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Recent progress and clinical importance on pharmacogenetics in cancer therapy

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Abstract

Recent advances have provided unprecedented opportunities to identify prognostic and predictive markers of efficacy of cancer therapy. Genetic markers can be used to exclude patients who will not benefit from therapy, exclude patients at high risk of severe toxicity, and adjust dosing.

Genomic approaches for marker discovery now include genome-wide association studies and tumor DNA sequencing. The challenge is now to select markers for which there is enough evidence to transition them to the clinic.

The hurdles include the inherent low frequency of many of these markers, the lengthy validation process through trials, as well as legislative and economic hurdles. Attempts to answer questions about certain markers more quickly have led to an increased popularity of trials with enrichment design, especially in the light of the dramatic phase I results seen in recent months.

Personalized medicine in oncology is a step closer to reality.

Keywords

biomarkers; cancer therapy; pharmacogenetics

INTRODUCTION

Especially in the field of oncology, it is no longer sufficient to depend on traditional factors, namely tumor stage and histology, to direct treatment or to determine survival. Increasingly, molecular biomarkers have been incorporated into treatment decision algorithm. These markers are classified broadly into 2 groups: firstly, markers that are used to identify genetically vulnerable subjects to extreme treatment toxicity, and secondly markers that (a) guide the selection of treatment with the best chance of disease control or (b) stratify risk of progression or recurrence in order to rationalize decision for or against aggressive treatment. The former (toxicity) is in general a property of the patient's (germline) genome while the latter is generally a property of the tumour (somatic) genome. Predictive markers allow physicians to improve the efficacy of cancer therapy, and prognostic markers allow for selection of patients with high risk of cancer recurrence for treatment, and those with low risk of recurrence for less intensive treatment or observation only. Advances in the

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identification of both germline and somatic mutations, and the understanding of their predictive and prognostic values, have paved the way for personalized treatment, a key goal of today's oncology.

There still exist many challenges going forward: The pace of identifying such markers has not been matched by the speed of validation studies. Patient and physician education remains much to be improved upon. Improvement in legislation and administrative processes is still ongoing and in the midst of being fine tuned. Nonetheless, the future for the development of pharmacogenetics in cancer therapy remains promising.

PROMISES OF PHARMACOGENETICS

The concept of pharmacogenetics and personalized medicine have been anticipated for ages, from the time of Pythagoras, in 6th century BC, prohibiting the ingestion of fava beans amongst his followers, to the 20th century, when Sir William Osler recognized that "Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike, and behave alike under the abnormal conditions we know as disease".(1) We have come a long way since then. The link between glucose-6-phosphate dehydrogenase deficiency, hemolytic anemia, and fava beans was established in the 1950s.(2) The completion of the Human Genome Project now allows access to the entire human sequence of genetic information, and an easier evaluation of genetic variation.(3)

The understanding of various germline polymorphisms in association with treatment toxicity, as well as survival benefits or lack thereof, opens up the possibility of this knowledge directly serving to complement the array of chemotherapeutic agents available. Pharmacogenetic testing may enable clinicians to identify patients who are less likely to benefit from expensive drugs, those who are susceptible to severe treatment related toxicities at standard doses, and also reduce the delay of the patient receiving perhaps the correct alternative treatment. This is all more important in cancer therapy because many chemotherapeutic agents have a narrow therapeutic index and not uncommonly result in life threatening toxicities.(4)

The utility of pharmacogenetics extends beyond cancer therapy in the clinic. It has the potential to facilitate the identification of drug targets, accelerate the discovery and development of several drugs.(5–9) Tumor tissues frequently acquire mutations in oncogenes, which can confer sensitivity or resistance to drugs.(10) A better understanding of molecular processes and somatic mutations of tumors have led to an increasing number of targeted agents being discovered and developed. The effective and appropriate use of expensive cytotoxic and targeted agents can ultimately translate into more cost effective treatments and eventually reduce overall healthcare costs. To evaluate the progress thus far, a simplistic classification and examples are cited.

PROGRESS OF PHARMACOGENETICS IN ONCOLOGY: HAS IT DELIVERED?

Predictive markers for response

The clinical application of pharmacogenetic markers has been most successful in treatment response prediction. There are at least 16 FDA approved anticancer drugs with validated predictive markers for treatment response (Table 1). These predictive markers are all tumor or somatic genomic alterations frequently characterized by DNA base mutations, gene copy numbers changes, chromosomal rearrangement and epigenetic alterations. There is a growing body of evidence that there are genetically defined subtype of tumors that might depend upon one or more specific pathways or mechanisms to drive tumor growth and

survival. Dramatic clinical responses may be seen when these tumors are treated with drugs targeting oncogenes to which tumors are dependent to for their growth, survival, and metastatic potential.(10, 11)

A prime example is the epidermal growth factor receptor (EGFR) tyrosine kinase domain mutation and response to gefitinib and erlotinib in lung cancer. Differential responses and outcomes to targeted agents have led to the recognition of phenotypic characteristics (non-smokers, female, Asians and adenocarcinoma) that predicts for better response, and the eventual validation of genetic markers.(12) Somatic mutations in EGFR, including deletion mutations in exon 19 and leucine to arginine substitution at amino acid position 858 (L858R) in exon 21, have been identified for their ability to predict sensitivity to tyrosine kinase inhibitors (e.g. gefitinib or erlotinib).(13) These mutations cause constitutive activation of the EGFR receptor, resulting in uncontrolled replication and survival of tumor cells. At the same time, because of the dependence of the cell cycle on these activating mutations, there is also increased sensitivity and susceptibility to inhibition by tyrosine kinase inhibitors.(14) The objective response rates to tyrosine kinase inhibitors range from 55% to as high as 80%, compared to response rates to chemotherapy of 30–45% for the same group of patients.(12, 13, 15, 16) On the other hand, it has also been shown that the T790M mutation at exon 20 is the most commonly found mutation that confers resistance through steric hindrance.(13, 17)

Treatment directed at specific drug targets have created much excitement in oncologic research, and have accelerated the development of targeted anti-cancer drugs. Under this new model, many confirmatory phase III trials are designed with some form of enrichment, i.e. testing the drugs in selected people deemed most likely to respond. This is especially so in tumors where somatic biomarkers for response have had established proof of concepts, like lung, breast and colon.(18)

In contrast, the clinical utility of germline markers predicting for treatment outcomes are less well established. One of the most extensively studied examples is the relation between CYP2D6 activity and outcome. CYP2D6 is responsible for the biotransformation of tamoxifen to its active metabolite, endoxifen. The systemic exposure of endoxifen has been shown to correlate with CYP2D6 polymorphisms.(19, 20) Decreased CYP2D6 activity was previously thought to be associated with poorer clinical outcomes when breast cancer patients were treated with tamoxifen in the adjuvant setting.(21–23) However, the recent retrospective analyses of 2 large adjuvant breast cancer trials, failed to establish a relationship between CYP2D6 polymorphisms and treatment outcome of patients treated with tamoxifen.(24, 25) Although the reasons for the disparities are unclear, it is evident that tumor heterogeneity, such as human epidermal growth factor receptor 2 (HER2) status and concomitant use of selective serotonin reuptake inhibitors (SSRI) can affect treatment outcome.(19, 26) In addition, the studies did not include the ultra-(rapid)metabolizers. Whether variation in the dose of tamoxifen would affect the outcome is also still not known. To complicate matters, rates of adherence to hormonal therapy may affect tamoxifen efficacy. In a study of 8,769 patients of whom 43% were taking tamoxifen, 26% taking aromatase inhibitors and the remaining taking both, only 49% took adjuvant hormonal therapy for the full duration at the optimal schedule.(27) Younger women were at the highest risk of non-adherence, while women of Asian decent were more likely to comply with the treatment prescribed. In a prospective observational trial, CYP2D6 extensive metabolizers had higher discontinuation rates at 4 months. The extensive metabolizers who potentially may be more likely to benefit from tamoxifen were also paradoxically more likely to stop the drug early.(28, 29)

Currently, it is still recommended that patients who are on tamoxifen avoid potent CYP2D6 inhibitors (e.g. antidepressants such as paroxetine and fluoxetine).(30) Although the AmpliChip CYP450 test has been approved by the US FDA for the testing of CYP2D6 metabolizer status,(31) studies prospectively looking at the significance of CYP2D6 polymorphisms on tamoxifen clinical effects, as well as dose escalation of tamoxifen in patients with impaired CYP2D6 activity are ongoing.(32, 33)

Epigenetics is an emerging, promising field in oncology therapeutics. It involves the understanding of changes in gene function that occur without a change in the DNA sequence, and usually involve DNA hypo- or hypermethylation, histone modification, or microRNAs (miRNAs).(34) The main successes in its predictive value and clinical translation are currently found in the treatment of hematopoietic malignancies, with DNA methylation inhibitors azacitidine and decitabine both FDA approved for the treatment of myelodysplastic syndromes, as well as suberoylanilide hydroxamic acid (vorinostat), a histone deacetylase inhibitor, in the treatment of cutaneous T-cell lymphoma.(35–38) Patients with O^6-methylguanine-DNA methyltransferase (MGMT) gene silencing has been shown to benefit more from temozolomide in addition to radiotherapy as treatment for glioblastoma multiforme.(39) Other non-hematopoietic tumor types, such as ovarian, colon, and breast have also showed promising preliminary results as well.(40–43)

Predictive markers for toxicity

There are several anti-cancer drugs with labels reporting germline pharmacogenetic markers of toxicity (Table 2). Some of these may also affect efficacy, for example, thiopurine methyltransferase (TPMT) polymorphisms might affect 6-mercarptopurine (6-MP) response.(44) Even when treated at 10% of the standard dose of 6-MP, patients homozygous for TPMT variants have similar or superior survival compared with patients with at least one wild-type allele. Although the associations between germline polymorphisms and treatment toxicities are well established, they have not been embraced fully into clinical practice. The reasons will be discussed later in this review.

The majority of these markers were discovered by a candidate gene approach, where prior knowledge of pathophysiology, pharmacokinetics, pharmacodynamics and tumor biology is required. In recent years, the examination of population variation in all the annotated genes in the human genome has became possible.(45) Through statistical analyses and probability calculations, candidate genes can be identified without prior knowledge of the association. Most recently, Ingle et al. used genome wide association study (GWAS) to retrospectively identify the gene (T-Cell leukemia/lymphoma protein 1A gene, or TCL1A) that may predict for musculoskeletal side effects in women receiving anastrozole and exemestane.(46) TCL1A expression enhances Akt serine threonine kinase activity, functioning as an Akt co-activator, and is usually associated with hematopoietic malignancies. Functional studies suggested that the SNP variant (rs11849538) creates an estrogen response element, which leads to greater reductions in TCL1A and interleukin 17 receptor A (IL17RA) expression in women on aromatase inhibitors, giving rise to symptoms. The authors also suggested a link between a change in cytokines level and aromatase inhibitors musculoskeletal adverse effects. Although association between TCL1A, changes in cytokines and musculoskeletal adverse effects remain to be validated, it had demonstrated the potential ability of GWAS in identifying potential clinically relevant novel candidate gene variants.

Prognostic markers to guide treatment decision

Many predictive markers in oncology such as EGFR mutation status, are found to have prognostic impact as well, aiding physicians in making clinical decisions for treatment or observation.(47, 48) In recent years, gene expression has increasing been used to dissect

tumor heterogeneity, allowing clinicians to classify tumors into genomic subtypes with distinct clinical behavior and response to treatment. Based on variations in gene expression patterns derived from cDNA microarrays, Sorlie *et al.* classified breast carcinoma into a basal epithelial-like group, an ERBB2+ group, a normal breast-like group, and a luminal estrogen receptor(ER) positive group, which was further divided into at least 2 subgroups with distinct expression profiles.(49) This was prospectively validated, showing that untreated patients with basal-like and ERBB2+ subtype had poorer prognosis compared to luminal A and normal-like tumors. In addition, basal tumors responded poorly to hormonal and cytotoxic therapy; whereas ERBB2+ tumors were more likely to respond to anti-HER2 therapy.(50)

Many multigene expression profiles for different tumors are now commercially available, including MammaPrint and Oncotype Dx (for breast cancer) and ColoPrint, (for colon cancer).(51–53) Multigene expression profiles in general utilize a recurrence score algorithm for prognostication, and aid decisions for adjuvant treatment in borderline risk patients. In Oncotype Dx for breast cancer, the risk score is generated from expression of 16 cancer-related genes and 5 reference genes. It can further stratify good risk breast cancer defined by 'traditional' staging, hormonal and HER2 status into 3 groups with distinct recurrence risk. As well as prognostication, some gene expression profiles also predict for treatment response in patients.(54) Most of these have been validated in previous randomized controlled trials, and are even included in several prospective trials for evaluation. However, several questions remain unanswered. For example, in breast cancer, whether patients who are deemed to be at intermediate risk (based on their recurrence score from both Oncotype Dx and MammaPrint) benefit from more aggressive treatment remains to be validated, and is the subject of ongoing trials, such as the TAILORx [Trial Assigning IndividuaLized Options for Treatment (Rx)] and MINDACT (Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy) trials.(55, 56)

Use of epigenetics for prognostication is currently still in its infancy, although many promoter methylations and CpG island methylation aberrancies have been identified, including lung and colon cancer.(57, 58)

CHALLENGES IN DEVELOPMENT AND VALIDATION

Development model for genetic markers and evaluation

Translation of pharmacogenetic knowledge from bench to bedside has been disappointingly limited thus far. Although several paradigmatic examples have been given, these have not been freely embraced by both physicians and patients. The main reason is the large imbalance between discovery and validation, with a bottleneck at the validation process.

The steps for the development of a pharmacogenetics marker include the initial discovery of the biomarker, followed by its functional characterization. As diagnostic tests are developed for it, clinical correlation needs to follow. Retrospective analyses can provide the fastest and most convenient way to test the clinical validity of a biomarker.

Retrospective analyses of somatic mutations of completed prospective randomized trials have led to results that changed medical practice, for example, the addition of cetuximab and panitumumab to chemotherapy in patients who are KRAS wild type resulted in longer overall survival.(59, 60) Prospective trials were designed thereafter with the aim to confirm the findings,(61, 62) although the recent Medical Research Council (MRC) CR-10 and NORDIC VII studies have shown conflicting results.(63, 64) The reasons for the discrepancies are not entirely clear.

In the retrospective analyses of previous trials for biomarker validation, it might be that not all the patients or samples may be available for analysis. It is pertinent though, that the available cohort of patients that are analyzed be representative of all the patients in the study, ideally a sizable number, or the validity of the analysis may fall short and be questioned.

In this age of evidence-based medicine, the current model still asks for prospective testing as the ultimate validation of a biomarker through very time consuming and expensive trials. Although alternative models should be considered and novel strategies developed to speed up the validation process, the importance of prospective validation cannot be ignored. Prospective studies allow for better profiling of sensitivity, specificity, absolute risks, predictive values, and also factor in environmental factors and treatment outcomes.(65) They should ideally also focus on clinical relevance, as well as optimal dosing strategy.(66)

Sargent *et al.* discussed strategies for evaluation of genetic markers by classifying cancer treatment trial designs into 2 simple groups: 1) Marker by Treatment Interaction Design and 2) Marker-Based Strategy Design. The authors defined the designs as such: In the Marker by Treatment Interaction design, “Patients in each marker group are randomly assigned to two different treatments, and the testing plan determines whether one treatment is superior to the other separately within each marker group”, while in the Marker-Based Strategy Design, “after the marker status is known, each patient is randomly assigned to either have his/her therapy determined by their marker status or to receive therapy independent of marker status”.(67) The former is reminiscent of classical randomized controlled trials with upfront stratification for the marker, while the latter is reflective of enrichment models. With improved knowledge of tumor molecular biology and a bottleneck at validation studies, it has become more pressing currently to identify an optimal design that answers questions regarding clinical relevance in an efficient and rapid manner.

Enriched trials as an alternative model?

Several alternative strategies have been considered for validation, including enrichment, biomarker-based strategies. Enrichment strategies are most appropriate when 1) the mechanism of drug action is already known, 2) a reliable, sensitive and specific detection method or assay is available, and 3) there is compelling preliminary evidence that patients with or without that marker profile do not benefit from the treatments in question. Enriched trials are more powered and need fewer randomized patients to validate a marker, as they include only patients who have a certain marker characteristic or profile, and patients are randomized to the new treatment vs. the standard treatment.(67) The caveat of such an approach is that predictive value of the pharmacogenetic marker in question cannot be fully established in the patients that were excluded from the study, this particularly relevant when the marker is not common in that patient population.(68) Furthermore, the numbers needed to screen to obtain the desired number of patients remains the same, and the perceived shorter duration of trial occurs only after recruitment.

Crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor, has created much excitement for treatment response rate of greater than 70% in non-small cell lung cancer (NSCLC).(9) However, the incidence of NSCLC harboring the echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) fusion gene, the target for crizotinib, in the unscreened population is low, with an estimated incidence of 2–7%.(9, 69, 70) EML4-ALK in lung cancer is known to be more prevalent in females who are non-smokers and the adenocarcinoma subtype.(71) The knowledge that EML4-ALK and EGFR mutations are mutually exclusive has high significance.(70, 72) Patients who are EGFR mutation negative with such phenotypic characteristics can be the target of randomized clinical trials for crizotinib, reducing the numbers needed for adequately powered trials, and

accelerating the development of crizotinib and increasing the chance of a successful trial. Vemurafenib has similar success with V600E BRAF mutation positive melanoma,(7) and both crizotinib and vemurafenib have transited with an accelerated pace from phase I trials directly to phase III.(5, 6) These newer approaches serve as paradigmatic examples of the enrichment model, and this strategy is likely to be increasingly employed in this era of targeted and personalized medicine.

PROBLEMS WITH CLINICAL IMPLEMENTATION

Frequency and relevance of polymorphisms

The prevalence of a marker is an important factor that needs to be considered when validation trials are designed to determine clinical effectiveness. Many pharmacogenetic markers have a low frequency in the population, making difficult their validation and clinical implementation. Even in patients who experience severe toxicity, the complex pharmacodynamic pathways may mean that the purported molecular marker identified may not be the only reason for the observed toxicity. Dihydropyrimidine dehydrogenase*2A (DPYD*2A) is the most common DPYD polymorphism associated with impaired DPD activity. Up to a quarter of patients suffering from severe 5-FU toxicity may have DPYD*2A polymorphism, although the allelic frequency of DPYD*2A is only about 1.8% in European Caucasians and less than 1% in Asian populations.(73–76) The majority, up to two-thirds, of patients who experienced severe treatment toxicity after 5-fluorouracil do not have a molecular basis for DPD deficiency.(77) Apart from DPD, thymidylate synthase is another important enzyme in folate metabolism, and is a key target for 5-FU. Thymidylate synthase catalyses the methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), the source of intracellular thymidylate vital for DNA repair and replication.(78) Although many polymorphisms for DPYD and the thymidylate synthase gene (TYMS) have been identified and studied, these polymorphisms have relatively modest or inconsistent associations with 5-fluorouracil toxicity, and several studies have failed to replicate the results. One such study, Schwab *et al.*, looked to assess the predictive value of polymorphisms in DPYD, TYMS for severe toxicities related to fluorouracil treatment.(79) The sensitivity of DPYD genotyping for overall toxicity was low with a positive predictive value of barely half. Interestingly, while women had a higher risk for toxicity, DPYD genotype was not a dependent factor. The proposed algorithm for 5-FU dosing remains a theoretical exercise with no clinical utility.

Pharmacoethnic variation is an important factor that needs to be considered when applying a genetic testing model across ethnic borders. The knowledge of the predominant polymorphisms and their respective frequencies should be borne to mind. In Caucasian populations, the UGT1A1*28 polymorphism is the most common variant but this is present in only 1.2–5% of South East Asian and Pacific populations.(80, 81) In East Asians, the predominant functional polymorphism is UGT1A1*6, with a reported allelic frequency of 13–23%.(82) Indeed, the Japanese Ministry of Health and Welfare approved the use of testing for both UGT1A1*28 as well as UGT1A1*6 to predict for toxicity from irinotecan in the treatment of colorectal cancer.(83) The application of testing for UGT1A1*28 only would not be clinically relevant in the Japanese (and other Asian) population.

Costs and availability of pharmacogenetics

The finite nature of healthcare budget requires for treatments and biomarkers to be cost effective. Pharmacogenetics can potentially reduce healthcare cost by allowing the clinician identify patients that are most likely to benefit from treatment, thus reducing unnecessary treatment and minimize cost incurred during management of treatment related toxicities and hospitalizations.

It has been demonstrated that the mean calculated cost per life-year gained by TPMT genotyping in acute lymphoblastic leukemia patients treated with 6-MP was 2100€, based on genotyping costs of 150€ per patient.(84) Unfortunately, there is a paucity of studies focusing on the impact of pharmacogenetic testing on health economics. Economic evaluation is often a complicated, tedious process. Several models for economic evaluation, for example the Cost Utility Analysis (CUA) and Cost-effectiveness analysis (CEA), serve to better quantify the potential benefits of pharmacogenetic testing in oncology.(85) However, limitations of individual economic evaluation models include not being able to capture abstract but important factors, such as opportunity costs, willingness of the patient to pay, psychological impact and patient preference.

A more efficient pharmacogenetic test is often not necessarily the cheapest test, but one that predicts more reliably the intended outcome, and allows for selection of the optimal treatment. With advances in technology, the cost and time of whole human genome sequencing have dramatically been improved, with eventual realization of the “$1000” genome.(86) In consideration of the dropping cost of genotyping, the incorporation of genomic scans in patient evaluation becomes a dynamic and ongoing process that should be constantly checked and updated by policy makers in accordance to the depreciating costs, to allow for more accessibility for genotyping and its benefits as more evidence becomes available.

The integration of pharmacogenetics into the clinic is often hindered by the cost of testing or lack of reimbursement from public or private insurers. Many countries especially developing ones, do not even have access to pharmacogenetic testing. However, pharmacogenetics can, in the long haul, lead to a more cost-effective healthcare system. Several initiatives on reimbursement policies have recently shown that insurers are now beginning to move towards supporting pharmacogenetic integration into clinical practice.(87, 88) Researchers, diagnostic firms, and the regulatory authorities are still seeking to establish methodologies by which to judge the effectiveness of pharmacogenetic integration to clinical practice. The full application of pharmacogenetics into clinical practice will require dramatic changes in regulations, legislative protection for privacy and reimbursement policies. Several recent regulatory policies, providing guidelines for genomic data management, pharmacogenetic testing, and designing of adaptive clinical trials, have been implemented to support genomic and personalized medicine.(89–93)

Preconceived notion of genetic testing

There exist an acute lack of education of both the physicians and the patients regarding pharmacogenetics and personalized care. The current knowledge of healthcare professionals regarding pharmacogenetics is still low, and medical school curricula are only slowly including teaching of this subject in their courses.(94–96) Even when included, the depth of teaching may be limited.(97) Pharmacogenetic knowledge is rapidly developing and changing, and it is imperative that healthcare professionals keep abreast of the advances and clinical indications.

Unfortunately, many have perceived notions that toxicity such as neutropenia can be easily managed, especially with advances in supportive care such as granulocyte colony stimulating factors. The large number of chemotherapeutic options available also means that physicians are often spoilt for choice, and have a low threshold to consider alternative therapies when toxicity becomes unmanageable. The need to evaluate the genetic basis for side effects becomes less clinically relevant in such circumstances.

However, it is often forgotten that genetic testing does not only predict for treatment related toxicity or allow for dose adjustment, and that it also determines response or lack thereof. It

is frequently imperative that testing is done before treatment, as giving inappropriate treatment may result in an outcome poorer than the alternative. Patients who are EGFR wild types had a poorer outcome when treated with gefitinib.(12) A 'treat-and-see' approach has ethical and legal implications in this era where genetic testing is readily available, as it delays and even potentially deprives patients of appropriate treatment, and deterioration is often rapid without it.

CONCLUSION

With increasing knowledge and understanding of the human genome, the clinical relevance of pharmacogenetics in oncology will invariably improve, especially with more validation studies and lowering costs of testing. Several obstacles still exist before pharmacogenetics can be fully embraced, for institutions, clinicians and patients. As more genetic and somatic information become easily accessible and available, we will be one step closer to making personalized medicine a reality.

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Table 1

Examples of somatic predictors for response to anti-cancer drugs approved by the US FDA (Non-standard abbreviations: EGFR=epidermal growth factor receptor, PCR=polymerase chain reaction, HPLC=high performance liquid chromatography, FISH=fluorescent in situ hybridization, IHC=immunohistochemistry, MGMT=O^6-methylguanine–DNA methyltransferase, PDGFR=platelet derived growth factor receptor, ER=estrogen receptor, PR=progesterone receptor, HER2=Human epidermal growth factor receptor 2)

Target	Drugs	Tumours	Markers	Test	Significance
EGFR	Cetuximab Panitumumab	Colorectal	KRAS mutations at codon 12, 13, 61 and 146	Direct sequencing or commercial kits available eg DxS Therascreen KRAS mutation test kit (PCR)	Resistance(98)
			BRAF mutations at exon 11, 15, (V600E)	Direct sequencing or commercial kits available, eg DxS BRAF mutation test kit (PCR)	Resistance(98)
				IHC not commonly used to predict for response for cetuximab	Response(99)
	Cetuximab	Lung	EGFR gene copy number	FISH	Response(100)
EGFR	Gefitinib Erlotinib	Lung	EGFR mutations include exon 19 deletions, exon 18 (G719A/C/S), exon 21 (L858R, L861Q)	Direct sequencing, denaturing HPLC, length analysis, PCR-based assays such as Amplification Refractory Mutation System ARMS®	Response(12)
			Exon 20 mutations T790M and insertion		Resistance(12)
			EGFR gene copy number	FISH	Response(101)
CD20	Rituximab Ibritumomab tiuxetan	B cell Non Hodgkin's Lymphoma	CD 20	IHC	Response(102,103)
CD52	Alemtuzumab	Chronic Lymphocytic Leukemia	CD 52	IHC	Response(104)
MGMT	Temozolomide	Glioblastoma Multiforme	MGMT methylation	Methylation specific PCR	Response(39)
Bcl-abl, KIT, PDGFR	Imatinib	Gastrointestinal stromal tumor, Chronic Myeloid Leukemia(106)	CD 117	IHC	Response(105,107)
			KIT mutations	Direct sequencing, denaturing HPLC	
			Exon 11		Longer duration of response(107)
			Exon 9		Relative resistance(107)
			Exon 13, 17		Resistance(107)
			PDGFRA mutation		
			Exon 18(D842V)		Sensitive(107)
			Exon 12, 14		Resistance(107)

Target	Drugs	Tumours	Markers	Test	Significance
ER/PR	Tamoxifen Anastrozole Letrozole Exemestane Fulvestrant	Breast	ER/PR	IHC	Response(108)
HER2	Trastuzumab	Breast Stomach	HER2	IHC 3+/FISH	Response(109–111)
	Lapatinib	Breast			

Table 2

Examples of FDA approved predictive markers for toxicity in oncology. (Nonstandard abbreviations: DPYD=Dihydropyrimidine dehydrogenase, TPMT=Thiopurine methyltransferase, UGT=UDP-glucuronasyltransferase)

Drug	Germline markers	Single Nucleotide Polymorphisms	Tests	Toxicity	Risk of Developing Toxicity
5-Flurouracil (5-FU), capecitabine	DPYD	More than 40 different polymorphisms of DYPD reported, of which 17 mutations are found in patients with severe 5-FU toxicity. (112) Approximately 3–5% of the population is heterozygous and0.1% is homozygous for alleles with impaired DPYD function.(113) DPYD*2A most common polymorphism associated with decreased activity, ~1.8% in Caucasians and <1% in Asians(75,76)	Commercially available assays, including TheraGuide 5-FU	Severe diarrhea, Neutropenia Neurotoxicity	Up to two-thirds of patients who experienced treatment toxicity do not have a molecular basis for DPYD deficiency.(77) The sensitivity of DPYD*2A genotyping for overall toxicity was 5.5% with a positive predictive value of only 46%. Inclusion of additional DPYD variants improved prediction only marginally.(79)
6-Mercaptopurine (6-MP), thioguanine	TPMT	TPMT*2 (0.4%), TPMT*3A, (4.4%) TPMT*3C (0.2%) account for95% of low activity phenotype in Caucasians.(114) TPMT*3C most common in Asians (1–2.4%) (115)	Commercially available, including Prometheus	Increased risk for myelotoxicity, Higher incidence of etoposide-induced myeloid leukaemia.(116) Higher incidence of radiation-induced brain metastases.(117)	1 in 300 are homozygous variant, at risk of severe toxicity(114) 1 in 10 increased risk of toxicity due to heterozygous genotypes(114)
Irinotecan	UGT1A1	UGT1A1*28, most common variant in Caucasians, (~10%)(81) UGT1A1*6 most common variant in Asians (~15%)(82)	Commercially available Invader Assay FDA approved for the detection of UGT1A1*28	Neutropenia is the most common toxicity with Severe diarrhea is also associated but less so compared to neutropenia (117)	Homozygotes, as well as double heterozygotes (*6/*28) are associated with an increased risk of toxicity due to decreased clearance of SN-38.(82) Up to 35% of patients experience dose limiting toxicities.(82) Association for doses greater than 150mg/m^2 in patients homozygous for UGT1A1*28.(118) No association was seen at lower doses (100–125mg/m^2), which is the dose often used for weekly dosing. (118)
Nilotinib	UGT1A1	As above	As above	Hyperbilirubinemia	Not known to be glucuronidated by UGT1A1 Inherent low UGT1A1 activity and further inhibition by nilotinib increases rate of hyperbilirubinemia, though elevation is benign.(119)
Pazopanib	UGT1A1	As above	As above	Hyperbilirubinemia	Similar to nilotinib, elevation of bilirubin through competitive inhibition of UGT1A1 is benign.(120)