REVIEW

Use of pharmacogenetics for predicting cancer prognosis and treatment exposure, response and toxicity

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Cancer treatment is complicated because of a multitude of treatment options and little patient-specific information to help clinicians choose appropriate therapy. There are two genomes relevant in cancer treatment: the tumor (somatic) and the patient (germline). Together, these two genomes dictate treatment outcome through four processes: the somatic genome primarily determines tumor prognosis and response while the germline genome modulates treatment exposure and toxicity. In this review, we describe the influence of these genomes on treatment outcomes by highlighting examples of genetic variation that are predictors of each of these four factors, prognosis, response, toxicity and exposure, and discuss the translation and clinical implementation of each. Use of pre-treatment pharmacogenetic testing will someday enable clinicians to make individualized therapy decisions about aggressiveness, drug selection and dose, improving treatment outcomes for cancer patients.

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INTRODUCTION

Oncologists have a variety of pharmacological treatment options for many tumor types. Large clinical trials are useful for determining which drug is superior across the patient population, but tell us little about which drug is best for an individual. Within a population of treated patients, there is substantial variability in response to a given drug. The unpredictability of response leads to administration of ineffective therapy for some patients, which is associated with the following types of costs. Cancer treatment can be quite expensive, and ineffective therapy is a waste of financial resources. Also, the cost to the patient's quality of life from treatment-related toxicity is acceptable only if the tumor is responding. Finally, there is an opportunity cost of treating a patient with an ineffective drug and allowing the tumor to continue to grow, making it more difficult to control with future lines of therapy. These costs make it critical that we develop strategies for selecting optimal treatments for individual patients.

When devising a treatment plan for a patient there are two relevant genomes: that of the patient's germline and the cancer cells.¹ The tumor genome, referred to as the somatic genome, will mainly determine the features of the tumor such as its aggressiveness and sensitivity to treatment. The patient, or germline, genome primarily dictates how the body handles and reacts to the chosen treatment. In this review, we will discuss the influence of variability in the somatic and germline genome on prediction of prognosis, efficacy, exposure

and toxicity (Figure 1, Table 1). For each topic we will use specific pharmacogenetic examples to highlight key aspects of discovery and translation.

SOMATIC GENETICS

A healthy cell turns cancerous by losing its ability to appropriately regulate its replication. This initial genetic aberration can be a simple change in DNA sequence or a change that impacts an entire gene or chromosomal region. This malignant cell is the seed from which a tumor grows, and the genome of this cell is the founder somatic genome. Through repeated cellular replication this somatic genome acquires additional abnormalities.² Some of these acquired variants will further drive cancer progression, such as mutations in genes that are responsible for maintaining DNA replication fidelity or controlling metastatic spread.³ The initial and acquired aberrations determine the behavior of the primary tumor, its ability to metastasize and the treatment mechanisms that it will be sensitive to. Thus, prediction of tumor prognosis and response can be accomplished by understanding somatic genetics.

Prognostic predictors

Prediction of cancer outcome, or prognosis, is dependent on local tumor growth and distant tumor spread. It is not surprising that the hallmark prognostic factors used in cancer therapy are tumor size and

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Figure 1 Pharmacogenetic predictors of cancer treatment outcome. Tumor prognosis is partially determined by variation in both the somatic and germline genome, which dictate tumor behavior independent of treatment. The somatic genome also dictates tumor sensitivity to treatment, enabling prediction of efficacy. The germline genome dictates drug pharmacokinetics (absorption, distribution, metabolism, excretion (ADME)) that can indirectly determine efficacy and toxicity, or the germline genome can directly influence patient sensitivity to toxicity.

Table 1 Prediction of cancer outcomes using germline and somatic genetic variation

Outcome prediction	Genome	Genes	Treatment decision	Examples discussed
Prognosis	Somatic or germline	Oncogenes, tumor suppressors, DNA repair mechanisms, metastasis genes	Aggressiveness	Gene expression (breast cancer) <i>BRCA2</i> (ovarian cancer)
Exposure	Germline	Enzymes, transporters	Dose	<i>UGT1A1</i> (irinotecan and SN-38 exposure)
Efficacy	Somatic	Tumor drivers, drug targets	Drug	<i>BRAF V600E</i> (vemurafenib) <i>TSC1</i> (everolimus)
Toxicity	Germline	Drug targets, cellular response mechanisms, proteins relevant to toxicity mechanism	Drug	<i>TUBB2A</i> , <i>FGD4</i> , <i>FANCD2</i> (paclitaxel-induced peripheral neuropathy)

extent of metastasis at diagnosis.⁴ The aggressiveness with which a tumor will continue to spread is largely a consequence of somatic genetics. Understanding the genetic makeup of the tumor at diagnosis can tell us a lot about its aggressiveness and likely behavior in the future.

This information is clinically vital. Prognostic staging systems that utilize the above-mentioned clinical factors to dictate treatment aggressiveness exist for many tumor types. The addition of accurate genetic prognostic determinants to these staging systems will improve our ability to make appropriate decisions on treatment aggressiveness for individual patients. Patients with tumors with good prognosis can be treated less aggressively, or not at all, avoiding the secondary costs of unnecessary treatment. On the other hand, patients with tumors with poor prognosis can be treated aggressively, as the costs incurred are necessary to combat a dangerous disease. Somatic gene expression is one of the most widely used genetic tools for predicting cancer prognosis, particularly within breast cancer.

Breast cancer gene expression. Breast cancer treatment decisions are made by classification of tumors based on their expression of several receptors: estrogen, progesterone and HER2. An alternative system for classifying tumors into ‘intrinsic subtypes’ based on gene expression has been developed.⁵ The intrinsic subtypes, which are mostly concordant with receptor-based classification, have been demonstrated in independent patient populations to be predictive of disease recurrence,⁶ but gene expression analysis has not replaced receptor-based classification clinically.⁷

Two gene expression tools have been approved for use in the United States or Europe to help clinicians decide whether a patient should be offered chemotherapy after local therapy with surgery and/or radiation. The first tool is OncotypeDx (Genomic Health, Inc., Redwood City, CA, USA), which was developed for hormone-positive, node-negative patients⁸ but may also be useful in low-risk, node-positive patients.⁹ The OncotypeDx system gives clinicians a recurrence score (0–100), which is most often used clinically to

identify patients with low-risk ($RS < 18$) tumors, that can be treated with hormonal therapy alone. The ongoing TailorX study is collecting data to help clinicians make treatment decisions for intermediate risk patients ($11 \leq RS \leq 25$).¹⁰ The Mammaprint (Agendia, NV, Amsterdam, The Netherlands) system was designed and validated for prognostic classification of premenopausal, node-negative patients^{11,12} and has been applied to postmenopausal patients.¹³ Similar to OncotypeDx, clinical utility of Mammaprint continues to undergo investigation, notably in the prospective MINDACT study which is asking, among other things, what the best treatment approach is for the ~ 1 in 4 patients whose gene expression and clinical factors have discordant risk classification.¹⁴ Interestingly, despite the differences in the patients used for development and the genes included in each panel, the classification of patients using these three gene expression systems are pretty concordant.¹⁵

Efficacy predictors

It has long been recognized that some tumors are highly sensitive to specific treatments. However, because the cause of this sensitivity was not understood, efficacy prediction was unachievable. We now have the tools to identify the genetic aberrations present in a given tumor and it is apparent that in many cases tumors are highly sensitive to drugs that target the malignancy driver. The next revolution in cancer, which is currently underway, is to develop drugs that target the known oncogenic mutations and select treatments based on the genetic abnormalities present within a patient's tumor.

There are two principal pathways for this translational work. One is identifying the genetic biomarkers that confer tumor sensitivity to drugs currently in use and the other is to design drugs that specifically target oncogenic aberrations found in tumors. Either way, at the end of this process you have a drug that is highly effective in tumors that are known to possess a somatic biomarker that can be tested for before treatment initiation. Treatment individualization based on somatic biomarkers is being piloted at several cancer centers,^{16,17} but prospective validation of this approach is a major challenge.¹⁸ Eventually, this model could transform cancer treatment, enabling pre-treatment identification of patients who are likely to respond to a specific drug while sparing patients who are unlikely to respond.

Efficacy biomarker identification for existing drug. Everolimus, an inhibitor of the mammalian target of rapamycin, was first approved in 2009 for use in advanced kidney cancer. It has since been approved in limited treatment settings for a variety of tumor types, including pancreatic and breast cancer, and has been tested in a variety of other tumor types in clinical studies. Although some of these clinical studies failed to meet their efficacy end points, select patients experienced extremely impressive, durable responses.

Using samples collected from one of these studies, a group of investigators genotyped a metastatic bladder tumor from a patient who achieved a complete response that lasted > 2 years. Many somatic mutations were present, including a deletion in the *tuberous sclerosis 1* (*TSC1*) gene. Interestingly, *TSC1* results in constitutive activation of mammalian target of rapamycin¹⁹ and everolimus is used to treat tuberous sclerosis, a disease characterized by mutation in the *TSC1* gene.^{20,21} This intriguing finding led the investigators to screen more bladder tumors, and more *TSC1* mutations were found. They then screened 13 patients from the original clinical study and found that the 6 patients with *TSC1* mutations had superior time to response (4.1 vs 1.8 months; hazard ratio (HR) = 18.5 (2.1–162), $P = 0.001$) and remained on everolimus treatment longer (7.7 vs 2.0 months, $P = 0.004$).²² This is an

exemplary case of biomarker discovery for a drug currently in use that awaits prospective validation and translation to clinical practice.

Drug developed to target a known oncogenic mutation. It has long been recognized that the RAS–RAF pathway is a major driver of many cancer types, including melanoma.²³ This led to programs directed at finding chemical inhibitors of BRAF. One such program used a high-throughput screening approach and discovered vemurafenib, which was particularly selective for the most common activating mutation in BRAF (V600E).²⁴ A phase I study was initiated in BRAF-mutated metastatic melanoma, which had extraordinarily promising results in this previously very difficult to treat tumor type.²⁵ These results instigated an accelerated development program including a pivotal phase III trial that was closed early based on impressive interim results.²⁶ Vemurafenib was approved soon thereafter with a validated companion diagnostic able to detect BRAF V600E-mutant melanomas.²⁷

GERMLINE GENETICS

The patient's germline genome directs the processes functioning throughout the body by coding for the proteins involved. Thus, variability in the germline genome can have implications for any system operating within the patient. An inherited variant in a gene responsible for DNA replication fidelity or regulating cellular replication can predispose a patient to cancer, perhaps even a specific type.²⁸ Alternatively, germline variation in genes encoding enzymes or transporters can have consequences for the patients exposure to the drugs administered²⁹ or can influence a patient's sensitivity to the adverse effects of treatment. In this section, we describe the potential influence of germline variation on prediction of tumor prognosis, drug exposure or toxicity.

Prognostic predictors

Although most of the genetic determination of tumor prognosis takes place within the tumor genome, the patient genome can also have a role. It is widely accepted that many germline genetic loci contribute a small amount to the heritability of cancer,^{30,31} but it is unclear how many of these disease susceptibility loci have prognostic importance. The Cancer Genome Atlas (TCGA) is a large effort to categorize somatic mutation, expression, copy number and epigenetic modification within various tumor types.³² TCGA is also collecting germline DNA and limited outcome data, which enables researchers to look for associations between genetic variation and cancer prognosis.

TCGA has published their analyses of the first several tumor types including glioblastoma, ovarian, breast, lung and colorectal cancers.^{33–36} One interesting finding from the ovarian cancer analysis was a suggestion that patients carrying germline variants in the *BRCA1* or 2 gene had superior survival compared with patients who did not carry a mutation in either gene.³⁴ A more detailed analysis of this data confirmed specifically that patients who carried *BRCA2* mutations had superior overall and progression-free survival compared with other patients.³⁷ A large pooled analysis from Bolton *et al.*³⁸ reported that patients with *BRCA2* mutation have the best 5-year survival (52%) followed by *BRCA1* carriers (44%) and then non-carriers (36%).

There is also a possibility that germline genetics, through an influence on the tumor microenvironment, may influence tumor growth and metastasis. One intriguing line of research has identified several germline genes that may determine metastatic potential across cancer types: *SIPA1*,^{39–41} *BRD4*⁴² and *RRP1B*,^{43,44} possibly through

regulation of the Rap GTPase-activating protein SPA-1.⁴⁵ We are just now beginning to appreciate the influence of the tumor microenvironment on cancer progression, and we are a long way from fully understanding the role of host genetics on the behavior of the tumor *in vivo*.

Exposure predictors

The current chemotherapy treatment paradigm is to administer the dose that will maximize drug exposure, and hopefully treatment effectiveness, with an acceptable risk of toxicity. Unfortunately, most drugs have substantial interpatient pharmacokinetic (PK) variability.⁴⁶ For many drugs, the only factor that is incorporated into dosing decisions is patient size (body surface area (BSA), body weight, and so on).⁴⁷ Body size explains some of the PK variability⁴⁸ but the rest is a consequence of variability in absorption, metabolism, distribution and/or excretion (ADME) of the drug and metabolites.

For each drug there are several enzymes and transporters that carry out the ADME processes. The expression and activity of these enzymes and transporters are highly variable between patients, partially because of germline genetic variability. Germline variants in the coding region can change protein activity while variation outside of the coding region is more likely to influence protein expression.

Most pharmacogenetic association studies assess the relationship between variants and clinical outcomes; however, for variants in PK genes this indirect association is a consequence of a direct effect on drug exposure. Consequently, clinical implementation of these findings would typically be to modulate the patient's dosage in order to achieve optimal drug exposure.⁴⁹

There are many examples of germline variants that may influence patient exposure to a cancer agent.⁵⁰ In this section, we highlight one of the more well-established examples, the influence of germline polymorphisms on exposure to irinotecan and its active metabolite, SN-38.

UGT1A1 polymorphisms and irinotecan (SN-38) exposure. Irinotecan is used in colorectal cancer and is associated with severe diarrhea and neutropenia. Both the efficacy and toxicities of irinotecan are attributable to SN-38, which is formed when carboxylesterases bioactivate irinotecan. SN-38 is inactivated by glucuronidation via uridinediphosphate glucuronosyltransferase isoforms 1A1 (UGT1A1) and eliminated via biliary elimination, which is in part coordinated by the hepatic transporter OATP1B1 (*SLCO1B1*).

Transcription of UGT1A1 is variable among patients, partially due to germline variability in the promoter region. The number of thymine-adenine (TA) repeats in the TATA box is typically six but some patients have an additional dinucleotide repeat, known as TA₇ or UGT1A1*28, which diminishes glucuronidation activity.⁵¹ This led to investigations of whether patients carrying the *28 allele had differential exposure to SN-38. A small pilot study found, as anticipated, that the homozygous *28 patient had the highest ratio of SN-38/SN-38 glucuronide.⁵² Since these initial studies many groups have reported analyses in large populations of irinotecan treated patients, most of which have detected an increase in active SN-38 in patients who carry or are homozygous for the *28 allele.^{53–55} The influence on SN-38 exposure has also been extended to other UGT1A1 polymorphisms and haplotypes, and other UGT1A isoforms.^{56–59}

As SN-38 exposure determines efficacy and toxicity, low activity UGT1A1 polymorphisms are of potential clinical relevance.^{60,61} A relationship between UGT polymorphisms and irinotecan clinical

outcome has been replicated in many patient cohorts, as reviewed by Di Paolo *et al.*⁶² Thus, translation of this pharmacogenetic association into clinical practice is underway. As explained previously, because the polymorphism is a predictor of drug exposure, the appropriate clinical solution would be to modify the dose for patients carrying low activity variants. But what is the ideal dose for patients of a given genotype?

Several groups have carried out genotype-guided early-phase clinical studies. Three studies in Japanese patients are difficult to interpret due to differences in toxicity definition and genotype grouping, and an upper limit of approved dosage (150 mg m⁻²) (Table 2). Two studies suggested that homozygous *1 patients could tolerate doses beyond 150 mg m⁻² while *28 patients could not.^{63,64} However, a third study that excluded homozygous *28 patients reported that irinotecan could not be tolerated at 165 mg m⁻², and the recommended dose for *1 carriers was set at 150 mg m⁻².⁶⁵ On the basis of the results of these dose escalation studies, Okuyama *et al.* conducted a phase II study in which *28 homozygous patients would be started at 100 instead of 150 mg m⁻². Despite the dose decrease, the single UGT1A1*28 homozygous patient enrolled experienced grade 4 neutropenia.⁶⁶

Two UGT1A1 genotype-guided dose escalation studies have been carried out in European patients. The recommended dose for *1 homozygous patients was 370–390 mg m⁻² and for heterozygous patients 310–340 mg m⁻².^{67,68} Only Marcuello *et al.* enrolled *28 homozygous patients and recommended a dose of 130 mg m⁻². In a genotype-guided phase II study, Freyer *et al.*⁶⁹ were able to safely administer high-dose FOLFIRI, including irinotecan 260 mg m⁻², to patients who carried UGT1A1*1 and had favorable thymidylate synthase genotypes.

These studies point the way toward irinotecan dose individualization based on factors other than BSA, which itself explains little PK variability.⁷⁰ Beyond UGT1A1, there are many other enzymes and transporters involved in determining SN-38 exposure. Germline variation within and around these genes has also been evaluated for relationships with irinotecan PK and treatment outcome.^{71–74} In the future, pre-treatment pharmacogenetic analysis of multiple variants from these genes could enable clinicians to select appropriate doses for individual patients to target an optimal exposure of SN-38 that will achieve the greatest clinical benefit with acceptable risk of toxicity.

Toxicity predictors

Clinical factors, such as impaired liver function or drug interactions, influence a patient's likelihood of experiencing toxicity by affecting drug exposure, similar to that described in the previous section. Alternatively, at equivalent exposure some patients are highly sensitive to the adverse effects of certain treatments. In this section, we will discuss the influence of germline genetics on sensitivity to drug toxicity. As we know much less about pharmacology and pharmacodynamics than we do about PK, our understanding of the genetic predictors of toxicity lags far behind that of the genetic predictors of exposure previously discussed.

Sensitivity to toxicity could be a consequence of several biological processes. Cells that have high expression of a drug target or rely on that target for cellular homeostasis could be exquisitely sensitive to that drug. Alternatively, cells that are unable to mount the appropriate response to a stimulus, such as DNA damage, could be highly sensitive to chemotherapy that induces that stimulus. A third possibility, which exists not on the cellular but on the physiological scale, is the possibility that some patients have an underlying condition that mimics the toxicity, which is aggravated by the drug.

Table 2 Genotype-guided irinotecan dose escalation studies

Author and year	Country	Concomitant treatment	Infusion time and schedule	Definition of dose limiting toxicity	Genotype group	N	Dosing (mg m ⁻²)		TTAEs at final dose level (no. of patients with TTAE/no. of patients treated at dose)	Recommended dose
							Start	Final		
Hazama, 2010 ⁶³	Japan	Doxifluridine (5'-DFUR)	2 h Q2W	G3 toxicity	*1/*1	18	70	150	Neutropenia (1/6)	> 150 ^a
					*1/*28	9	70	100	Diarrhea, neutropenia, leucopenia, nausea, vomiting (3/3)	70
Satoh, 2011 ⁶⁴	Japan	None	1.5 h Q2W	G4 hematological or G3 diarrhea	*1/*1	41	150	150	Anorexia, fatigue (1/40)	> 150 ^a
					*1/(^a *28 or ^a *6)	20	100	150	None (0/16)	> 150 ^a
					(^a *28 or ^a *6)/(^a *28 or ^a *6)	21	75	150	Neutropenia, diarrhea (6/15)	150
Sunakawa, 2012 ⁶⁵	Japan	FOLFOXIRI	2 h Q2W	G4 hematological or G3 nonhematological	*1/(^a *1 or ^a *6 or ^a *28)	10	165	165	Neutropenia, infection (2/4)	150
Toffoli, 2010 ⁶⁸	Italy	FOLFIRI	2 h Q2W	G4 hematological or G3 nonhematological	*1/*1	35	215	420	Anorexia, asthenia, diarrhea (2/3)	370
					*1/*28	24	215	370	Neutropenia, leucopenia, asthenia (2/4)	310
Marcuello, 2011 ⁶⁷	Spain	FOLFIRI	2 h Q2W	G4 hematological or G3 nonhematological	*1/*1	42	180	450	Diarrhea, vomiting, asthenia (2/5)	390
					*1/*28	38	110	390	Neutropenia, asthenia (2/2)	340
					*28/*28	14	90	150	Neutropenia, asthenia, constipation (2/5)	130

Abbreviations: FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, irinotecan; Q2W, every 2 weeks; G3, grade 3 or higher; G4, grade 4 or higher; TTAE, treatment terminating adverse event.

^aRecommended dose not reached due to dosing restriction limiting dose to 150 mg m⁻².

Germline variation could be the underlying cause of any these mechanisms of sensitivity. Regardless of the mechanism, a patient that carried a sensitizing germline variant would not be able to tolerate the dose required for treatment efficacy. Thus, clinical implementation of a germline polymorphism that sensitizes a patient to toxicity is likely to be selection of an alternative treatment agent. In this section, we highlight examples of these three mechanisms of toxicity sensitivity in the context of paclitaxel-induced peripheral neuropathy (PIPN).

Paclitaxel-induced peripheral neuropathy. Peripheral neuropathy is an adverse event commonly associated with treatment from microtubule targeting agents including taxanes and vincas.⁷⁵ The taxanes, including the particularly neuropathic paclitaxel, work by binding to the microtubule β -tubulin subunit, causing microtubule stability and cellular apoptosis.⁷⁶ The exact mechanism of PIPN is unclear, but may be related to the role of microtubules in neuronal axon guidance and development.⁷⁷ PIPN manifests as parasthesia in the hands and feet, which can progress in severity with continued treatment. As neuropathy is common, debilitating and necessitates treatment discontinuation, prediction of PIPN sensitivity is of great interest to clinicians.

Expression of drug target. β -Tubulin, the paclitaxel target, exists in multiple isoforms that are differentially expressed throughout the body. β -Tubulin has garnered some interest as a possible somatic marker of tumor sensitivity, however, somatic variation within the *TUBB* genes is exceedingly rare and the reported findings are likely due to genotyping errors.⁷⁸ Several β -tubulin isoforms are expressed in peripheral neurons, the likely site of action causing peripheral

neurotoxicity. Leandro-Garcia *et al.* recently reported an analysis of germline variants within the *TUBB2A* promoter, which encodes the neuronally expressed β -tubulin class IIa isotype. They reported an association with a promoter single-nucleotide polymorphism (-112A>G, rs909965), increased gene transcription and protection from PIPN.⁷⁹

Inadequate stimulus response. Pharmacological understanding aside from the mechanism of action may provide hypotheses for investigating cellular sensitivity. As an example, Sucheston *et al.* looked specifically at the genes encoding two proteins involved in DNA repair, *BRCA1* and *FANCD2*. The investigators selected tag single-nucleotide polymorphisms within each gene to assess as much of the existing genetic variability as possible. Although there were no associations with *BRCA1*, the authors reported significant associations with neuropathy risk and single-nucleotide polymorphisms and haplotypes within *FANCD2*.⁸⁰ This same strategy could be applied to other known mechanisms of cellular response to chemotherapeutic agents.

Underlying pathophysiology. Peripheral neuropathy is not only a treatment-related adverse effect; it is a condition that afflicts healthy people that can be hereditarily acquired. Charcot-Marie-Tooth disease is a familial neuropathy condition that has many subtypes, some of which have causative germline variants that have been discovered. Charcot-Marie-Tooth Disease Type 4H is caused by a variant in the *FGD4* gene, which encodes FGD1-related F-actin-binding protein (Frabin).⁸¹ Patients with other variants in *FGD4*, or proteins that interact with FGD4, are likely to have subclinical

neuropathy or extreme sensitivity to chemotherapy-induced neuropathy. A recent genome-wide association study of PIPN discovered an association between an *FGD4* polymorphism (rs10771973) and increased neuropathy risk in 855 Caucasian patients ($HR=1.57$ (1.13–3.28), $P=2.6 \times 10^{-6}$), and then replicated the association in two smaller cohorts of Caucasian ($HR=1.72$ (1.06–2.80), $P=0.013$) and African-American ($HR=1.93$ (1.13–3.28), $P=6.7 \times 10^{-3}$) patients. It is likely that variants in other genes known to be involved in familial neuropathy conditions also influence patient sensitivity to peripheral neuropathy.

CONCLUSION

The mapping and understanding of the human genome has been a major boon for cancer research. Both the somatic and germline genome can inform treatment decisions. The somatic genome can assist in predicting the tumor's behavior if untreated (prognosis) or treated (efficacy prediction). The germline genome can also influence prognosis and is involved in determining drug exposure and toxicity. The clinical implementation of these pharmacogenetic factors depends on which system they influence. Prognostic factors can be useful in deciding treatment aggressiveness; toxicity and efficacy predictors can be helpful in selecting the appropriate drug for the patient/tumor; and exposure predictors may inform dosage selection. Continued progress in our discovery and translation of these pharmacogenetic factors will someday enable integration of germline and somatic genetic information into individualized treatment decision making for cancer patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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