug therapy.

There is evidently a need to improve both in silico and experimental methods for functional prediction of missense mutations. However, already today NGS-based approaches provide more accurate and more individualized information for pharmacogenomic predictions of drug action than the current array based techniques that focus solely on common genetic variants. To facilitate the translation of this perception into clinically actionable information and to fully harness the added value of clinical NGS, overcoming the indicated limitations thus constitutes one of the most important frontiers of future pharmacogenomic research.

Genetic biomarkers in the somatic cancer genome

Currently, cancer affects around 90 million individuals and causes nearly 1 in 6 deaths worldwide.[23] Underlying the formation of neoplasms is the accumulation of somatic mutations that activate the so-called oncogenes and inactivate tumor suppressors. Every tumor harbors a unique combination of acquired genetic variants and cancer genomics, i.e., the analysis of genetic differences between tumor and non-tumor cells aims to unveil the genetic basis that confers cancer cells their proliferative capacity and the ability to escape apoptosis. By revealing its molecular underpinnings and identifying clinically actionable variants that can be targeted by approveddrugs, this approach allows to tailor therapy to the specific tumor, opening new avenues for personalized oncology.

To date, the most commonly identified oncogenic variants affect signal transduction systems, cell cycle genes, metabolic enzymes, the epigenetic machinery, or factors involved in transcription, splicing, or translation. Prominent examples of such mutations result in the constitutive activation of growth factor signaling. Approved targeted therapies are available for variants in receptor tyrosine kinases, such as EGFR (also termed HER1), ERBB2 (also termed HER2), PDGFRA, KIT, ALK, and JAK2 that are commonly mutated in various cancers. Furthermore, targeting activating mutations, amplifications, or gene fusion events of FGFRs represents promising therapeutic opportunities for various solid tumors with multiple clinical trials currently ongoing.[24]

In contrast, EGFR inhibition did not result in improved clinical outcomes in glioblastoma patients compared to conventional chemo- and radiation therapy.[108] However, even in patients that are initially responsive to targeted therapy, drug resistance can arise most commonly due to the acquisition of additional mutations. In NSCLC patients, the EGFRT790M variant decreases the affinity of tyrosine kinase inhibitors (TKIs) to bind to the

ATP binding pocket of EGFR and represents the most common mechanism of EGFR inhibitor resistance.[25]

Mechanisms of imatinib resistance include point mutations in BCR-ABL1, amplifications of the chimeric gene as well as BCR-ABL1-independent mechanisms, such as overexpression of efflux transporters or downregulation of the imatinib importer OCT1. By now, a variety of therapeutic options is available for the treatment of imatinib-resistant CML. Nilotinib and dasatinib are effective against most imatinib-resistant point mutants with the exception of cells with the T315I mutation. For BCR-ABL1T315I-positive CML, the recently approved TKI ponatinib (full FDA approval in 2016) demonstrated a major cytogenetic response in 56% of patients irrespective of BCRABL1 mutation status and thus significantly improves clinical outcomes for the respective patients.[26]

The examples provided above give an impression of the complexity of genetic variability in cancer cells. Due to increasing throughput and decreasing costs of sequencing, genetic information of primary cancers as well as metastases becomes progressively more available. This massive amount of data can be accessed at central data hubs, such as the Genomic Data Commons provided by the National Cancer Institute that currently provides genomic information of 14,551 cases and the Catalog Of Somatic Mutations In Cancer hosted by the Sanger Institute, which constitutes the largest database of somatic cancer mutations. However, the translation of this unveiled landscape of oncogenetic variability into clinical advice remains difficult despite the multitude of computational tools that assist in detection and interpretation of cancer genome alterations.[28]

Emerging technologies facilitating biomarker discovery

The knowledge we have gained about pharmacogenomic biomarkers, particularly regarding the importance of rare and population-specific variants, can be attributed to the increase in speed and accuracy of NGS technology, combined with decreasing prices. However, certain challenges of short-read sequencing remain and particularly the mapping of structural variants, copy number variations (CNVs) and of large (> 1 kb) repetitive elements remains problematic.

Filtering variants called using standard filters for short-read sequencing results in the removal of low complexity regions, segmental duplications and variable number tandem repeats. As a consequence, the pharmacogenetic variability in important genes, such as CYP2A6,

CYP2B6, CYP2D6, CYP3A4, GSTM1, HLA-B, UGT2B15, and UGT2B17 cannot be interrogated by standard paired-end 150 bp sequencing. Similarly, a substantial proportion of variants cannot be called with high confidence forgenes containing repeats larger than 1 kilobase (kb), including ABCB1, SLC19A1, and SLC22A1.

Long-read sequencing technologies aspire to enhance the recovery of reads that cannot be unambiguously mapped by short-read sequencing. In recent years, multiple long-read sequencing approaches have been presented. Pacific Biosciences offers platforms for single-molecule real-time (SMRT) sequencing that have been successfully applied to medical genotyping as well as to the sequencing of human genomes.[29]

The long reads allow for accurate variant calling as well as phasing of multiple heterozygous variants whose genomic location might be several kilobases apart. As such, SMRT provides an excellent technology for the sequencing of complex CYP loci and, using CYP2D6 as an example, has been demonstrated to allow the simultaneous detection of SNVs and CNVs in multiplexed samples.[30]

In addition to genomic sequencing, SMRT allows direct decoding of epigenetic marks. Nanopore sequencing developed by Oxford Nanopore Technologies offers an alternative to the PacBio platform. Recent progress towards higher throughput, including whole genome sequencing (WGS), as well as detection of DNA methylation, also makes it well suited for biomarker discovery in complex regions of the genome. Furthermore, long-read sequencing combined with target capture methods based on the hybridization of biotinylated baits offers the possibility to focus on specific genomic regions of interest.[31]

A recent elegant approach demonstrated the utility of direct selection of DNA fragments in real-time by dynamic time warping and matching reads to the referencegenome. Thus, its portability, flexibility, and speed in data production make nanopore sequencing suitable for realtime applications, including direct point-of-care pharmacogenomic testing. Besides long-read sequencing, various approaches to generate synthetic long-reads have been presented. The main advantage of synthetic methods is that they can leverage the low cost and high accuracy of short-read sequencing. Illumina's TruSeq Synthetic Long-Read technology, previously referred to as Moleculo, is based on fragmenting genomic DNA to approximately 10 kb fragments, their clonal amplification, shearing, and indexing with a unique barcode. Similarly, contiguity preserving transposase sequencing from Illumina provide in vitro means

of generating libraries comprised of thousands of indexed pools, each containing thousands of sparsely sequenced long fragments, ranging from 5 kb up to 1 megabase.

The Chromium platform (10× Genomics) provides synthetic long reads by partitioning and barcoding the genome, followed by sequencing on any NGS platform. The barcoded linked reads can be aligned using Bread clouds, thereby overcoming the complexities of mapping reads in repetitive regions of the genome. All linked reads for a single barcode are aligned simultaneously, with the prior knowledge that the reads arise from a small number of long (10–200 kb) molecules. In summary, Breal as well as synthetic long-range sequencing represent promising emerging technologies that allow the phasing of variants, which can refine pharmacogenetic genotype calls and thus improve the phenotypic prediction regarding drug response.

Clinical implementation of pharmacogenomics

In Europe, a large prospective trial called PREPARE (PREemptive pharmacogenomic testing for Preventing Adverse drug REactions) has been initiated by the EU-financed Ubiquitous Pharmacogenomics project (http://upgx.eu/) that aims to implement and evaluate the impact of pharmacogenomic testing on therapeutic outcomes in seven European clinical centers.

Outcomes of this interesting trial are expected in 2020. In the USA, the NIH-funded eMERGE project has entered the final stage, which aims at analyzing the importance of rare genetic variants on patient phenotypes, developing technical and regulatory solutions to integrate genomic information into Electronic Health Records (EHR), assessing physician and patient attitudes towards the value of pharmacogenomic data, developing educational programs, and increasing the knowledge and awareness of clinically significant genetic variants. Additional programs conducted in the USA have been reviewed recently.[32]

Points to consider for studies of clinical pharmacogenomics

Importantly, certain pitfalls should be considered when evaluating the clinical importance of pharmacogenomic associations. The problems include the analysis of populations that are heterogenous regarding ethnicity or disease classification, the inappropriate pooling of data derived from noncompatible studies, the use of inappropriate methods for isolation or sequencing of genomic DNA, use of somatic DNA instead of germline DNA, and vice versa, concluding on the basis of inaccurate proxy polymorphisms and erroneous haplotype identification based on a set of genetic variants. Furthermore, the choice of genotyping

methodology, including appropriate selection of interrogated SNPs or genomic intervals as well as an assessment of the analytical validity of the chosen method, constitutes important aspects during the project planning phase. In case NGS-based approaches are used for genotyping, strategies should be in place to interpret encountered rare genetic variants with unknown functional consequences.

CONCLUSION

We conclude that pharmacogenomic data for patient stratification is useful for tailoring optimal treatment regimens, especially in oncology. However, in other therapeutic domains, the routine use of pharmacogenomic biomarkers in clinical practise is now rare, and the prospects for future application are being investigated by various international consortia.

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