CHAPTER

5

Pharmacogenomics in Cancer Therapeutics

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OUTLINE

INTRODUCTION

Cancer is a multifactorial disease driven by genetic alteration in the somatic genome of the malignant cell. Subsequent proliferation, with or without additional genetic and/or epigenetic alterations that could further distort the genetic content of malignant cells, eventually leads to disruption of cellular machinery and signaling, and unregulated proliferation. These genetic alterations not only represent divergence from the original germline sequence, they also play a major role in determining the aggressiveness of the tumor, and more importantly, its resistance or sensitivity to specific therapy. Therefore, identifying somatic mutations that drive genetic alteration(s) is critical in assessing and predicting disease prognosis and treatment response.

Our expanding knowledge of the molecular characteristics of different tumors [1] over the past two decades has enabled a paradigm shift in anticancer drug development from the nonselective cytotoxic agents of the past to targeted therapies that are designed to ameliorate specific molecular and/or oncogenic abnormalities [2,3]. Most of these targeted drugs are

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TABLE 5.1 Selected Genetic Variants Affecting Treatment Outcomes in Lung Cancer

Genes	Allelic Variants	Treatment Phenotype Association
EGFR	Constitutive activating mutations of tyrosine kinase-binding domain within exons 18 to 21 of *EGFR*	Patients harboring the gain-of-function mutation have better clinical response to tyrosine-kinase inhibitors
ALK	Translocation of *EML4* (2p21) and *ALK* (2p23) results in the *EML4-ALK* fusion-type tyrosine kinase	Patients with *ALK* rearrangement show better response to ALK inhibitors
KRAS	Constitutive activation mutations of the RAS signaling pathway, primarily in codons 12 and 13 of exon 2 of *EGFR*	Limited data suggesting *KRAS* mutation as a negative predictive biomarker to tyrosine-kinase inhibitors

codeveloped with their associated predictive companion diagnostic tests, which usually empower clinicians to identify patients suitable for a given drug targeting tumor-specific genetic alteration, in contrast to empirically selecting cytotoxic agents solely based on cancer tissue of origin. Although targeted cancer therapy often focuses on somatically mutated genes, it should be noted that germline genetic variation associated with increased risk of cancer in carriers of mutated genes (e.g., mutations in tumor suppressor genes breast cancer 1 [*BRCA1*] and *breast cancer 2 [BRCA2]*) or altered drug sensitivity may also influence disease outcome and/or treatment responses.

In general, cancer biomarkers can be categorized as prognostic (associated with disease outcome) and predictive (associated with response to anticancer drug treatment). As a scientific discipline, pharmacogenomics evaluates genetic determinants of drug-response variability. For application within the field of oncology, pharmacogenomics should then be viewed as a clinical tool or scientific means to utilize the knowledge of the unique genetic makeup of the patient and his/her cancer, not only for identification of likely responders to specific targeted therapies but also to increase the overall clinical success rates. In this brief chapter, an overview of the role of cancer genomics and pharmacogenomics in precision oncology therapeutics, highlighting specific key examples, will be presented.

Therapy for Non-small-Cell Lung Cancer

Non-small-cell lung cancer is the most common type of lung cancer with several histological subtypes including adenocarcinoma, large-cell carcinoma, and squamous-cell carcinoma. The two most common mutated genes in patients with non-small-cell lung cancer are epidermal growth factor receptor (*EGFR*, *HER1*, or *c-ErbB-1*) and anaplastic lymphoma kinase (*ALK*), which usually occurs as a fusion product with another gene: echinoderm microtubule-associated protein-like 4 (*EML4*).

Activating *EGFR* mutation initiates a cascade of downstream EGFR signal transduction, increased tyrosine kinase activity, and cell proliferation (Table 5.1). In general, small molecule inhibitors of tyrosine kinase of EGFR (e.g., gefitinib, erlotinib) have shown significant activity in patients whose tumors harbor activating *EGFR* mutations [4]. The historical observation of limited clinical activity of gefitinib in a small subset of lung cancer and subsequent demonstration of significant response in lung cancer patients with somatic mutations in *EGFR* is described in more details in Chapter 3. Since that era of initial tyrosine kinase inhibitors, additional small molecules with more refined tyrosine kinase inhibition, e.g., afatinib and osimertinib, have been evaluated and approved.

The *EML4-ALK* fusion product is a mutation commonly found in about 4%–5% of non-small-cell lung cancer tumors (Table 5.1).

Activating mutations result in uncontrolled cell growth and differentiation as well as apoptosis inhibition [5]. In addition to being a positive predictive biomarker for tumor response in non-small-cell lung cancer patients harboring the mutation, *ALK* rearrangements are almost mutually exclusive with *EGFR* mutations, and limited data have suggested an association between *ALK* rearrangements and resistance to EGFR tyrosine kinase inhibitors [6]. Therefore, in contrast to patients with *EGFR* mutations who are typically treated with tyrosine kinase inhibitors, patients with *ALK* mutations are treated with specific ALK inhibitors. Crizotinib, ceritinib, and alectinib are examples of a rapidly expanding class of ALK inhibitors approved by the Food and Drug Administration (FDA) since 2011 [7].

Therapy for Chronic Myeloid Leukemia

Imatinib is another early example of the paradigm change in oncologic drug development for chronic myeloid leukemia. Imatinib competitively blocks the adenosine triphosphate (ATP)-binding site of B cell receptor–Abelson murine leukemia viral oncogene homolog (Bcr-Abl) kinase, which is the constitutively active product of *Bcr-Abl* fusion gene associated with the well-recognized Philadelphia translocation [8]. After its approval in 2002, it soon became apparent that imatinib therapy is associated with primary and secondary resistance in about one-third of the patients receiving the drug. Primary resistance occurs because of low systemic exposure that could be related to interindividual differences in activity of the organic cation transporter 1 that mediates imatinib influx into the leukemic cells [9]. The effect of polymorphism in the gene encoding the organic cation transporter 1 is also described in Chapter 3.

As importantly, secondary resistance to imatinib commonly occurs and is primarily related to acquired Bcr-Abl kinase domain mutations (e.g., D816V, two codon duplication in exon 9), leading to decreased drug sensitivity. Nevertheless, such resistance can be overcome by using higher doses of imatinib [10]. Therefore, testing for the mutational status can help in imatinib-dose optimization or determination of suitable patients for imatinib therapy [11]. Since the initial approval and experience with imatinib, newer Bcr-Abl tyrosine kinase inhibitors have been developed and include bosutinib, dasatinib, nilotinib, and ponatinib [12].

Therapy for Breast Cancer

The human epidermal growth factor receptor 2 (HER2/neu or ErbB-2) has been used as a biomarker for patient stratification in treatment of breast cancer. HER2 overexpression occurs in 15%–22% of breast cancers, and elevated level of HER2 is associated with a more-aggressive tumor type and adverse clinical outcome (poor prognosis and shorter survival) [13,14]. Trastuzumab is the first humanized monoclonal antibody developed and approved to target HER2. Clinical efficacy of trastuzumab in HER2-positive breast cancer was shown both as monotherapy and in combination with other anticancer drugs including paclitaxel and docetaxel [15–17]. In addition, clinical trial data showed that the treatment outcomes were positively correlated with the extent of HER2 overexpression. To avoid unnecessary toxicities in patients who would not benefit from the therapeutic benefits of the drug, use of trastuzumab is restricted to those who overexpress HER2, the level of which can be determined with a number of companion diagnostic tests (e.g., INFORM HER2 dual ISH DNA Probe Cocktail) [18,19] approved by the FDA. Clinical guidelines provided by professional organizations also endorse the testing of HER2 status [20,21]. Over the years, several other drugs that target HER2, e.g., ado-trastuzumab emtansine, lapatinib, and pertuzumab, have also been approved along with their companion diagnostic tests [22].

In addition to HER2, the estrogen receptor as a driver for breast tumor growth, serves as the pharmacological target for antiestrogenic compounds such as tamoxifen. The use of tamoxifen for patients with estrogen positive breast cancer is associated with up to 50% reduction in disease recurrence and 30% decrease in mortality. However, significant interindividual differences in tamoxifen response exist, which is at least partially related to variable extent of drug metabolism in tamoxifen-treated patients. Tamoxifen is extensively metabolized by multiple cytochrome P450 isoenzymes, including cytochrome P450 2D6 (CYP2D6), to two active metabolites: 4-hydroxy-tamoxifen and endoxifen [23,24]. The activity of CYP2D6, and hence the amount of endoxifen formed, can be modulated by *CYP2D6* polymorphism and/or concurrent administration of CYP2D6 inhibitors such as selective serotonin reuptake inhibitors [25–27].

Despite altered response rate and increased risk of cancer recurrence in CYP2D6 poor metabolizers [28], conflicting data from studies evaluating association between tamoxifen response and *CYP2D6* status have put a damper on the potential use of CYP2D6 genotyping to guide tamoxifen therapy [29,30]. Thus, the current FDA-approved tamoxifen label does not include a recommendation for *CYP2D6* testing. Although the current evidence does not support routine clinical testing, the study results of Irvin et al. and Kiyotani et al. suggest an increased tamoxifen dose could be an effective way to maintain an effective endoxifen concentration in patients who are carriers of decreased function or null alleles of *CYP2D6* [31,32]. Additional approach to provide further insight regarding *CYP2D6* genotyping for tamoxifen response was recently provided in a prospective clinical trial by Zembutsu et al. The investigators reported that the expression of a proliferation biomarker Ki-67 protein [33] was significantly associated with estrogen receptor expression level, and changes in Ki-67 expression could be potentially a useful surrogate biomarker for tamoxifen efficacy [34].

Therapy for Metastatic Colorectal Cancer

Over the years, molecular biomarkers have been identified that could provide both prognostic and predictive information to clinicians treating patients with colorectal cancer. Examples of these biomarkers include EGFR, v-ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), microsatellite instability, and thymidylate synthase (Table 5.2).

TABLE 5.2 Selected Genetic Variants Affecting Treatment Outcomes in Colorectal Cancer

Genes	Allelic Variants	Treatment Phenotype Association
KRAS	Constitutive activation mutations of the RAS signaling pathway, primarily in codons 12 and 13 of exon 2 of *EGFR*	Lack of response to anti-EGFR monoclonal antibodies in patients with KRAS mutation
Mismatch repair (MMR) genes	*MLH1, MSH2, MSH6, PMS1, PMS2*	Proficient MMR- or low MSI-status predicts response to 5-FU
TYMS	*TSER*2, TSER*3G, TSER*3C*	Homozygous carriers more likely to experience 5-FU toxicity
DYPD	*DYPD*2A*	Limited data on association between SNP with decreased DPD activity and 5-FU toxicity
UGT1A1	*UGT1A1*28, UGT1A1*6*	Homozygous carriers of either variant more likely to experience neutropenia and diarrhea with irinotecan treatment

Increased expression of EGFR has long been suggested to be a prognostic marker for a wide range of cancers, including colorectal cancer. The high expression is associated with poor clinical outcome and anti-EGFR monoclonal antibodies (e.g., cetuximab, panitumumab) had been investigated [35–38] and approved as targeted therapies for treatment of colorectal cancer since 2004. Nevertheless, EGFR-based drug regimens are only effective in a subset of patients that are related to the mutational status of the *KRAS* gene, a downstream conductor of *EGFR* signaling. *KRAS* mutations (in codon 12 and 13) are observed in approximately 30%–40% of colorectal cancer patients in the United States and act as an important prognostic biomarker [39]. More importantly, *KRAS* mutations allow tumor escape from EGFR regulation, and are predictive of resistance to cetuximab or panitumumab therapy [40,41]. To exclude patients who are not likely candidates to receive anti-EGFR monoclonal antibodies, testing for *KRAS* mutations are needed before starting therapy with cetuximab and panitumumab [42,43].

The antimetabolite 5-fluorouracil (5-FU) is commonly used in the treatment of advanced colorectal cancer. Microsatellite instability (MSI) associated with mismatch repair (MMR) genes (*MLH1, MSH2, MSH6, PMS1, or PMS2*) account for 15%–20% of sporadic colorectal cancer. Tumors with a *MMR* mutation have an absence of MMR protein expression, which, when coupled with high MSI, have been shown to be predictive biomarkers of decreased benefit from 5-FU-based chemotherapy in patients with Stage II and III disease [44–47].

In addition, thymidylate synthase is a folate-dependent enzyme and the inhibitory target of 5-FU. Polymorphisms in *TYMS*, the gene that encodes thymidylate synthase, have also been evaluated. Tandem repeat variants at the promoter enhancer region (TSER) (rs34743033) results in *TSER**2* (two copies of the 28-base pair tandem repeat [2R]) with low enzyme expression and *TSER**3* (three copies of the 28-base pair tandem repeat [3R]) with enzyme expression approximately 2.6× that of *TSER**2*. In addition, a G>C single-nucleotide polymorphisms (SNP) within the second repeat of *TSER**3* is associated with altered *TS* transcription [48]. Overexpression of thymidylate synthase has been linked to 5-FU resistance due to higher in vivo tumor thymidylate synthase activity [49,50] and thymidylate synthase SNPs have been associated with increased 5-FU toxicities in different populations [51,52]. Despite the attractiveness of *TSER* genotyping to better predict response to 5-FU-based regimen, current literature does not appear to provide sufficient evidence for measuring TYMS levels in tumors [53].

The enzyme dihydropyrimidine dehydrogenase (DYPD) mediates the metabolism of 5-FU, and genetic polymorphisms in the *DYPD* gene encoding DYPD result in DYPD-deficient phenotypes with an overall frequency of about 3%–5%. Of all known SNPs associated with grade 3- and grade 4-toxicities in 5-FU treated patients, the G>A point mutation within intron 14 (c.IVS14+1G>A, also known as rs3918290, or c.1905+1G>A) associated with the *DYPD**2A* allele results in a protein with no catalytic activity [54]. Homozygous and heterozygous carriers of this common variant allele of *DYPD* have a complete absence of and 50% reduced DYPD activity, respectively, resulting in significant and sometimes life-threatening 5-FU-related toxicities [55,56].

Additional Biomarkers for Drug Toxicity

Other than DYPD, additional germline mutations that have been shown to impact anticancer drug toxicities include thiopurine-S-methyl transferase and uridine-diphosphate glucuronosyltransferase. The pharmacogenetic relevance of these two Phase II metabolic enzymes is discussed in the first chapter and summarized in Table 5.3 of this chapter. Although genotyping for the uridine-diphosphate

TABLE 5.3 Genetic Variants in Drug Metabolizing Enzymes Affecting Toxicity Responses

Genes	Impact on Drug Exposure	Treatment Phenotype Association
DYPD	Increased level of 5-FU in carriers of *DYPD*2A*	Increased risk of neurological toxicities, grade 3 diarrhea, and possibly hand–foot syndrome
TPMT	Increased level of 6-MP in homozygous and heterozygous carriers of *TPMT* variants	Increased hematological toxicities in homozygote and heterozygote, requiring dosage reduction as recommended in clinical guidelines
UGT1A1	Significant increase in SN-38 concentrations in carriers of *UGT1A1*28* and treated with irinotecan	Homozygous carriers more likely to experience severe neutropenia and diarrhea with irinotecan treatment

glucuronosyltransferase 1A1*28 allele (*UGT1A1*28*) are not currently considered routine, clinical data do suggest the need for irinotecan-dose reduction to decrease the risk of severe diarrhea and neutropenia in patients who are homozygous carriers of the *28 allele. In contrast, thiopurine-S-methyl transferase is currently the only drug-metabolizing enzyme with widespread acceptance for genotyping and availability of clinical guideline through the Clinical Pharmacogenetics Implementation Consortium [57,58]. On the other hand, although thiopurine-S-methyl transferase gene variants have been reported to be associated with a higher risk of cisplatin-related ototoxicity, there is currently no recommendation for thiopurine-S-methyl transferase genotyping in cisplatin-treated patients.

The Path Forward for Implementation of Precision Oncology

At present, identification of patients who harbor *ALK* or *EFGR* mutations are included in current clinical guidelines and accepted as standard procedure for precision oncology practice in managing patients with non-small-cell lung cancer. However, the works by Chen et al. and Iorio et al. [59,60] are an indication that, through systematic expansion of our knowledge regarding cancer genomes, we will have additional insight about potential new biomarkers, therapeutic targets, and treatment options. Nevertheless, despite significant success of targeted therapies for management of several types of cancer (some of which are briefly reviewed in this chapter), similar progress has not been experienced in other areas of medical oncology.

In addition to continued effort to expand a well-supported and rigorous database of drug–target interactions [60], other potential barriers need to be addressed before large-scale adoption of implementation includes widespread availability of genomic and clinical data [61], and the need of different clinical trial designs to address genomics-based investigations [62–66]. In addition, viable infrastructure is needed to support the additional bioinformatics and laboratory resources deemed necessary for such refined clinical trials, along with practical assistance for practicing clinicians in using the abundant and complex information, and integration of validated bioinformatics tools and data platform into existing workflow.

In a way that is analogous to the concept of a medical consult service, molecular tumor boards and oncology practice models have been initiated at different cancer centers and academic institutions to assist in clinical decision and patient management. Experiences with these programmatic supports have been published in the literature [67–70]. A decision-support framework for genomics-guided cancer therapy has recently been developed to provide assistance for clinicians to make decisions in practicing precision oncology [71,72]. Further refinement of these two approaches and maybe even their integration with one another would enable clinicians to

benefit from both peer sharing of expertise and onsite support with fully incorporated bioinformatics for clinical decision-making.

Nevertheless, similar to implementation barriers in other medical specialties (discussed in Chapter 4, the major challenge lies with additional in-depth knowledge of tumor biology, and the level of evidence deemed necessary before any specific biomarker is considered "actionable" and subsequently utilized on a large scale. These challenges are "tied" to each other in that defining the functional significance of variant alleles pave the way to establishing the minimal level of evidence acceptable to all stakeholders, which would impact patient selection both for clinical trials and personalized treatment plan in practice. Clinical utility and practical implementation of precision oncology will also likely be shaped by future results from ongoing trials such as the National Cancer Institute-Molecular Analysis for Therapy Choice (ClinicalTrials.gov Identifier: NCT02465060), and the National Cancer Institute-Children's Oncology Group Pediatric Molecular Analysis for Therapy Choice (ClinicalTrials.gov Identifier: NCT03155620) [73].

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