Clinical Implications of the Cancer Genome

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Terms in [blue](#) are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Cancer is a disease of the genome. Most tumors harbor a constellation of structural genomic alterations that may dictate their clinical behavior and treatment response. Whereas elucidating the nature and importance of these genomic alterations has been the goal of cancer biologists for several decades, ongoing global genome characterization efforts are revolutionizing both tumor biology and the optimal paradigm for cancer treatment at an unprecedented scope. The pace of advance has been empowered, in large part, through disruptive technological innovations that render complete cancer genome characterization feasible on a large scale. This article highlights cardinal biologic and clinical insights gleaned from systematic cancer genome characterization. We also discuss how the convergence of cancer genome biology, technology, and targeted therapeutics articulates a cohesive framework for the advent of personalized cancer medicine.

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INTRODUCTION

The idea that cancer results from a deranged genome originated in 1914, when the German cytologist Boveri¹ first proposed that chromosomal defects might cause a cell to proliferate abnormally. Although this premise now seems self-evident, during the ensuing decades, an equally intense interest accumulated around the notion that cancer was primarily caused by viruses. Indeed, viral etiology stood as a prominent hypothesis when Bishop and Varmus² set out to study the *src* sequences present within the Rous Sarcoma Virus genome that transferred malignant properties to normal avian cells. When these future Nobel laureates queried *src* within avian cells rendered malignant by Rous Sarcoma Virus infection, they made the pivotal and unexpected discovery that *src* sequences were already present in the normal avian genome—even in uninfected chicken cells.² This observation gave birth to the revolutionary notion that cancer might arise from the altered function of normal cellular genes.

The subsequent recognition by many groups that most viral cancer-causing genes (oncogenes) were in fact variants of normal cellular genes (or proto-oncogenes) suggested that mutation of the genome—either sporadic or induced by carcinogens, radiation, and so on—might provide a mechanism through which the tumor-promoting function of proto-oncogenes could be unleashed. The definitive evidence for human oncogenes as mutated versions of normal cellular genes came

from studies of the *HRAS* gene in bladder cancer. Here, DNA transfer studies clearly showed that *HRAS* derived from human bladder cancer cells functioned as an oncogene, whereas *HRAS* from nontransformed bladder cells did not.³ Elegant genetic and DNA sequencing experiments led to the discovery that a single somatic nucleotide change at codon 12 provided the basis for *HRAS* oncogenicity.⁴ With this landmark finding, the genomic basis of cancer became firmly established.

CATEGORIES OF TUMOR GENOMIC ALTERATIONS

Work spanning the next decade elaborated several major classes of genomic alterations that give rise to cancer (Fig 1). The RAS oncogene family (*HRAS*, *KRAS*, and *NRAS*) became the exemplar of nucleotide substitutions (or base mutations) that generate somatically altered proteins. Base mutations may aberrantly activate the corresponding proteins (as occurs with many oncogenes) or result in a loss of protein expression or function, which is typical of many tumor suppressor genes.

The longstanding recognition that cancers frequently harbor chromosomal derangements visible through karyotype analysis prompted the concomitant discovery of additional categories of tumor genomic alterations. The minute chromosome, which was subsequently termed the Philadelphia chromosome and is invariably present in chronic myelogenous leukemia cells,⁵ was the first consistent

Fig 1. The major classes of genomic alterations that give rise to cancer. TS, tumor suppressor; CML, chronic myelogenous leukemia.

chromosomal abnormality described in any malignancy. Rowley⁶ later found that the Philadelphia chromosome consisted of a translocation between the long arms of chromosomes 9 and 22. *ABL1*, which had previously been identified as a viral oncogene, was ultimately identified as the critical gene activated by the 9;22 translocation.⁷ Thus, chromosomal translocations (or DNA rearrangements) became recognized as an additional major class of genomic events. These events cause cancer through dysregulation of normal genes or generation of novel chimeric genes (gene fusions) that direct the development and/or maintenance of the malignant state.

By 1982, base mutation and chromosomal rearrangement were established as key genetic mechanisms capable of driving cancer. During that same year, *MYC* was identified as the cellular homolog of another viral oncogene (*v-myc*, an operant in avian myelocytomatosis virus)⁸ and was shown to be targeted by a chromosomal translocation observed in Burkitt's lymphomas.⁹ However, translocation was not the only method by which *MYC* could undergo oncogenic deregulation; this oncogene (as well as its homolog *NMYC*) was also found to undergo high-level gene amplification in several cancer types.¹⁰⁻¹⁴ Genomic amplifications and copy gains, therefore, became recognized as additional cardinal mechanisms of cancer gene deregulation.

Studies of a rare type of cancer, retinoblastoma, led to the discovery of the first tumor suppressor gene, *RB1*. The two-hit hypothesis of tumor suppressor genes originated from an observation by Knudson¹⁵ that the onset of retinoblastoma followed second-order kinetics, implying that two independent genetic events were necessary. This phenotype was consistent with a single recessive gene that required mutations in both alleles. According to the two-hit hypothesis, the first

event is typically viewed as a point mutation that inactivates one copy of a tumor suppressor gene; the second hit involves a deletion within the other chromosome that eliminates the remaining wild-type allele. Another important variation of the two-hit hypothesis involves focal deletion of a tumor suppressor locus followed by loss of the remaining allele; this results in a complete or homozygous deletion of the relevant gene(s). Tumor suppressor genes, such as *CDKN2A* and *PTEN*, are commonly affected by homozygous deletion. Thus, chromosomal deletions resulting in complete or partial genomic loss comprised another prominent mechanism contributing to tumorigenesis and progression.

In summary, three fundamental categories of cancer genomic aberrations—base mutation, copy number alteration (gain or loss), and translocation/rearrangement—had been discovered by the mid-1980s. Epigenetic modifications of genomic DNA or histones by methylation, acetylation, and other mechanisms also became recognized as key mediators of the cancer phenotype.¹⁶ Knowledge of cancer genes perturbed by hallmark structural genomic changes continued to accumulate steadily. However, genome-scale approaches to identify recurrently mutated cancer genes required a revolution in technology and analytic capacity that began during the 1990s and has continued unabated to the present day.

BIOLOGIC IMPACT OF COMPREHENSIVE CANCER GENOME CHARACTERIZATION

The human genome era heralded a fundamental shift toward global views of genomes and transcriptomes in human biology and disease;

Molecular alterations in cancer	Initial high-throughput technology	Emerging technology
DNA <ul style="list-style-type: none"> Chromosomal aberrations <ul style="list-style-type: none"> Copy number gains or losses Loss of heterozygosity Rearrangements, fusion genes Epigenetic modifications Point mutations, substitutions, deletions 	DNA microarray DNA microarray Candidate gene approach, FISH Bisulphite sequencing, methyl-specific PCR Capillary sequencing	Massively parallel sequencing
RNA <ul style="list-style-type: none"> Altered transcript expression levels Altered allele-specific expression Differential alternative splicing 	RNA microarray RNA microarray RNA microarray	

Fig 2. Interrogating molecular alterations in cancer. Genomic alterations that give rise to cancers occur at both the RNA and DNA level. Interrogation of the many types of changes and consequent pathway dysregulation has been restricted to date, in part as a result of limiting technologies. Massively parallel sequencing is one emerging technology that enables the myriad cancer-causing alterations to be interrogated on a tumor-by-tumor basis. FISH, fluorescent in situ hybridization; PCR, polymerase chain reaction.

the shift was made possible by increasingly powerful experimental and analytic methodologies (Fig 2). By the late 1990s, oligonucleotide microarrays and high-throughput DNA sequencing began to provide unprecedented insights across entire cancer genomes and their compendia of expressed genes. These advances, coupled with integrative computational approaches, enabled a massive acceleration of discoveries that linked each major class of tumor genomic alteration to critical functional roles in many cancer types.

Insights From Base Mutation Discovery Through DNA Sequencing

By 2002, several groups had initiated systematic *exon* resequencing efforts in cancer, focusing initially on prioritized gene families such as protein and lipid kinases. One of the first pivotal discoveries to emerge from systematic tumor sequencing was that of activating mutations within *BRAF*, which encodes a serine/threonine kinase oncogene that transmits proliferative and survival signals downstream of RAS in the mitogen-activated protein (MAP) kinase cascade.¹⁷ *BRAF* mutations (most commonly involving a valine-to-glutamic acid substitution at codon 600) occur in more than 50% of cutaneous melanomas and are also observed in colon cancer, papillary thyroid cancer, and other malignancies. This discovery was followed by the identification of activating point mutations in *PIK3CA*¹⁸—a catalytic subunit of PI3 kinase—in 20% to 30% of breast and colon cancers; it was also present in endometrial and ovarian cancers, among others. Shortly thereafter, activating point mutations and small insertions/deletions were found in *EGFR*, an oncogene encoding a *receptor tyrosine kinase*, in 10% to 15% of non-small-cell lung cancer in whites and approximately 25% of non-small-cell lung cancer in patients of East Asian descent.^{19–21} The receptor tyrosine kinase family, together with the MAP kinase and PI3 kinase cascades, collectively encompasses the most important known signal transduction mechanisms governing tumor cell growth and survival. Base mutation discovery through systematic DNA sequencing provided decisive genetic evidence that these same pathways play crucial roles in tumorigenesis and maintenance while also clarifying new avenues for the rational deployment of *targeted therapeutics*.

Large-Scale Studies of Chromosomal Copy Number Alterations

Analyses of somatic DNA copy number variations in cancer also expanded substantially during this time, aided by advances in microarray technology (array comparative genomic hybridization, high-density single nucleotide polymorphism arrays, and so on) that enabled interrogation of copy gains, deletions, and loss of heterozygosity at ever-increasing resolution (Fig 2). An exemplary advance herein involved the integration of high-resolution chromosomal copy number information with gene expression data to enable the discovery of *MITF* as an amplified oncogene in melanoma.²² *MITF* represented the prototype member of a new class of oncogenes (termed lineage survival oncogenes) that unveiled the propensity of several tumor types to co-opt developmental lineage-restricted survival mechanisms for tumor maintenance functions.²² Subsequent analyses of chromosomal copy number data identified *NKX2-1* and *SOX2* as lineage survival oncogenes that are amplified in 10% to 15% of lung adenocarcinomas²³ and lung/esophageal squamous cancers,²⁴ respectively. Thus, the role of lineage dependency, as a novel tumor survival mechanism enacted by chromosomal aberrations, was exquisitely demonstrated through systematic analyses of global chromosomal copy number data.

Systematic chromosomal copy number analyses also catalyzed seminal findings in hematologic malignancies. A genome-scale survey of more than 240 pediatric acute lymphoblastic leukemia (ALL) samples, using high-resolution single nucleotide polymorphism arrays, found that *PAX5* and other prominent transcriptional regulators of B lymphocyte differentiation were recurrently deleted or otherwise disrupted in this malignancy.²⁵ Moreover, in the *BCR-ABL1* translocation–positive subset of ALL, deletions of the *IKZF1* gene (which encodes the *transcription factor* Ikaros, another key B-cell developmental regulator) occurred in more than 80% of patients.²⁶ *IKZF1* alterations were also predictive of poor outcome in pediatric patients with ALL.²⁷ Together, these findings provided compelling evidence that lymphoid leukemogenesis results from dysregulation of normal cellular pathways that direct B-cell lineage maturation.

Importance of Chromosomal Rearrangements in Human Solid Tumors

Knowledge of translocations and other structural rearrangements initially lagged behind that of nucleotide and copy number alterations—particularly in solid tumors—in large part because the aforementioned technologies showed limited ability to systematically interrogate cancer genomes for these events. This constraint began to diminish when Tomlins et al^{28,29} applied a computational approach to search for outliers within cancer gene expression data. Their efforts led to the breakthrough discovery that ETS transcription factors—encoded by genes such as *ERG*, *ETV1*, and *ETV4*—were targeted by translocation or other chromosomal rearrangements in more than 40% of prostate cancers.^{28,29} This observation was followed by the discovery of *ML4-ALK* translocations in 5% to 6% of non-small-cell lung cancers.³⁰ Conceptually, these advances completed the cycle of discovery propelled by the massive technological expansion accompanying the genome era. The archetypal triad of base mutation, chromosomal copy number alteration, and rearrangement that emerged two decades earlier was firmly established as a normative framework that linked the disciplines of cancer genomics, tumor biology, and clinical oncology.

ADVENT OF COMPLETE CANCER GENOME SEQUENCING

Disruptive technologies have continued to advance DNA sequencing capacity at previously inconceivable rates. Whereas initial genome-scale efforts involved laborious Sanger-based methods in breast and colon tumors,³¹ parallel progress across disparate fields such as microscopy, surface chemistry, nucleotide biochemistry, polymerase engineering, computation, and data storage has brought forth several powerful new sequencing methods. The resulting development and commercialization of massively parallel DNA sequencing³²⁻³⁵ has lowered the cost per sequenced nucleotide by several orders of magnitude. Indeed, the sequence data generated per dollar is increasing at a rate faster than Moore's law, which describes the rate of increase of integrated transistors in computing hardware (doubling every eighteen months; Fig 3). The widespread availability of massively parallel platforms has effectively democratized the field by making tremendous sequencing capacity accessible to individual investiga-

tors (Shendure and Ji provide a review of massively parallel sequencing technologies³⁶).

The first published reports of complete cancer genome sequencing focused on individual genomes in acute myeloid leukemia,^{37,38} metastatic breast cancer,³⁹ melanoma,⁴⁰ and small-cell lung cancer.⁴¹ These efforts identified *IDH1* gene mutations in 16% of cytogenetically normal AML samples,³⁸ thereby extending results of an earlier genome-scale sequencing effort that found *IDH1* mutations in 12% of glioblastomas.⁴² *IDH1* encodes an isoform of isocitrate dehydrogenase, a key enzyme in the citric acid cycle. Although the role of *IDH1* in carcinogenesis remains to be fully elucidated, the discovery of recurrent mutations in this gene highlights the increasing importance of altered cell metabolism in the regulation of tumorigenesis.^{42a}

Complete cancer genome sequencing requires approximately 30-fold average depth of coverage, amounting to 90 billion nucleotides sequenced per sample. Both the tumor and the matched germline DNA must be sequenced to this depth of coverage to identify bona fide somatic variants (as opposed to previously unrecognized germline events). Although the cost of generating this magnitude of sequencing data remains considerable, recent technological innovations capable of meeting or exceeding this depth of coverage have reportedly reduced reagent expenditures to less than US\$5,000.⁴³ Thus, complete sequencing of normal and tumor-derived DNA could become commonplace in both research and diagnostic settings during the next several years.

HALLMARK CLINICAL INSIGHTS FROM CANCER GENOME CHARACTERIZATION

Elaboration of the myriad oncogenes and tumor suppressor genes targeted by tumor genomic alterations provides a facile conduit through which basic cancer biology may guide clinical oncology. Tumor genomic alterations increasingly provide tractable diagnostic avenues, inasmuch as they are identifiable in the clinical setting, using genetic and molecular techniques. Indeed, oncoproteins, which were discovered through early cancer genetic studies, happened through serendipity to represent exquisitely druggable cellular targets, thereby paving a relatively straightforward path for therapeutic development. The resulting convergence of cancer genetics, tumor biology, and drug development has yielded three cardinal principles in particular that undergird the clinical significance of cancer genome analysis.

Recurrent Genomic Alterations Often Denote Driver Mechanisms in Cancer

As global views of the cancer genome have emerged, the magnitude of its complexity has become expressly manifest. A typical cancer genome may harbor well over 3,000 base mutations and dozens or even hundreds of chromosomal copy number alterations and rearrangements. Most of these events represent passenger alterations that are largely inconsequential to tumorigenesis or maintenance. Thus, intense efforts in recent years have focused on the identification of driver events that decisively influence the viability and clinical behavior of a given tumor.

Basic properties of tumor **driver mutations** may be gleaned through statistical first principles. For example, true mutated cancer genes should harbor mutations at a greater frequency than that expected by chance (after correcting for false discovery rates).³¹ Statistical approaches to identify driver genes must take into account

Fig 3. Advances in massively parallel technologies have dramatically reduced the cost of sequencing. The blue line shows the exponential decrease in cost (US dollars) of sequencing as a function of time. The extrapolated timeline represents human whole-genome sequencing for US\$100. The yellow line represents Moore's law—the doubling of computer instructions-per-second (IPS) per dollar every 18 months—indicated as a decrease in cost as a function of time (US\$/IPS).

individual tumor background mutation rates as well as regional variations in mutation rates across the genome.⁴⁴ Toward this end, some tumors exhibit a mutator phenotype that may result from alterations in mismatch repair genes or prior chemotherapy. Moreover, large genes often exhibit higher background mutation rates. Taking these factors into account, several groups have nominated driver cancer genes that undergo statistically significant mutation frequencies in large-scale sequencing studies.^{42,45,46} Related efforts have incorporated both frequency and magnitude measurements to distinguish driver from passenger loci affected by chromosomal copy alterations.^{23,47,48,48a} Gratifyingly, these studies have identified multiple genes that have been discovered through prior experimental efforts that span 2 to 3 decades as well as many new driver genes.

Statistical identification of driver tumor genomic events is critically influenced by sample size. Most structural genomic studies performed to date have been powered to detect relatively high-frequency driver events, and only a few have exceeded 100 to 200 samples per tumor type. Ongoing efforts such as the Cancer Genome Atlas and the International Cancer Genome Consortium aspire to characterize several hundred tumors per cancer type, which should afford sufficient power to discover driver events that occur at much lower frequencies (eg, approximately 3% to 5%).

The propensity for recurrent genomic events to denote driver mechanisms does not necessarily imply that all—or even most—driver alterations are recurrent. Indeed, many somatic mutations that show evidence of positive selection during tumor evolution represent low-frequency events when considered at a per-gene level.^{49,50} It therefore remains unclear what fraction of driver mechanisms operant in any given tumor is elaborated by structural genomic alterations as opposed to epigenetic or other regulatory mechanisms. Undoubtedly, many driver mechanisms manifesting as low-frequency events when evaluated as gene-level mutations will prove more frequent when considered at the protein-family or molecular-pathway level.^{45,50} The proliferation of complete genome sequencing efforts across thousands of tumors over the next few years seems poised, together with evolving statistical and other analytic methods, to uncover many new types of driver mechanisms that become dysregulated during tumorigenesis.

Tumors May Exhibit Excessive Reliance on Cellular Mechanisms Elaborated by Driver Genomic Alterations

Initially, the enormous complexity of cancer genome alterations—even within a single tumor—raised the worrisome possibility that targeting a single mechanism might prove insufficient to elicit a meaningful clinical benefit. Although cure or long-term control of tumors will undoubtedly require new drug combinations, a large body of evidence indicates that many tumors become highly dependent on the function of even a single oncogene for proliferation and survival, despite the presence of many other genomic and epigenetic alterations. Weinstein⁵¹ and Weinstein and Joe⁵² introduced the term “oncogene addiction” to describe this phenomenon. In its simplest form, oncogene addiction denotes a cellular context in which the signaling network becomes sufficiently deranged in the presence of a mutated oncoprotein that the protein plays a more essential role in the malignant setting than in its normal counterpart. In the appropriate clinical setting, the tumor addiction phenomenon can create a widened therapeutic window for targeted agents. The more inclusive term “genetic dependency” may provide a more apt description, given that

the cellular addiction need not be manifest solely in tumors harboring classic oncogene mutations. For example, tumor cells harboring deletions and/or loss of expression of the *PTEN* tumor suppressor gene typically exhibit dependency on dysregulated PI3 kinase activation; however, in this case it is the loss of a tumor suppressor—not the presence of a mutated oncoprotein—that confers cellular addiction to PI3 kinase signaling.

Tumor dependencies may coexist with or become induced by index driver genomic alterations, even if the dependencies in question involve distinct molecular mechanisms from the driver events themselves. The idea that such dependencies might also be exploited therapeutically stems from the notion of synthetic lethality, originally described in genetic studies of lower organisms.⁵³ Two genes are considered synthetically lethal to one another if an alteration affecting one or the other gene individually is compatible with survival but alterations in both genes cause cell death.⁵⁴ Considerable research is now underway to identify synthetic lethal tumor dependencies linked to recurrent driver alterations, particularly in cases in which the index genomic event cannot be treated well through existing therapeutic avenues. Mutated *KRAS* represents an instructive example of a highly prevalent driver oncogene whose corresponding protein proved refractory to multiple prior drug discovery efforts but for which several promising and potentially druggable synthetic lethal partners have recently been identified.⁵⁵⁻⁵⁷ This concept has also been termed non-oncogene addiction to reflect the fact that many such protein targets are not themselves subject to recurrent tumor genomic alterations.⁵⁷

The efficacy of poly-adenosine-disposphate-ribose polymerase (PARP) inhibitors in *BRCA1*- or *BRCA2*-mutated breast, ovarian, and prostate cancers provides a noteworthy clinical affirmation of the synthetic lethal concept. Indeed, the presence of *BRCA1/2* mutations appears to confer heightened sensitivity to PARP inhibition in clinical trials.^{58,59} Moreover, in combination with conventional chemotherapy, PARP inhibitors have been reported to significantly improve overall and progression-free survival in women with metastatic triple-negative breast cancer.⁶⁰ Together, these preclinical and clinical examples underscore the guiding premise that many driver genomic alterations denote the presence of concomitant tumor dependencies that may be amenable in principle to targeted therapeutic intervention.

Therapies Targeting Driver Dependencies May Elicit Major Clinical Responses in Genetically Defined Tumor Subtypes

The ultimate test of the genomic view concerns the extent to which this paradigm effectively guides cancer treatment decisions and predicts therapeutic response. Early conceptual support for its utility emerged after the clinical success of all-trans retinoic acid therapy in acute promyelocytic leukemia (characterized by chromosomal translocations involving retinoic acid receptor α , the target of all-trans retinoic acid)^{61,62} and trastuzumab in *ERBB2*-amplified breast cancer (*ERBB2* encodes *HER2/neu*, the target of trastuzumab).⁶³ The ensuing success of the selective ABL tyrosine kinase inhibitor (TKI) imatinib mesylate (and subsequently nilotinib) in the treatment of chronic myeloid leukemia (CML), which harbors the *BCR-ABL* fusion, seemed to provide a powerful clinical validation of the oncogene addiction principle.⁶⁴⁻⁶⁶

The enthusiasm expected from these results was initially tempered somewhat by skepticism as to whether CML exhibited the

genomic complexity or clinical aggressiveness typical of most lethal malignancies. The ability of imatinib to elicit objective responses in most patients with GI stromal tumor (GIST, which harbors oncogenic mutations in *KIT*, another target of imatinib) largely refuted these concerns, as GIST is a highly aggressive solid tumor that may harbor multiple genomic alterations in addition to oncogenic *KIT* mutation. Nonetheless, skepticism persisted concerning the generalizability of mutation-based cancer therapeutics; clinical successes of this emerging paradigm, although spectacular, were rare. The success of erlotinib—a small-molecule TKI that inhibits the epidermal growth factor receptor (EGFR)—in patients with non-small-cell lung cancer whose tumors contained activating *EGFR* mutations^{19–21,67} countered these concerns. Whereas CML and GIST were arguably rare malignancies, the efficacy of erlotinib in a genetically defined lung cancer subtype provided strong support for the relevance of the genome-based cancer treatment paradigm, even in subsets of the most common epithelial solid tumors.

Another question pertained to whether tumor mutations predictive of pharmacologic sensitivity in one cell lineage would prove similarly predictive in tumors from another lineage. The discovery of oncogenic *KIT* mutations in a subset of acral and mucosal melanomas⁶⁸ afforded a unique opportunity to address this issue, because several such mutations were identical to those predictive of imatinib response in GIST. Recent published observations, together with early clinical trial results, suggest that *KIT* inhibition using imatinib or nilotinib can indeed elicit substantial clinical responses in *KIT*-mutant melanoma.^{69,70} Although preliminary, these results suggest that the predictive power of at least some genomic mutations denote therapeutic vulnerability, regardless of the lineage context in which they occur.

An additional question facing the cancer genome paradigm has concerned the nature of driver mutations that will prove most amenable to targeted therapeutic intervention. It is straightforward to appreciate why gain-of-function mutations in receptor tyrosine kinase genes may provide exquisite pharmacologic vulnerabilities, given

that **tyrosine kinase receptors** often activate numerous critical signal transduction cascades in parallel. In contrast, targeting other driver mechanisms that lack this same breadth of functionality (eg, cytoplasmic serine/threonine kinases situated farther downstream within a particular signaling module) might prove less effective clinically. The disappointing results of clinical trials interrogating sorafenib in melanoma seem to augment this notion. Although sorafenib was initially believed to function primarily as an inhibitor of the RAF family of serine/threonine kinases, it provided no benefit in melanoma clinical trials^{71,72}—despite the presence of activating *BRAF* mutations in more than 50% of cutaneous melanomas and the extensive preclinical evidence supporting a MAP kinase tumor dependency in *BRAF*-mutant melanoma.^{73,74} Notably, emerging clinical studies of RAF inhibitors with greater selectivity and bioavailability⁷⁵ have blunted this concern. In a recently reported phase I study, effective RAF inhibition—as measured by more than 90% pathway downregulation in the presence of drug—was associated with a more than 70% partial response rate by Response Evaluation Criteria in Solid Tumors (RECIST) criteria.⁷⁴ This clinical benefit was only apparent in patients whose melanomas harbored the *BRAF*^{V600E} mutation. Thus, driver mutations at various points within cell signaling modules may be targeted effectively using novel cancer therapeutics.

In aggregate, these results provide an increasingly compelling rationale for the guiding premise that driver genomic alterations within individual tumors may define patient subpopulations that experience substantial clinical benefit from targeted therapeutic regimens (Table 1 summarizes exemplary cancer genes and corresponding targeted therapeutic agents). Tumor genomic profiling is equally capable of identifying subpopulations that are unlikely to benefit from targeted therapy. Recent observations that tumors harboring *KRAS* mutations fail to respond to EGFR-targeted therapies exemplify this point.^{71,76–79} These principles may therefore serve as a framework for the widespread emergence of individualized cancer treatment.

Table 1. Categories of Genomic Alteration and Exemplary Cancer Genes

Category of Genomic Alteration	Exemplary Cancer Gene	Type of Cancer	Targeted Therapeutic Agent
Translocation	<i>BCR-ABL</i>	Chronic myelogenous leukemia	Imatinib
	<i>PML-RARα</i>	Acute promyelocytic leukemia	All- <i>trans</i> -retinoic acid
	<i>EML4-ALK</i>	Breast, colorectal, lung	ALK inhibitor
	<i>ETS</i> gene fusions	Prostate	—
	Other	Leukemias, lymphomas, sarcomas	—
Amplification	<i>EGFR</i>	Lung, colorectal, glioblastoma, pancreatic	Cetuximab, gefitinib, erlotinib, panitumumab, lapatinib
	<i>ERBB2</i>	Breast, ovarian	Trastuzumab, lapatinib
	<i>KIT</i> , <i>PDGFR</i>	GISTs, glioma, HCC, RCC, CML	Imatinib, nilotinib, sunitinib, sorafenib
	<i>MYC</i>	Brain, colon, leukemia, lung	—
	<i>SRC</i>	Sarcoma, CML, ALL	Dasatinib
	<i>PIK3CA</i>	Breast, ovarian, colorectal, endometrial	PI3-kinase inhibitors
Point mutation	<i>EGFR</i>	Lung, glioblastoma	Cetuximab, gefitinib, erlotinib, panitumumab, lapatinib
	<i>KIT</i> , <i>PDGFR</i>	GISTs, glioma, HCC, RCC, CML	Imatinib, nilotinib, sunitinib, sorafenib
	<i>PIK3CA</i>	Breast, ovarian, colorectal, endometrial	PI3-kinase inhibitors
	<i>BRAF</i>	Melanoma, pediatric astrocytoma	RAF inhibitor
	<i>KRAS</i>	Colorectal, pancreatic, GI tract, lung	Resistance to erlotinib, cetuximab (colorectal)

Abbreviations: ALK, anaplastic lymphoma kinase; GIST, GI stromal tumor; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; CML, chronic myelogenous leukemia; ALL, acute lymphoblastic leukemia; PI3, phosphatidylinositol-3.

VISION FOR PERSONALIZED CANCER MEDICINE INFORMED BY GENOMICS

Clearly, the genomic view of cancer has introduced a re-evaluation of the prevailing clinical oncology paradigm, in which anatomic origins and stages of clinical progression may govern diagnostic and therapeutic principles in a manner agnostic to the underlying genetic changes. Adding a rigorous genomic view could provide enormous value by illuminating driver genetic events, revealing critical dependencies, and stratifying patients with cancer for targeted therapeutic implementation. Indeed, the ability to profile every patient for a comprehensive set of clinically actionable genomic alterations underpins the emerging vision of personalized cancer medicine (Fig 4). Early examples of the benefit of tumor mutation profiling may be gleaned from recent studies in colorectal cancer, in which multiple genetic or gene expression alterations may impact response to EGFR-directed therapies.⁸⁰⁻⁸²

The development of advanced diagnostic tests capable of reading multifaceted genomic information in an efficient and cost-effective manner should prove highly enabling for individualized cancer treatment. The ideal genome-based diagnostic will exhibit high sensitivity and specificity for mutation detection; interrogate a large panel of oncogenes and tumor suppressor genes for the presence of driver alterations; detect each major category of tumor genomic alteration; and perform robust mutation detection in DNA from both frozen and formalin-fixed, paraffin-embedded tumor material. Initial efforts toward this end have successfully employed technologies such as mass spectrometric genotyping or the polymerase chain reaction to profile approximately 100 to 400 known base mutations in as many as 34 cancer genes.^{83,84,84a} However, these approaches are limited to a small fraction of informative cancer genes, a finite number of mutations within these genes, and a single category of genetic alteration (base mutations and small insertions/deletions). It is likely that clinical tumor mutation profiling will proceed in phases, with the initial efforts

focused on a framework for interrogating the low-hanging fruit of actionable mutations and with subsequent efforts concentrated on maximizing the informative tumor genomic information that can be gleaned from tumor material in a cost-effective manner.

Massively parallel sequencing represents a promising technology for comprehensive tumor genomic profiling, although whole-genome sequencing may not become a practical diagnostic option in time to fulfill the immediate need of personalized cancer medicine. In the cancer genome, passenger alterations may vastly outnumber the driver events; thus, additional technical or analytic filters will be required to enrich for the somatic changes that direct tumor biology and therapeutic response. Several technical methods have recently been developed that reduce the effective genomic complexity by capturing the relevant exonic DNA before massively parallel sequencing.^{85,86} Incorporation of additional innovations, such as appending DNA barcodes and pooling of samples before sequencing, may offer additional opportunities to increase sequencing efficiency and lower cost. However, significant technical hurdles must be circumnavigated before these methods become widely available in the translational oncology arena. Over the long term, the cost of whole-genome sequencing may decrease enough to obviate the need for genome complexity reduction steps.

AS WE GO FORWARD

The breathtaking pace of advancement in technology and cancer genome biology seems poised to transform many aspects of oncology diagnosis, clinical trial design, and treatment. However, several important challenges and ethical considerations accompany this impending paradigm shift. The impetus for widespread tumor genomic profiling could impose significant new infrastructural demands on leading academic cancer centers, many of which are not fully configured to accommodate the expansion in patient informed consent,

Fig 4. Schema of personalized medicine. A genome-based vision for personalized cancer medicine will require a paradigm shift in both diagnosis and treatment. Traditionally, tumors are classified by site of origin. In the future, tumor nucleic acid will be profiled for a wide array of genomic alterations with a view to specific, tailored treatment options for each individual patient.

surgical, pathologic, and laboratory information management required for its successful execution. Universal standards and approaches to educate physicians regarding the appropriate interpretation and use of this information must be developed. Complex issues surrounding reimbursement for both the diagnostic approaches and the resulting therapeutic implications must be addressed, especially in cases in which tumor genomic information might suggest off-label treatment avenues. Addressing these challenges will require the dedicated engagement of thought leaders across major cancer centers, cooperative oncology organizations, health policy efforts, and patient advocacy groups. Personalized cancer genomic information, once widely available and thoughtfully implemented, holds considerable promise for improving the lives of many patients with cancer.

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Glossary Terms

Amplification/deletion: Chromosomal aberrations that result in amplification or deletion in regions of the chromosome. Chromosomal amplification results in a gain in copy number of genes, whereas chromosomal deletion results in gene loss from the chromosome.

Driver (mutations or gene): Driver mutations are those that are causally implicated in oncogenesis or tumor survival. Such mutations have been positively selected during carcinogenesis and often show a recurrent pattern within or across tumor types. This is in contrast with passenger events, which arise from the background mutation rate and do not contribute to oncogenesis.

Epigenetic: The transfer of information from one cell to its descendants without the information's being encoded in the nucleotide sequence of the DNA. The methylation of the promoter to inactivate a gene is an example of an epigenetic change. Epigenetic inheritance is typically transmitted in dividing cells. Although rare, it is occasionally seen in traits being transmitted from one generation to another. Epigenetic variants can arise spontaneously and just as spontaneously revert.

Exon: Segment of a gene that consists of a sequence of nucleotides that encodes amino acids in the protein. Genes are often made up of multiple exons separated by introns that do not encode amino acids in the protein.

Microarray: A miniature array of regularly spaced DNA or oligonucleotide sequences printed on a solid support at high density that is used in a hybridization assay. The sequences may be cDNAs or oligonucleotide sequences that are synthesized in situ to make a DNA chip.

Receptor tyrosine kinase: Transmembrane protein with intrinsic ability to transfer phosphate groups to tyrosine residues contained in cellular substrates. (See Tyrosine kinase receptors).

Somatic mutation: A change in the genotype of a cancer cell. This is distinguished from a germline mutation, which is a change in the genotype of all the normal cells in a patient's body. Germline mutations may be passed to offspring, but somatic mutations may not.

Targeted therapeutics: Therapeutic agents that are specifically modeled to inhibit very specific molecules in signal transduction pathways implicated in the disease.

Transcription factors (transcriptional regulatory complexes): Complexes of proteins that regulate the transcriptional activity in cells. Specific regulatory sequences exist in genes or in mRNAs that bind specific transcriptional factors. TFIIA, B, and C, for example, are transcriptional factors regulating RNA polymerase II activity. The number and type of regulatory elements can vary in each gene or mRNA, giving rise to a combination of transcriptional factors, each exerting different regulatory control. Transcriptional complexes are also unique for different cell types.

Tyrosine kinase inhibitors: Molecules that inhibit the activity of tyrosine kinase receptors. They are small molecules developed to inhibit the binding of ATP to the cytoplasmic region of the receptor (eg, gefitinib), thus further blocking the cascade of reactions that is activated by the pathway.

Tyrosine kinase receptors: Receptors belonging to the tyrosine kinase family (eg, EGFR, PDGFR) are activated through the auto- or transphosphorylation of tyrosine residues in the cytoplasmic region of the receptors in an ATP-dependent manner.