Cancer Genomics: Diversity and Disparity Across Ethnicity and Geography

Abstract: Ethnic and geographic differences in cancer incidence, prognosis, and treatment outcomes can be attributed to diversity in the inherited (germline) and somatic genome. Although international large-scale sequencing efforts are beginning to unravel the genomic underpinnings of cancer traits, much remains to be known about the underlying mechanisms and determinants of genomic diversity. Carcinogenesis is a dynamic, complex phenomenon representing the interplay between genetic and environmental factors that results in divergent phenotypes across ethnicities and geography. For example, compared with whites, there is a higher incidence of prostate cancer among Africans and African Americans, and the disease is generally more aggressive and fatal. Genome-wide association studies have identified germline susceptibility loci that may account for differences between the African and non-African patients, but the lack of availability of appropriate cohorts for replication studies and the incomplete understanding of genomic architecture across populations pose major limitations. We further discuss the transformative potential of routine diagnostic evaluation for actionable somatic alterations, using lung cancer as an example, highlighting implications of population disparities, current hurdles in implementation, and the far-reaching potential of clinical genomics in enhancing cancer prevention, diagnosis, and treatment. As we enter the era of precision cancer medicine, a concerted multinational effort is key to addressing population and genomic diversity as well as overcoming barriers and geographical disparities in research and health care delivery.

Introduction

Cancer is a genomic disorder. Carcinogenesis is driven by inherited genomic variation as well as accumulation of multiple somatic genetic events including mutations, rearrangements, or amplification that lead to uncontrolled cell proliferation, evasion of apoptosis, and angiogenesis.1 The striking successes of applied somatic genomics in the clinic has heralded the era of precision medicine, where molecular genetic analysis can accurately identify specific actionable genomic abnormalities linked to correspondingly effective molecularly targeted therapy, often with dramatic subversion of tumor growth and survival. Examples include imatinib for c-KIT GI stromal tumor, vemurafenib for BRAFV600E melanoma, and crizotinib for ALK-rearranged non-small-cell lung cancer (NSCLC).2-4 Patient stratification based on genomic biomarkers has become an integral component of modern clinical cancer diagnosis and treatment.

Despite these successes, not all patients benefit equally. It has long been recognized that genetic and environmental variation between ethnicities and geographic regions contribute to population-based disparities in cancer risk and treatment outcomes.5 Variation in frequency of inherited and somatic mutations (eg, difference in prevalence of specific driver oncogenes between ethnicities) is one of the main reasons for this diversity.6 Environmental factors such as diet, health care policy, and economic discrepancy contribute to disparities in risk and outcome between ethnic groups or geographic regions. Many well-established genomic tests commonly used in Western countries are not yet available in developing countries. Even if both the test and molecular-targeted therapy are available, the high cost remains prohibitive.

Key points

- Patient stratification based on genomic biomarkers has become an integral component of modern clinical cancer diagnosis and treatment.
- It has long been recognized that genetic and environmental variation between ethnicities and geographic regions contribute to population-based disparities in cancer risk and treatment outcomes.
- Variation in frequency of inherited and somatic mutations (eg, difference in prevalence of specific driver oncogenes between ethnicities) is one of the main reasons for this diversity.
for many patients from developing countries. In this review, we explore the reasons behind genomic diversities between ethnic groups and geographic regions and discuss the implications on the clinical management of two common malignancies.

Genomic diversity and cancer

Humans display significant phenotypic complexity and diversity beyond other living organisms. In addition to inherited and somatic genomic alterations, diversity is generated through transcriptional and epigenetic regulation, with further contributions by noncoding elements including microRNA, long noncoding RNA, and post-translational modifications (Figure 1). Ethnic and geographic differences in a wide variety of traits can be attributed to genomic diversity. This diversity is the consequence of mutation and the evolutionary forces that act to establish mutational frequencies over time and across populations. On the basis of earlier molecular anthropologic studies, it is estimated that each individual differs by approximately only 0.1% of the entire genome. Moreover, despite the significant genetic distance between populations, the majority of genetic variation (85% to 90%) is still largely found within geographic regions (eg, within continents). With large-scale sequencing projects such as the 1000 Genomes Project, differences in ethnicities and geographic regions can be accounted for through a combination of effects in rare and common variants of the human genome, underscoring the impact of an individual’s inherited genome in determining phenotype. Efforts such as the Encyclopedia of DNA Elements (ENCODE) aim to further elucidate the epistatic effects of multiple genes, transcription factors, and the epigenetic landscape so as to facilitate elaborate interaction maps of individual whole genomes.

Cancer is influenced by all of the earlier mentioned phenomena. Individual risk of
from 2007 to 2011. The International Agency for Research on Cancer GLOBOCAN program estimates that prostate cancer is also the leading cancer in terms of incidence and mortality in men from Africa and the Caribbean. Therefore, men of African descent around the world suffer disproportionately from prostate cancer compared with men of other races or ethnicities. The International Agency for Research on Cancer also estimates that prostate cancer is a growing problem in Africa, with a predicted near doubling of prostate cancer-related deaths from 55,522 in 2010 to more than 100,000 deaths by 2030. Furthermore, AA men experience the highest rates of aggressive prostate cancer and prostate cancer-specific mortality of any ethnic group in the United States. Our understanding of this disparity remains limited. The majority of sub-Saharan African (SSA) patients with prostate cancer are diagnosed with aggressive disease, often at late (usually incurable) stages. In both SSA and AA men, this pattern may be a result of a combination of biologic aggressiveness and late detection. Thus, there may be common features of prostate cancer etiology in men of African descent that may explain observed mortality patterns. Knowledge gained from studies of prostate cancer in SSA may in turn improve our understanding of aggressive prostate cancer in men of African descent around the world, including AAs. In addition to being common, prostate cancer is also particularly deadly in African descent men. The reasons for the large burden of prostate cancer risk and poor outcomes remain unresolved. Access to care (including screening and appropriate treatment) is likely to be an important factor in explaining prostate cancer disparities. Studies suggest that if health care access is equalized among the races (eg, in the Veterans Affairs system), major disparities are ameliorated but not entirely eliminated even after accounting for treatment differences. Epidemiologic risk factors have not explained a large proportion of variation in prostate cancer risk.

Key points

- Ensuing cancer hallmarks, such as proliferation, invasion, metastasis, and traits related to treatment such as acquired drug resistance, are realized through additional somatic mutations.
- African Americans (AAs) suffer from the highest rates of prostate cancer in the world, and in the United States, the average (and growing) annual incidence rate was 224 per 100,000 in the period from 2007 to 2011.
- The International Agency for Research on Cancer also estimates that prostate cancer is a growing problem in Africa, with a predicted near doubling of prostate cancer-related deaths from 55,522 in 2010 to more than 100,000 deaths by 2030.
- In both SSA and AA men, this pattern may be a result of a combination of biologic aggressiveness and late detection.
- African Americans (AAs) suffer disproportionately from prostate cancer compared with men of other races or ethnicities.

Inherited genomics of cancer: the example of prostate cancer in African descent populations

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Genetic analysis has identified many risk loci, but few genome-wide association studies (GWAS) have been undertaken in African descent, and most GWAS hits have not been replicated in African descent populations. The scope of etiologic studies in African descent populations has been circumscribed, which limits our understanding of the cause of unfavorable outcomes in this population. Additional genomic studies in African descent men are needed to understand prostate cancer etiology and outcomes.

Prostate cancer has the highest familial risks and heritability of any major cancer. GWAS studies have identified prostate cancer susceptibility loci, and there is evidence that the contribution of these risk alleles to prostate cancer differs across populations. To date, more than 100 independent loci have been associated with prostate cancer and 4,678 AA control patients. Of the 82 SNPs studied, 83% were directionally consistent with previous reports, and 37% achieved a P ≤ .05. Thus, the inference of association of GWAS hits identified in non-AA populations was not as strong in AA men. Haiman et al undertook a GWAS using a sample of more than 6,000 African descent patients with prostate cancer and African descent controls that overlapped with the sample of Chang et al. Haiman et al also did not replicate most of the previously reported loci identified in European or Asian descent populations, but identified a novel locus on chromosome 17 that was later validated as a prostate cancer risk locus in European descent populations. In a small study in Ghana, a novel locus on chromosome 10 was identified that was not detected in other populations. Thus, studies of African populations may provide critical insight into the genetic etiology of prostate cancer throughout the African diaspora.

Population diversity also provides unique opportunities to gain insight into disease. Currently, there has been limited clinical or public health impact of many genomic discoveries. However, the future promises that both clinical applications and improved biologic insight into cancer may be achieved. For instance, currently, the ability to predict which prostate cancer tumors will lead to death remains limited. In SSA, the majority of prostate tumors are diagnosed at late stages. We recently reported that 16% to 30% of men in SSA are diagnosed with widely metastatic disease; castrate-resistant disease is common in SSA. Therefore, prostate cancer research in SSA populations provides unique opportunities to understand aggressive prostate cancer. It is possible in Africa to more fully explore the natural history of aggressive prostate cancer including the commonly occurring metastatic and hormone-refractory forms.
of the disease. The knowledge gained from studies of aggressive disease in SSA may improve our understanding of aggressive prostate cancer diagnosed anywhere in the world, including prostate cancer in AA men who suffer from the highest prostate cancer mortality in the United States. It is possible that these contrasting outcomes are a result of underlying genomic differences. In contrast to whites, somatic alterations such as TMPRSS2-ERG or PTEN deletion occur less frequently in AAs in the United States, with a higher incidence of SPINK1 overexpression, a marker for aggressive prostate cancer.17 Whether patients of African descent may harbor distinct genomic signatures or drivers remains to be elucidated. Furthermore, molecularly targeted therapy based on somatic alterations has yet to be validated in prostate cancer. In contrast, the clinical impact of the somatic mutation landscape has dramatically changed the treatment and diagnostic paradigm of NSCLC, illustrating the transformative potential of rationally applied cancer genomics.

Somatic genomics of cancer: the example of lung cancer in Asian descent populations

Lung cancer is the most common fatal malignancy, with more than 1.6 million new cases globally every year.18 Incidence is increasing in China but declining in the United States.38 This phenomenon is best explained by a tobacco-control policy that resulted in a reduction in the prevalence of smokers in the United States, whereas there is a lack of such a policy in China.39 However, the tobacco-related lung cancer rate in Western countries continues to be higher than in Asia.40 It was estimated that approximately 30% of all patients with lung cancer from China are nonsmokers and predominantly women.41

Epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement are the two most frequently occurring targetable genetic alterations in NSCLC and were discovered in 2004 and 2007, respectively.42–44 These two genetic alterations have had far reaching implications in the clinic, fundamentally changing diagnostic algorithms and workflows in pathologic evaluation, defining new standards of care of genomic-based personalized therapy for management of advanced NSCLC globally, and ultimately improving patient outcomes through novel targeted therapeutics. The epidemiology of these alterations and availability of molecular testing and targeted drugs are the major causes for diversity and disparity in management of advanced-stage NSCLC. Base-pair deletion in exon 19 and point mutation L858R in exon 21 are the most common activating EGFR mutations, and their prevalence is significantly higher in Japanese, Korean, and Chinese patients than white patients from the United States or Europe.45 Histologic cell type (adenocarcinoma vs. non-adenocarcinoma), ethnicity (Asian vs. non-Asian), and tobacco exposure (never-smoker vs. ex-smoker vs. current smoker) are clinical factors that determine the incidence of EGFR mutation. This observation is validated in multiple epidemiologic studies and clinical trials. The incidence of activating EGFR mutations in Asian nonsmokers or light smokers with advanced-stage adenocarcinoma was 59.5% in the landmark Iressa Pan-Asia Study (IPASS) study that was conducted in Asia and established the importance of EGFR testing. In contrast, the incidence was only 15% in non-Asian patients from the BR.21 study, one of the earliest phase III trials that performed retrospective EGFR mutation testing on archival samples.46,47 It is not clear whether different ethnic groups or populations have significant variation in prevalence of EGFR mutations as a result of the relative paucity of systematic large-scale EGFR mutation testing studies. One such epidemiologic study (IGNITE) reported the incidence of EGFR mutations in adenocarcinoma to be 49% and 18% in 2,291 East Asian and 924 Russian patients, respectively; the mutation rates in

Key points

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- Epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement are the two most frequently occurring targetable genetic alterations in NSCLC and were discovered in 2004 and 2007, respectively.
- The epidemiology of these alterations and availability of molecular testing and targeted drugs are the major causes for diversity and disparity in management of advanced-stage NSCLC.
- Base-pair deletion in exon 19 and point mutation L858R in exon 21 are the most common activating EGFR mutations, and their prevalence is significantly higher in Japanese, Korean, and Chinese patients than white patients from the United States or Europe.
- This observation is validated in multiple epidemiologic studies and clinical trials.
nonadenocarcinoma were 14% and 4%, respectively. However, the prevalence of EGFR mutations in other ethnicities is less well known. This is partly attributed to the variation in sensitivity of different testing methods, quality of tumor samples, and difference in clinical selection criteria. Figure 2 summarizes the incidence of EGFR mutations detected by sequencing in lung adenocarcinoma and illustrates the regional variation. It is a curious observation that the natives of certain parts of South America seem to have a similar incidence of EGFR mutation as Asians, whereas most other ethnicities share similar incidence as whites.

The distinct phenotype of Asian NSCLC has led to several GWAS studies, with discovery cohorts comprising never-smokers (377 patients, 377 controls), never-smoking women in Asia (584 patients, 585 controls), a Japanese population (1,695 patients, 5,333 controls), and recently, the largest study yet in never-smoking women in Asia (5,510 patients, 4,544 controls). Although specific susceptibility variants unique to Asian never-smokers have been identified, such as V711A, the fact that variants in TERT and p63 emerge in both Asian-specific never-smoker studies and studies examining all-comer lung adenocarcinoma highlights the complex biology contributing to lung carcinogenesis.

ALK rearrangement is less common, accounting for 2% to 7% of all NSCLCs. Similar to EGFR mutations, the incidence is associated with histologic cell type, ethnicity, and tobacco exposure. Clinical trials and epidemiologic studies also provide insight on the incidence. The PROFILE 1007 study conducted the largest screening for ALK rearrangement in patients with advanced-stage NSCLC. Of 4,967 patients screened, 347 (6.9%) were positive for ALK rearrangement by fluorescence in situ hybridization (FISH) and eligible for study. Blackhall et al used immunohistochemistry and FISH to test for ALK rearrangement in 1,281 resectable early-stage adenocarcinomas from

![Figure 2: Worldwide incidence of EGFR mutations in lung adenocarcinoma tested by Sanger sequencing (unless otherwise indicated). (*) Testing by Scorpion amplification refractory mutation system.](image-url)

**Key points**

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European patients and reported incidence rates of 6.2% and 2.2% by immunohistochemistry and FISH, respectively. Thus, the incidence of detection of ALK rearrangement also depends on the method of testing. Ethnic variation between Asians and non-Asians is less obvious considering the low incidence in all populations. A single study using the rapid amplification of cDNA ends polymerase chain reaction method reported an exceptionally high incidence of 11.5% in China, whereas the majority of reports do not reflect a significant difference between Asian and non-Asian populations.

Tyrosine kinase inhibitors (TKIs) targeting EGFR mutations and ALK rearrangement are established first-line therapy for patients who harbor the genomic alterations. Multiple randomized phase III studies from Asia and Europe have confirmed the role of gefitinib, erlotinib, and afatinib in patients with EGFR mutations.46,79–83 Although Asians seem to have numerically higher response rates and progression-free survival in some trials of EGFR or ALK TKIs (Table 1), no statistically significant differences in clinical outcomes have been observed between ethnic groups, in part because of underpowered, post hoc analyses. Similarly, PROFILE 1014 confirmed the role of first-line crizotinib in patients with ALK rearrangement, and again, treatment outcomes are not different between Asians and non-Asians.4,84 Rational, science-driven drug development has also shortened the timelines for introducing novel effective therapies to the clinic. For instance, while the historical median overall survival of unselected patients with stage IV NSCLC is 6 months, a recent cohort of 79 ALK-positive patients receiving two ALK inhibitors (first and second generation) sequentially was a remarkable 49 months,126 underscoring the increasing importance of implementing patient access strategies in both developed and developing countries.

Regional disparities can be a result of limited availability of molecular testing facilities and the high cost of molecular targeted drugs. A recent survey on 22,193 patients from 11 Asian countries reported that only 31.8% of surveyed patients with NSCLC underwent EGFR mutation analysis.91 The testing rate ranged from 18.3% in developing country such as China to 64.8% in more developed Asian country such as Japan. Cytologic samples account for 66.7%, 73.3%, and 98% of all tested samples in Vietnam, the Philippines, and Indonesia, respectively. The quality of DNA material from cytologic samples is known to be inferior to biopsy. In contrast, Spicer et al30 performed a survey of 562 oncologists from 10 developed countries, including Canada, France, Germany, the United States, and others, and reported a testing rate of 81%, where inadequate tumor tissue was the main reason for test omission. To date, there have been limited studies on the prevalence of EGFR mutations in Africans and AAs. Two cohort studies have reported EGFR mutation rates in AAs of 2% (one of 53 patients with NSCLC) and 19% (23 of 121 patients with adenocarcinoma),50 whereas with the exception of one study from Morocco (21%, 29 of 137 patients),59 there have been no such profiling studies arising from the African continent. Geographic disparity in testing remains significant.

EGFR TKIs are generally expensive, costing between US$2,500 and US$4,000 per month. Many developed countries such as the United States and Canada follow a health care policy that provides full or partial reimbursement to all patients with known EGFR mutations. This approach would guarantee that almost all patients receive an EGFR TKI if they test positive for EGFR mutations. Other countries, such as Hong Kong, may provide limited partial reimbursement according to a patient’s financial need. However, a majority of developing countries do not reimburse at all. This implies that many patients from developing countries have limited access to EGFR TKIs even if they are proven to have EGFR mutation–positive NSCLC. In light of this disparity, several options have been explored to overcome this issue.

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### TABLE 1 - Outcomes of targeted agents in the context of a selection biomarker in different populations

<table>
<thead>
<tr>
<th>Disease</th>
<th>Biomarker and test</th>
<th>Drug</th>
<th>Patients</th>
<th>Response rate</th>
<th>PFS</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td><strong>NSCLC</strong></td>
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<tr>
<td>EGFR</td>
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<tr>
<td>China</td>
<td>PCR based</td>
<td>Erlotinib</td>
<td>Asian (n = 82)</td>
<td>83%</td>
<td>13.1 months</td>
<td></td>
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<tr>
<td>Europe</td>
<td>PCR based</td>
<td>Erlotinib</td>
<td>White (n = 86)</td>
<td>56%</td>
<td>9.7 months</td>
<td></td>
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<tr>
<td>South America</td>
<td>Sequencing</td>
<td>Not stated</td>
<td>White/Latin American (n = 109)</td>
<td>60.6%</td>
<td>15.9 months</td>
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<tr>
<td><strong>ALK</strong></td>
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<tr>
<td>Asian vs. non-Asian</td>
<td>EML4-ALK FISH</td>
<td>Crizotinib</td>
<td>Asian (n = 77); non-Asian (n = 172)</td>
<td>Asian: 70%; non-Asian: 74%</td>
<td>Asian: 13.6 months; non-Asian: 10.9 months</td>
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<tr>
<td>Asian vs. white</td>
<td>EML4-ALK FISH</td>
<td>Ceritinib</td>
<td>Asian (n = 82); white (n = 156)</td>
<td>Asian: 69%; white: 57%</td>
<td>Asian: 10.1 months; white: 6.9 months</td>
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<tr>
<td><strong>Other cancer</strong></td>
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<tr>
<td>GI stromal tumor</td>
<td>c-KIT exon 11</td>
<td>Imatinib</td>
<td>Korean (n = 176); white (n = 86)</td>
<td>Korean: 63.6%; white: 86%</td>
<td>Korean: 49.4 months; white: 63 months</td>
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<tr>
<td>Breast cancer</td>
<td>HER2 IHC 3+ or FISH</td>
<td>Trastuzumab-docetaxel ± pertuzumab</td>
<td>Asian (n = 261); black (n = 30); white (n = 480); other (n = 37)</td>
<td>Asian: HR, 0.68 (95% CI, 0.48 to 0.95); ROW: HR, 0.61 (95% CI, 0.49 to 0.76)</td>
<td>Asian: HR, 0.82; (95% CI, 0.58 to 1.17); white: HR, 0.63 (95% CI, 0.49 to 0.82)</td>
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<tr>
<td>Gastric cancer</td>
<td>HER2 FISH amplification</td>
<td>Capecitabine-oxaliplatin ± lapatinib</td>
<td>Asian (n = 193); North America (n = 17); ROW (n = 277)</td>
<td>Asian: 65% vs. 39%; ROW: 44% vs. 40%</td>
<td>Asian: HR, 0.68 (95% CI, 0.48 to 0.95); median OS, 16.5 months; ROW: HR, 1.04 (95% CI, 0.79 to 1.37); median OS, 10.0 months</td>
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EML4, echinoderm microtubule-associated protein-like 4; FISH, fluorescent in situ hybridization; HR, hazard ratio; IHC, immunohistochemistry; NSCLC, non–small-cell lung cancer; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; ROW, rest of world.
explored to improve treatment access to patients. For example, a pharmaceutical company from China has developed icotinib, which has been shown to be noninferior to gefitinib.\textsuperscript{93} In a randomized phase III study of 400 unselected patients, median progression-free survival times of icotinib and gefitinib were 4.6 and 3.4 months, respectively ($P = .13$). Only a small fraction of enrolled patients were found to harbor EGFR mutations. Although the scientific strength of the study is questionable, icotinib was nevertheless approved based on this trial. Other countries such as India basically allow generic versions of gefitinib even when the drug is still protected under international patent.

### Implications of genomic variation

It is anticipated that expanding knowledge of inherited and somatic genomics will further advance our understanding of cancer genetics and lead to improved strategies for prevention, detection, and treatment of cancer. For instance, although current screening programs are still directed against high-risk cohorts based on lifestyle, age, or family history, it is conceivable that population-specific susceptibility variants will open possibilities for risk stratification or risk reduction interventions. In the case of prostate cancer, preventive interventions may also reduce the adverse consequences of screening experienced by some men.

However, there remain important considerations before clinical implementation of susceptibility variants emerging from GWAS studies, which is underscored by the limited translation, to date, of the inherited genome into clinically relevant tools that can be used for risk prediction or targeted prevention or treatment. As implied earlier, population genomic features strongly influence the ability to detect and interpret genetic associations, and many variants identified to date from GWAS studies in white or Asian populations have not been replicated in AA populations. Lack of replication is a feature of many GWAS studies of disease and nondisease traits\textsuperscript{94,95} and can be explained by a variety of factors including limited capture of the population being studied (eg, African-specific alleles), limited consideration of African-specific linkage disequilibrium, and inadequate knowledge of population substructure. Indeed, most GWAS studies to date have been undertaken using SNP panels based on the European or Asian genome, with limited representation of the African genome.\textsuperscript{96} A more complete and detailed representation of the genomes across different continents may improve our ability to identify susceptibility loci, because haplotype diversity in certain populations (eg, SSAs) is large and levels of linkage disequilibrium vary. Thus, specific studies in SSA populations, such as localization and fine mapping of susceptibility alleles and improved evaluation of population structure to avoid biases as a result of population stratification, will be crucial to enhance interpretation of GWAS results and the potential clinical value of susceptibility loci.\textsuperscript{97}

An appreciation of overall genomic architecture across diverse populations can also provide additional understanding about variant associations. For example, use of population genetics tools at previously described prostate cancer susceptibility loci can reveal evolutionary (eg, selective) forces that may have led to differences between African and non-African populations. Data obtained from multiple ethnicities can help explain why associations differ by different race/ethnicity groups (ie, because they have experienced different evolutionary forces). For example, why does a prostate cancer susceptibility haplotype confer evolutionary advantage in Africans but result in increased prostate cancer susceptibility in AAs? Such an approach can allow prioritization of specific loci as being more likely to explain the underlying cause of disparities across populations/ethnicities.

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**Key points**

- In a randomized phase III study of 400 unselected patients, median progression-free survival times of icotinib and gefitinib were 4.6 and 3.4 months, respectively ($P = .13$).
- Only a small fraction of enrolled patients were found to harbor EGFR mutations.
- It is anticipated that expanding knowledge of inherited and somatic genomics will further advance our understanding of cancer genetics and lead to improved strategies for prevention, detection, and treatment of cancer.
- Most GWAS studies to date have been undertaken using SNP panels based on the European or Asian genome, with limited representation of the African genome.
- A more complete and detailed representation of the genomes across different continents may improve our ability to identify susceptibility loci, because haplotype diversity in certain populations (eg, SSAs) is large and levels of linkage disequilibrium vary.
- An appreciation of overall genomic architecture across diverse populations can also provide additional understanding about variant associations.
- Data obtained from multiple ethnicities can help explain why associations differ by different race/ethnicity groups (ie, because they have experienced different evolutionary forces).
Regarding variation in the somatic genome, it remains feasible to screen for clinically relevant alterations at a scale and breadth that can be achieved through multiplexed profiling platforms,\textsuperscript{98,99} obviating the need to strictly limit the number of genetic markers for a specific population. We envision an increasing need for routine profiling of an expanding list of pharmacogenomic markers that can stratify patients to maximize efficacy and minimize risk of adverse events (Table 2). Moreover, the ability to interrogate whole exomes and genomes within clinically relevant time frames and cost will provide unprecedented opportunities to study the inherited and somatic genomes systematically. Studies examining the role of integrative large-scale genomics and transcriptomics to assign therapies have yielded promising results.\textsuperscript{109,110} although the therapeutic plateau imposed by acquired drug resistance and intratumoral heterogeneity remains a major challenge.\textsuperscript{111} Recent efforts at noninvasive biomarkers (eg, circulating free DNA) have facilitated the detection of emerging resistant clonal subpopulations over time, providing an avenue to interrogate mechanisms of drug resistance.\textsuperscript{112,113}

A recent study further demonstrated the feasibility of detecting genetic alterations in plasma from more than 80% of patients encompassing a broad range of cancer types, highlighting the potential role of blood-based genomic profiling as a noninvasive test for disease monitoring and screening.\textsuperscript{114}

There is an inadequate workforce available to undertake genomic studies. Training of the next generation of scientists who can undertake these activities is critical. Among the few who have this training, there are issues of professional retention and development to encourage continued work in this area, as well as to avert "brain drain" to developed countries. Ongoing training and sustained mentoring are important parts of professional development and retention. This may include the identification of funding for researchers and clinicians to attend relevant professional meetings. Second, there is inadequate infrastructure for quality data generation. These limitations include inadequate capacity for biospecimen handling and transfer from collection sites to processing sites; inadequate database systems for receipt and documentation of specimen tracking, reporting, and archiving; and lack of basic working equipment for genomic and biomarker analysis. An important limitation in this regard is ready access to an uninterrupted supply chain of quality reagents. Third, protocols and practices may not be optimal or standardized for the needs of the local environment. Standard operating procedures, quality assurance, and quality control protocols often need to be put in place. Ongoing internal and external review mechanisms may not exist and may have to be established, particularly if clinical applications of the data are to be instituted.

Even after establishing sequencing facilities, limited clinical infrastructure also hampers the implementation of genomic medicine, such as availability of genetic counseling, access to novel therapeutics, and sustainable funding structures for such genomic tests. Furthermore, the increasing depth and coverage required to uncover less common variants will result in large magnitudes of data and the need for stable secure bioinformaticians. Such genomic repositories linked to real-time capture of clinical phenotypes and outcomes are crucial to achieve clinically meaningful research across diverse geographic and socioeconomic settings.
### TABLE 2 - Single studies that have compared the prevalence of clinically actionable biomarkers across different ethnic groups

<table>
<thead>
<tr>
<th>Cancer and biomarker</th>
<th>Method</th>
<th>Population prevalence</th>
<th>Clinical implication</th>
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<tbody>
<tr>
<td><strong>Colorectal cancer</strong></td>
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<tr>
<td>KRAS&lt;sup&gt;100&lt;/sup&gt; (s)</td>
<td>Sequencing</td>
<td>African American: 23% (44/194); non-Hispanic white: 15% (13/86)</td>
<td>Mutant KRAS predicts for lack of response to EGFR monoclonal antibodies</td>
</tr>
<tr>
<td>MSI&lt;sup&gt;100&lt;/sup&gt; (g)</td>
<td>Nucleotide markers: NR21, NR22, NR24, NR27, BAT25, BAT26</td>
<td>African American: 9% (38/409); non-Hispanic white: 9% (12/86)</td>
<td>MSI-high implies impaired DNA mismatch repair; may indicate underlying Lynch syndrome; also may predict for response to immune checkpoint inhibitors</td>
</tr>
<tr>
<td><strong>Prostate cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMPRSS-ERG&lt;sup&gt;101&lt;/sup&gt; (s)</td>
<td>FISH</td>
<td>Japanese: 15.9% (7/44); white American: 50.0% (21/42); African American: 31.3% (20/64)</td>
<td>May imply sensitivity to abiraterone acetate</td>
</tr>
<tr>
<td>PTEN&lt;sup&gt;102&lt;/sup&gt; (s)</td>
<td>FISH</td>
<td>Chinese: 5.4% (5/93); white United Kingdom: 29.7% (46/155)</td>
<td>May predict for sensitivity to certain PI3K inhibitors</td>
</tr>
<tr>
<td>PTEN&lt;sup&gt;103&lt;/sup&gt; (s)</td>
<td>FISH</td>
<td>White: 19.8% (19/96); African American: 6.9% (7/101)</td>
<td>May predict for sensitivity to certain PI3K inhibitors</td>
</tr>
<tr>
<td><strong>Lung cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR&lt;sup&gt;45&lt;/sup&gt; (s)</td>
<td>Sequencing</td>
<td>Japan: 27% (71/263); Taiwan: 34% (32/93); United States: 14% (11/80); Australia: 7% (6/83)</td>
<td>Predicts for sensitivity to EGFR tyrosine kinase inhibitors</td>
</tr>
<tr>
<td>EGFR&lt;sup&gt;104&lt;/sup&gt; (s)</td>
<td>Sequenom</td>
<td>African American: 8.7% (12/137); white: 6.0% (20/335)</td>
<td>Predicts for sensitivity to EGFR tyrosine kinase inhibitors</td>
</tr>
<tr>
<td>KRAS&lt;sup&gt;104&lt;/sup&gt; (s)</td>
<td>Sequenom</td>
<td>Chinese: 10.9% (10/91); white: 31.6% (44/139)</td>
<td>Predicts for resistance to EGFR tyrosine kinase inhibitors</td>
</tr>
<tr>
<td>ALK&lt;sup&gt;75,105&lt;/sup&gt; (s)</td>
<td>FISH</td>
<td>Chinese: 6.8% (54/793); white: 5.6% (20/358)</td>
<td>Predicts for sensitivity to ALK inhibitors</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple negative&lt;sup&gt;106&lt;/sup&gt; (s)</td>
<td>IHC</td>
<td>African (Nigerian): 48.1% (101/210); white (United Kingdom): 14.5% (44/304)</td>
<td>May imply higher sensitivity to platinum chemotherapy and PARP inhibitors</td>
</tr>
<tr>
<td>HER2 amplification&lt;sup&gt;107&lt;/sup&gt; (s)</td>
<td>IHC or FISH</td>
<td>Asian: 20% (2,006/8,441); black: 17% (941/4,848); white: 13% (7,700/50,248)</td>
<td>Predicts for sensitivity to HER2-targeting antibodies</td>
</tr>
<tr>
<td><strong>Gastric cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 amplification&lt;sup&gt;108&lt;/sup&gt; (s)</td>
<td>FISH or IHC 3+</td>
<td>Asia-Pacific: 23.9% (454/1,900); Europe: 23.6% (188/795); Central/South America: 16.1% (78/484)</td>
<td>Predicts for sensitivity to HER2-targeting antibodies</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; FISH, fluorescent in situ hybridization; g, germline/inherited; IHC, immunohistochemistry; MSI, microsatellite instability; NSCLC, non–small-cell lung cancer; PARP, poly (ADP-ribose) polymerase; PI3K, phosphoinositide 3-kinase; PCR, polymerase chain reaction; s, somatic.
In this regard, efficient sharing of treatment experience between health care providers across institutions should be prioritized to accelerate biomarker discovery and more timely implementation of genomics-driven cancer care. The success of these endeavors will be dependent on developing scaled approaches tailored to specific populations and deploying appropriate technologies in diverse economic settings. Such disparities can also be bridged by forging partnerships between cancer programs in developed and developing countries, facilitating professional development (eg, through fellowships or exchange programs), and undertaking collaborative projects that apply leverage to the unique phenotypes in either setting.

Impact of genomic diversity on global drug development strategies

Given the significant population diversity described earlier, due consideration should be given to evaluating novel therapeutic agents across different ethnic groups. An illustrative example is the development of gefitinib, where population differences were already revealed in four phase I trials conducted across three continents (Figure 3), and yet definitive registration trials were obligated to be conducted only in Asia, several years after the high-profile failures of phase III trials including mainly white patients. Pan-cancer sequencing efforts have since revealed the majority of common therapeutically tractable alterations, of which a proportion exhibit some degree of variation across different populations (Table 2). A question yet to be resolved is whether these differences are a function of race or ethnicity per se (including nongenomic correlates of race) or whether they simply reflect the difference in frequency of genomic changes observed across racial/ethnic groups. Although drug responses linked to defined genomic markers appear similar across populations (Table 1), whether this will apply to emerging candidates, some of which may be more susceptible to epistatic effects, remains to be seen. Certainly, we are beginning to observe examples of population differences in treatment responses as a result of genotype (eg, BIM deletion polymorphism in \( \text{EGFR} \) mutant NSCLC), as well as cell of origin–specific differences in...
EGFR feedback activation in BRAF mutant colon cancer and melanoma, suggesting that the quality of response can differ depending on the genetic and epigenetic context. Moving forward, knowledge of race/ethnicity and single genetic markers may not be sufficient, with spatial and longitudinal interrogation of the multidimensional “omic” landscape across individual tumors necessary to devise optimal treatment strategies. The next wave of therapeutics will likely require consideration of signaling networks, adaptive resistance mechanisms, and cell context-specific factors, where other factors such as enhancers, histone modification, and interaction with other DNA elements need to be established. In addition, novel anticancer strategies such as RNA interference delivered through lipid nanoparticles and stapled peptides (eg, MDM2-p53 peptide, NCT02264613) are beginning to enter the clinic, providing greater finesse in calibrating personalized therapeutic approaches. It is essential to understand the ethnic, geographic, and genomic diversity to apply such novel therapeutics on a global scale. Accumulation of data on genome-wide interindividual differences will eventually feature not just as prognostic and predictive biomarkers in cancer, but also the blueprint for developing unique, rational treatment combinations specific to each patient.

### Conclusion

Cancer genomics has yielded profound insights into disease biology and is poised to transform oncologic care. Integration of genomic tests into routine clinical practice has already made a significant impact on the outcomes of certain molecularly defined cancers. Unequal access to genomic tests and novel compounds remains a pervasive problem, as exemplified by NSCLC in Asia. Despite significant logistical challenges with cross-border research efforts, ethnic and geographic population differences represent prime opportunities to gain insights into unique disease traits. As illustrated by prostate cancer in African populations, inadequate research infrastructures in developing countries hamper these efforts but could be surmounted through bridging collaborative research programs with developed countries. Similar to a free-market economy, health care disparities in the genomic era are set to broaden unless actively addressed and regulated in a concerted manner. Multinational and multiethnic collaborations in cancer genomics and cohesive efforts on cost management are required to understand the diversity and to close disparities in cancer prevention, detection, and treatment.

### Key points

- Novel anticancer strategies such as RNA interference delivered through lipid nanoparticles and stapled peptides (eg, MDM2-p53 peptide, NCT02264613) are beginning to enter the clinic, providing greater finesse in calibrating personalized therapeutic approaches.
- Integration of genomic tests into routine clinical practice has already made a significant impact on the outcomes of certain molecularly defined cancers. Unequal access to genomic tests and novel compounds remains a pervasive problem, as exemplified by NSCLC in Asia.
- Multinational and multiethnic collaborations in cancer genomics and cohesive efforts on cost management are required to understand the diversity and to close disparities in cancer prevention, detection, and treatment.

### References


