

# Molecular Profiling in Metastatic Colorectal Cancer

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**ABSTRACT:** Colorectal cancer (CRC) is a commonly diagnosed malignancy. Although chemotherapy remains the backbone of treatment, the landscape of treating metastatic CRC (mCRC) is changing with the understanding of its heterogeneity and molecular blueprint. Colon cancer sidedness has proven to hold prognostic implications, with right-sided tumors having higher incidence of *BRAF* and *KRAS* mutations and being microsatellite instability-high (MSI-H); overall, they have a worse prognosis compared with left-sided tumors. Results of molecular research have demonstrated the need to profile each mCRC patient for *RAS* and *BRAF* mutations, MSI-H status, *HER2* amplifications, and *NTRK* fusions. Ongoing clinical trials using targeted agents aim to further improve survival outcomes. We emphasize the epidemiology, knowledge of primary tumor location, and mutational landscape of mCRC, as well as novel treatment options for patients harboring unique subtypes of these characteristics.

## PERSPECTIVE

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## Introduction

Colorectal cancer (CRC) is a commonly diagnosed malignancy and the third leading cause of cancer death in the United States, with 147,950 estimated new cases and 53,200 estimated deaths in 2020.<sup>1</sup> Despite improvements in CRC screening methodologies, approximately 20% of patients are diagnosed with metastatic CRC (mCRC), which carries a 14.2% 5-year survival rate.<sup>2</sup> Although patients with stage IV CRC can occasionally undergo curative metastasectomies, treatment of patients with mCRC is for the most part palliative in nature and aims to prolong and improve the quality of life. A better understanding of the heterogeneity of mCRC, including primary tumor location, microsat-

ellite instability (MSI) status, and other clinically actionable tumor mutations, is reshaping the therapeutic landscape. Here we review the current molecular profiling practice for mCRC along with its prognostic implications and potential therapeutic targets.

## Colon Cancer Sidedness

Colon tumor sidedness has been a topic of great interest. The activated pathways in mCRC differ between the left and right sides.<sup>3</sup> The difference in sidedness may stem from embryonic origin: the right side of the colon arises from the midgut, whereas the left side arises from the hindgut, affecting blood supply.<sup>4</sup> Differences in gut microbiome, related to increased bile acid exposure on the right

side and predominant bacteria on the 2 sides of the colon—including *Prevotella*, *Pyramido-bacterium*, *Selenomonas*, and *Peptostreptococcus* (right); and *Fusobacterium*, *Escherichia-Shigella*, and *Leptotrichia* (left)—may all play a role in the phenotype of CRC sidedness.<sup>4</sup> The right side of the colon includes the cecum through to the proximal two-thirds of the transverse colon, and the left side of the colon includes the distal third of the transverse colon through to the sigmoid colon.<sup>4</sup> Most studies define right-sided tumors as those that arise from the cecum through but not including the splenic flexure, and left-sided tumors are those found in the splenic flexure through the sigmoid colon.<sup>5</sup> Rectal cancers are frequently included with left-sided colon cancers for the purpose of sidedness analyses.

The results of many studies have shown that patients with left-sided colon tumors tend to have superior overall survival (OS) compared with patients with right-sided tumors.<sup>6-10</sup> The CALGB/SWOG 80405 trial results revealed that the addition of cetuximab (an anti-EGFR monoclonal antibody) vs bevacizumab (an anti-VEGF monoclonal antibody) to standard chemotherapy in the first-line treatment of patients with *KRAS* exon 2

TABLE. Alterations, Frequency, Sidedness, and Targeted Therapies

Alteration	Frequency	Sidedness	Therapeutic agents if altered	Therapeutic agents if WT	Ongoing clinical trials
<b>KRAS mutation</b>	40%-50%	Right	—	EGFR inhibitor (cetuximab, panitumumab) <sup>a</sup>	G12C mutation: NCT04006301 NCT03785249 NCT04165031/NCT04185883 NCT03114319  G12D mutation: NCT03745326  G12V mutation: NCT03190941
<b>NRAS mutation</b>	4%-5%	—	—	EGFR inhibitor (cetuximab, panitumumab) <sup>a</sup>	—
<b>BRAF V600E mutation</b>	8%-10%	Class 1 right Class 2-3 left	Vemurafenib; dabrafenib; trametinib; encorafenib + binimetinib	EGFR inhibitor (cetuximab, panitumumab) <sup>a</sup>	—
<b>HER2</b>	5%-26.7%	Rectum/left	Trastuzumab <sup>c</sup> ; lapatinib <sup>c</sup> ; pertuzumab <sup>c</sup> ; tucatinib <sup>c</sup>	—	NCT03365882 NCT03043313
<b>NTRK fusion</b>	1%	—	Larotrectinib; entrectinib	—	NCT03215511
<b>dMMR/MSI high/TMB<sup>b</sup></b>	—	Right	Nivolumab +/- ipilimumab; pembrolizumab <sup>d</sup>	—	NCT02997228 NCT02912559 NCT02563002

dMMR, mismatch repair deficient; MSI, microsatellite instability; TMB, tumor mutational burden; WT, wild type.

<sup>a</sup>Regimens combining an anti-EGFR antibody with chemotherapy are appropriate only for patients who are WT for KRAS, NRAS, and BRAF.

<sup>b</sup>Combinations of encorafenib plus cetuximab or panitumumab are appropriate for patients with BRAF V600E mutations.

<sup>c</sup>Combinations of trastuzumab plus pertuzumab or lapatinib are appropriate only for patients with HER2-amplified and wild-type RAS and BRAF.

<sup>d</sup>Pembrolizumab use is for TMB-high patients.

wild-type (WT) mCRC did not improve OS, necessitating further study by dividing these patients into subsets to discover how best to direct standard therapeutic recommendations.<sup>11</sup> A follow-up study utilizing the same patient population (N = 782) confirmed primary tumor location as an independent prognostic factor for OS, with right-sided tumors being associated with inferior survival (HR, 1.392; 95% CI, 1.032-1.878;  $P = .031$ ).<sup>11</sup> Right-sided compared with left-sided colorectal tumors were found to have a higher BRAF mutation frequency and were more likely to be MSI-high (MSI-H).<sup>12,13</sup>

The NCIC CO.17 trial (N = 399) demonstrated that right-sided colon tumors (N = 150) were more poorly differentiated and had a higher rate of KRAS mutations than left-sided tumors.<sup>5</sup> For patients with KRAS WT tumors only, those with left-sided tumors had an increased progression-free survival (PFS)

benefit from cetuximab compared with best supportive care (median PFS, 5.4 vs 1.8 months; HR, 0.28;  $P < .0001$ ), whereas those with right-sided tumors received no such benefit (median 1.9 vs 1.9 months; HR, 0.73;  $P = .26$ ).<sup>5</sup> Investigators from other trials also identified a response to chemotherapy plus anti-EGFR therapy in patients with left-sided BRAF/RAS WT tumors, while those with right-sided tumors had adverse outcomes to anti-EGFR therapy but benefited from chemotherapy plus VEGF inhibition.<sup>5,8,11,14-16</sup>

### RAS Mutations

Mutations in any 1 of 3 RAS oncogenes—KRAS, NRAS, and HRAS—have been found to lead to autonomous growth and differentiation of cells driving cancer progression. A recent study of CRC patients (N = 13,336) identified KRAS mutations in 51.9% of specimens, with NRAS and HRAS mutations occur-

ring at lower rates.<sup>17</sup> These study results revealed that KRAS-mutated colorectal tumors were less likely to be mismatch repair deficient (dMMR).<sup>17</sup>

The presence of KRAS or NRAS mutations correlates with worse outcomes and resistance to anti-EGFR therapy, with or without chemotherapy.<sup>17-22</sup> Investigators in the phase 3 PRIME trial (N = 1183) randomized patients with treatment-naïve mCRC to receive panitumumab plus FOLFOX (5-FU, leucovorin, and oxaliplatin) or FOLFOX alone.<sup>23</sup> This study demonstrated that in patients with KRAS/NRAS WT disease, the addition of panitumumab to FOLFOX resulted in superior median PFS (10.1 vs 7.9 months; HR, 0.72;  $P = .004$ ) and median OS (26.0 vs 20.2 months; HR, 0.78;  $P = .04$ ). BRAF mutations were a negative prognostic and predictive factor, as patients with BRAF mutations did not benefit from panitumumab.<sup>23</sup>

RAS mutations, specifically *KRAS* and *NRAS* mutations, are used as predictive biomarkers for therapeutic resistance to upstream EGFR inhibitors. However, the successful development of targeted therapies to *KRAS* and other downstream signaling proteins means that *KRAS* mutation testing may play another role. Multiple phase 1 trials are testing small molecule agents that target the *KRAS* glycine-to-cysteine (G12C)-mutated protein (NCT04006301, NCT03785249, NCT04165031, NCT04185883). In addition to direct mutational targeting, agents targeting SHP2—which, encoded by *PTPN11*, is needed to activate RAS-MAPK—may become a viable therapeutic option for *KRAS* G12C-mutated CRC (NCT03114319). Additional targeted *KRAS* therapies include lymphocytes genetically engineered to express murine T-cell receptors that recognize G12V and G12D mutations (NCT03745326, NCT03190941).

### **BRAF Mutations**

Similar to the effects of *KRAS* mutation, patients with *BRAF*-mutated mCRC do not respond to anti-EGFR monotherapy (panitumumab or cetuximab) and have shorter PFS and OS compared with patients with *BRAF* WT tumors.<sup>19,24</sup> Approximately 8% to 10% of mCRCs contain a mutation in *BRAF*, a gene that encodes a signal transduction protein that is involved in the MAPK pathway.<sup>25,26</sup>

Due to its link to poor patient prognosis, the *BRAF* V600E mutation is a worthy target in CRC. However, *BRAF* inhibition alone has limited efficacy in the treatment of patients with mCRC. Vemurafenib is a small molecule tyrosine kinase inhibitor (TKI) that specifically targets the ATP-binding domain of *BRAF* V600E, hence activating the MAPK pathway in advanced malignancies with *BRAF* V600E mutations.<sup>26</sup> In mCRC, vemurafenib monotherapy is rarely effective due to incomplete inhibition of MAPK signaling and a re-

flexive activation of EGFR.<sup>26</sup> Kopetz and colleagues studied the efficacy of irinotecan plus cetuximab with or without vemurafenib in 106 patients with refractory *BRAF*-mutated mCRC.<sup>27</sup> PFS was improved with the addition of vemurafenib (median 4.4 vs 2.0 months;  $P < .001$ ), and there was a trend toward increased response rate (16% vs 4%) and disease control rate (67% vs 22%). Hence, vemurafenib plus irinotecan and cetuximab provided clinical benefit and became a new treatment option for this subset of patients.<sup>27</sup>

In addition to combined inhibition of EGFR and *BRAF*, the inhibition of the MAPK pathway has been explored through the combined inhibition of MEK, EGFR, and *BRAF*. The phase 3 BEACON study randomized patients with previously treated *BRAF* V600E-mutated mCRC 1:1:1 to triplet therapy of encorafenib (a *BRAF* inhibitor), cetuximab, and binimetinib (a MEK inhibitor); doublet therapy with encorafenib and cetuximab; or the control arm of chemotherapy (FOLFIRI or irinotecan) with cetuximab (N = 665).<sup>28</sup> Patients treated with the triplet and doublet had significant longer median OS when compared with the chemotherapy arm: 9.3 and 9.3 vs 5.9 months, respectively. Objective response rate (ORR) was also higher with the triplet (27%) and doublet (20%) compared with the chemotherapy arm (2%;  $P < .0001$ ).<sup>28</sup> As there was not a statistical numerical difference in terms of OS between the triplet and doublet, encorafenib and cetuximab (without binimetinib) was approved by the FDA.<sup>29</sup> The ongoing phase 3 ANCHOR trial is evaluating the triplet in the first-line setting.

### **MSI, TMB, PD-L1**

The PD-1 pathway is a negative feedback system that regulates cytotoxic Th1 immune response to prevent damage to host cells.<sup>30</sup> Tumor cells upregulate the PD-1 receptor or PD-1 ligand (PD-L1 or PD-L2) to evade destruction by the host's

immune system. The PD-1 pathway has been exploited in cancer immunotherapy. By blocking the PD-1 pathway with antibodies to PD-1 or PD-L1/PD-L2, the adaptive immune response is activated against tumor cells, resulting in an anti-cancer response. This has been observed in patients with a number of advanced cancers, including melanoma, non-small cell lung cancer, renal cell carcinoma, and others.<sup>30</sup> Further exploration of the PD-1 pathway has demonstrated the connection between response to PD-1 immune checkpoint inhibitors and dMMR. CRC with dMMR or MSI-H have a poor response to chemotherapy regimens, resulting in a worse prognosis for patients with metastatic disease.<sup>31</sup>

Tumors with dMMR contain large numbers of mutation-associated neoantigens; the immune system is more likely to recognize these antigens as foreign and launch an immune response. The clinical benefit of PD-1 blockade with pembrolizumab (an anti-PD-1 antibody) was first documented in a phase 2 study (N = 41), which enrolled patients with metastatic carcinoma with and without dMMR, and results revealed that only those with dMMR benefit from PD-1 blockade. Eleven patients with dMMR had CRC: 4 patients achieved a partial response and 5 had stable disease.<sup>30</sup> In a larger study of this population, the ORR of patients with dMMR CRC (N = 40) was 52%, with a 2-year PFS of 59%.<sup>32</sup> Of the posttreatment biopsies obtained and analyzed (N = 20), 12 showed inflammation, fibrosis, and mucin, but no evidence of tumor cells. This demonstrated an immunological anticancer response to PD-1 inhibitor therapy.<sup>32</sup> The phase 2 KEYNOTE-164 trial evaluated pembrolizumab in larger cohort of 124 patients with metastatic MSI-H/dMMR mCRC and demonstrated an ORR of 33%.<sup>33</sup> Additionally, analysis of tumor mutational burden in the phase 2 KEYNOTE-158 trial led to the FDA approval of pembrolizumab across solid tumors harboring a tumor

mutation burden (TMB) of 10 or more mutations/megabase after progression on prior therapy and showed a response rate of 29%.<sup>34,35</sup>

The anti-PD-1 antibody nivolumab was also found to be an effective therapy for patients with MSI-H/dMMR mCRC. Investigators of the CheckMate 142 trial (N = 74) reported ORRs, by RECIST 1.1, of 31.1%. Disease control rate at >12 weeks was found to be 68.9%.<sup>31</sup> Of note, tumor expression of PD-L1 was not found to be predictive of response because an objective response and disease control were also found in subjects with and without PD-L1 expression.<sup>31</sup> Additionally, nivolumab and other checkpoint inhibitors may exhibit greater activity than conventional chemotherapy or targeted therapy in patients with MSI-H, *BRAF*-mutant tumors, as shown by unprecedented response rates of 25% in patients with *BRAF*-mutant tumors.<sup>31</sup> Evidence from nivolumab and pembrolizumab studies indicates that these agents have efficacy in mCRC with MSI-H activity/dMMR.

To further enhance the possible therapeutic benefits of immunotherapy, the CheckMate 142 study also explored combination therapy with nivolumab and ipilimumab. Ipilimumab is an antibody targeting the CTLA-4 receptor; combination therapy with an anti-PD-1 antibody was shown to be more active than nivolumab monotherapy. Combination therapy appeared to provide a higher response rate (55%) relative to that of the monotherapy group (31%).<sup>36</sup> At 12 months, nivolumab plus ipilimumab had longer survival (PFS, 71%; OS, 85%) than nivolumab alone (PFS, 50%; OS, 73%).<sup>36</sup>

To investigate the therapeutic benefit of PD-1 immunotherapy in the first-line setting for patients with dMMR or MSI-H mCRC, the KEYNOTE-177 trial is currently ongoing (NCT02563002). The PFS data were presented at the American Society for Clinical Oncology 2020 Virtual Scientific Program, and

there was a clear improvement with pembrolizumab with a doubling of median PFS over investigator's choice of chemotherapy (16.5 vs 8.2 months; HR, 0.60; 95% CI, 0.45-0.80;  $P = .0002$ ) and only one-third of the grade 3-5 adverse event rate (22% vs 66%).<sup>37</sup> These findings have changed the standard of care to immunotherapy in the first-line setting for patients with dMMR or MSI-H mCRC and recently resulted in FDA approval.<sup>35</sup> The COMMIT study is another randomized, open-label phase III study that compares mFOLFOX6/bevacizumab vs atezolizumab monotherapy vs mFOLFOX6/bevacizumab plus atezolizumab as first-line interventions for patients with dMMR/MSI-H mCRC (NCT02997228).

### HER2 Amplification

Gene amplification of *HER2*, also referred to as *ERBB2*, is well described in breast and gastric cancers. Recently, *HER2* amplification emerged as a therapeutic target in mCRC. *HER2* overexpression is defined by immunohistochemistry (IHC) and amplification by fluorescence in situ hybridization (FISH). By IHC, colorectal tumor samples that show intense staining (3+) in greater than 50% of cells are designated *HER2*-positive. By FISH, an *ERBB2*:*CEN17* ratio of 2.0 or less in 50% or more of cells (when counting *ERBB2* and *CEN17* signals from 100 nuclei per case) indicates *HER2* amplification.<sup>38</sup> Using this analytical methodology, the incidence of *HER2/neu* amplification in mCRCs overall is low (approximately 5%). However, when analyzing mCRCs with a known rectal primary, the incidence can range from 12.4% to 26.7%.<sup>38-40</sup>

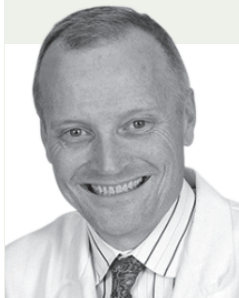
The open-label phase 2 HERACLES trial enrolled 27 patients with *KRAS* exon 2 WT, *HER2*-positive mCRC who were treated with the *HER2* monoclonal antibody trastuzumab and the dual *HER2/EGFR* TKI lapatinib.<sup>41</sup> Results revealed an ORR of 30%, median PFS of 21 weeks (95% CI, 16-32), median OS of 46 weeks (95% CI, 33-68), and manage-

able toxicities.<sup>41</sup> In a follow-up analysis, the plasma copy number of *ERBB2* amplifications was assessed in 48 plasma samples from 29 of the HERACLES trial's *HER2*-positive patients.<sup>42</sup> The MyPathway phase 2 basket trial enrolled a subset of patients with treatment-refractory *HER2*-positive mCRC (N = 57) and treated them with dual *HER2*-targeted therapy, trastuzumab and pertuzumab.<sup>43</sup> The treatment regimen was generally well tolerated and the response rate was 32%.<sup>43</sup> Ongoing clinical trials are further investigating *HER2*-targeted therapies vs standard chemotherapy (NCT03365882, NCT03043313). The novel antibody-drug conjugate trastuzumab deruxtecan showed a promising 45.3% response rate in a heavily pretreated patient population with *HER2*-positive mCRC.<sup>44</sup>

### NTRK Fusions

*NTRK* gene fusions, which encode TRKs, are rare but highly actionable. *NTRK* fusions lead to oncogenic overexpression of chimeric oncoproteins, which independently activate downstream signaling.<sup>45</sup> One multiphase trial explored the ORRs of TRK fusion-positive cancer patients (N = 55) to larotrectinib, a highly selective TRK inhibitor.<sup>46</sup> Seven percent (N = 4) of the patients treated had CRC, and their ORR was 75% (95% CI, 61%-85%), with durable responses seen at 1 year.<sup>46</sup> The results from two phase 1 trials, ALKA-372-001 and STARTRK-1, which tested the safety and efficacy of entrectinib, a multitargeted pan-TRK, ROS, and ALK inhibitor, in the treatment of TKI treatment-naïve patients with advanced or metastatic solid tumors, were reported together; they revealed that entrectinib was well tolerated and led to durable clinical responses lasting as long as 2 years.<sup>47</sup> Of the 119 patients treated, 15% had gastrointestinal primary tumors (N = 18). In the phase 2 portion of these studies, 1 patient with mCRC and an *NTRK* fusion had disease response lasting 2.6 months, which demonstrated

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PERSPECTIVE BY

**John L. Marshall, MD**

## The Prospective Incorporation of Molecular Profiling Will Transform Global Cancer Care

**W**e began the new decade with the satisfying news of a palpable, praiseworthy decrease in cancer mortality in the United States. This success is a result of continued research and investment in the understanding of cancer biology, and it is reflective of improved screening, improvements in adjuvant therapy, and maybe most impactful, the dramatic breakthroughs that immuno-oncology has brought. These results could not be obtained without decades of hard work within our highly collaborative environment composed of academic researchers, industry innovation and investment, supportive regulatory policies, and the “all-in” engagement of our patient partners.

Although I always held out hope, I never thought I would see such dramatic advances in my lifetime. Significant progress has been made in many of our most recalcitrant cancers, including lung cancer, kidney cancer, melanoma, hematological malignancies, and many others. But as we celebrate these achievements, we must remember that the successes we have achieved do not reliably equate with cures, which are our patients’ fundamental expectation and our true goal. We must remember that we continue to practice “in the dark,” unsure of who should get which drugs, and who might not need any drugs, radiation, or even surgery. We practice trial-and-error medicine, full of waste and residual toxicity. Cancer care is far from optimized, and much work remains ahead.

The first year of a new decade is a perfect time to reflect on the bigger picture of cancer care around the world. While we in the United States

and other richer regions of the world have enjoyed many medical successes, most of our brothers and sisters coinhabiting our planet have not. Cancer care has become a luxury item, available only to those with either significant personal wealth or the good fortune to live in countries with strong economies. The difference between “the haves” and “the have-nots” is striking, and in no medical discipline is this more dramatic than in oncology.

Let’s face it—cancer care is complicated: It requires a large, highly trained, multidisciplinary team for it to be optimally delivered. The best teams must include experienced, specialized surgeons; medical oncologists; radiation oncologists; all of the affiliated professionals who assist in the diagnosis and management of patients, such as gastroenterologists, pulmonologists, and interventional radiologists; and, of course, nurses, nutritionists, and a building full of pieces of highly complex equipment, with skilled individuals who know how to run them.

Most of the world’s population faces a very different level of health care. They struggle to have clean water and clean air, and to have basic health needs met. Such people are forced to make hard choices, or have had the will and foresight to make strategic changes that we, in the United States, have not yet been bold enough to make. Here, unanswered questions include: Is health care a right or privilege? Should everyone have access to unlimited care? What is the value of medical services? If you had to buy these services yourself, with your own money, would you?

We know that the health care

system in the United States is not sustainable for much longer, and cancer care—specifically, the widespread use of immunotherapy—is accelerating the oncoming economic crisis. Other nations have made the tough choices, in some cases limiting access to newer, expensive therapies that do not meet economically derived value metrics. How will we respond as a nation when we face the same social and economic decision points?

At a time when nations are building walls, we in the cancer community must deepen our commitments to each other through collaborative research and data sharing. Our only way forward is to work together, especially as we expand our understanding and the ability to measure the complexities of cancers. The next great frontier for cancer research is precision medicine; with it comes the expanded incorporation of complex molecular profiling, linked to artificial intelligence-based machine learning, into our therapies and decision-making.

While recognizing that basic molecular testing of tumors is part of everyday practice, we are just beginning to understand this rapidly evolving field. If we reflect back, even on the past decade, we have evolved from a culture where no molecular testing was done for most cancers, to a time when single or “oligo” testing was performed, to today, when broad molecular profiling is rapidly becoming the standard of care. In less than a decade, genetic sequencing has moved from being a research question with no insurance coverage, to garnering FDA approvals, to becoming accepted by insurance companies as the standard of care.

As our tests have become increas-

ingly complicated, we have come to recognize the importance of tissue quality and of preanalytic management of the specimen. We see more clearly the need to understand the actual assays that are being run, and to appreciate how one type of assay compares with another—eg, tissue vs liquid samples. Also, as with any new technology, we have seen a widening knowledge gap among us clinicians. As the technology and complexity of precision medicine have changed, we have fallen behind in our ability to interpret our patients' results. Some clinicians have become so frustrated and confused that they have stopped ordering molecular testing altogether. Others choose to order tests that yield a relatively low percentage of results that dramatically alter treatment decisions. Still others misinterpret results, causing additional medical expense and patient anxiety. And then, in many parts of the world, clinicians simply do not want to know the results of any tests they could theoretically order because, while they know that those results could indicate applicability of the latest promising treatment (eg, checkpoint inhibitors for microsatellite instability–high tumors), they do not have access to these therapies, leaving them only with regret over what might have been.

The rising cost of drug development is typically the first reason put forward to explain the rising cost of drugs, once they are approved. No doubt, drug development has become very expensive, and while the issue is multifactorial, a major reason is the rise of precision medicine. As we recognize that not all cancers are alike and subdivide them into smaller and smaller subgroups, trials become increasingly expensive. It costs more to find the patients, it takes longer to accrue the studies, and then, in the end, there is a smaller market of patients to purchase the therapy, limiting the return on investment.

At least within the United States, our government regulatory bodies have been keeping step with the rapid change in drug development and cancer technology. No longer is the only gold standard for drug approval a series of large phase 3 randomized trials. Don't get me wrong; this is still a standard route for drug discovery and approval. However, as we have increasingly identified molecular targets in patients with fatal cancers that portend a very high benefit rate (<50%) with improved safety signals, our regulatory agencies have granted rapid approvals. So instead of "slogging" through large randomized trials in the hope of a hazard ratio of .8, trials are now being designed with target hazard ratios of .5 and lower, results that don't actually require a statistician to confirm positivity. Given that our science is there, and our regulatory bodies are behind us, we need to play by new rules.

For the past several years, I have been fortunate to help build and lead a US-based collaborative group of investigators charged with studying the science of precision medicine, the Precision Oncology Alliance. It was only through coordinating our efforts and sharing our vast amounts of molecular and clinical data that we were able to uncover the many discoveries hidden within. Collectively, we understand the value in numbers, of the ability to characterize our patients into new subgroups, and of beginning to apply the latest therapies using prospective enrichment. As we move forward, increasingly complex molecular results are being analyzed using artificial intelligence/machine learning to provide us with more prognostic and predictive insights.

We are beginning to embrace tumor heterogeneity, and we continue to invest more in the practice of biomarker discovery. This work will uncover more targets and allow for better therapeutic decisions, meaning that we can

all ultimately fight a smarter, more efficient war against cancer. Critical to our success will be global outreach and expansion of cancer care markets. We have well-established science showing us that cancers vary by global distribution, maybe secondary to differences in the microbiome. This suggests that results from trials performed in one region of the world may not be applicable in other regions.

As part of our current work, representatives from around the world are building a global precision network, the Oncology Alliance for Individualized Medicine (Onco AI-Med), that links cancer centers in 4 continents. By analyzing tumors optimized for tissue quality—limiting ischemia time—and performing extensive testing that includes whole genome sequencing, whole RNA transcriptome, proteomics, and ultimately metabolomics on both the tumor and normal tissues, coupled with artificial intelligence learning, we expect to push the field of precision medicine to its next phase. We also hope that by having large populations of patients "profiled" prospectively, we will lower the cost of drug development through rapid patient identification.

Precision medicine, while still in its infancy, is accepted and here to stay. Rapid improvements in technology continue, which for all their benefits also create a widening knowledge gap, which we must close. To accomplish this, we must partner on a global scale, both because the science requires this and, more importantly, because we are morally compelled to share our success with our fellow global citizens. Cancer care can no longer be a luxury item, only for the rich. We must work toward wide access. Opening markets through collaborative science will secure the return on investment for our business partners, and secure our progress toward finding the cures for cancer.

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