The identification and characterization of gene signatures, driver events, and pharmacogenomics in molecularly homogeneous subsets of patients is likely to advance effective drug development strategies in colorectal cancer.

Colorectal cancer has been extensively molecularly characterized in recent years. In addition to furthering the understanding of biologic hallmarks of the disease, the ultimate goal of these studies has been to provide tools that would allow us to identify subgroups of colorectal cancer with prognostic and predictive implications, either for the anticipation of toxicity or for selection of the best therapy, or both. As a result of these efforts, multiple genomic tests have become available for clinical use in early-stage and advanced colorectal cancer. Goldstein and colleagues have carefully reviewed the cost-effectiveness of these tests in this issue of ONCOLOGY[1]; their evaluation is timely, considering the widespread availability of high-throughput technologies for genomic profiling.

The authors recognize that the cost-effectiveness of a prognostic test can be easily measured only if it specifically guides treatment decisions. Given the lack of validated predictive biomarkers for benefit from adjuvant chemotherapy in early-stage colorectal cancer, clinicians are left with only prognostic tests that estimate risk of relapse to help them with treatment individualization. Because of the modest therapeutic benefit of fluorouracil (5-FU)-based treatment, prognostic biomarkers for its use have their greatest potential benefit in stage II disease, a setting in which they can facilitate the identification of subsets of patients with lower or higher risk of relapse and for whom adjuvant chemotherapy could be avoided or favored, respectively. Microsatellite instability (MSI), for example, has been consistently associated with low recurrence rates and a very good outcome without adjuvant treatment, supporting a no-adjuvant-treatment approach in patients with MSI tumors. On the other hand, predictions of poor prognosis based on pathologic factors have not been consistently tied to benefit from adjuvant chemotherapy in stage II colorectal cancer,[2] raising concern about the real value of complex alternative tests such as prognostic gene expression signatures in this setting. These genomic signatures could have the greatest clinical utility as complements to analysis of T stage and MSI status, specifically for patients who have pT3 microsatellite stable (MSS) stage II disease. The Oncotype DX colon cancer gene expression array is the prognostic score that has been most widely validated, and despite a high score being an independent risk factor for recurrence in multivariable models, differences in outcomes for low-risk and high-risk patients are only modest from a clinical perspective. Cross-comparison of Oncotype DX scores with poor-risk clinical and pathologic factors, such as those recommended by the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) guidelines, has not been extensively conducted. Prospective empiric evidence is scarce, and the test does not influence the treatment decision in the majority of patients.[3] Furthermore, economic studies assessing the cost-effectiveness of these signatures for selecting patients with colorectal cancer at high risk for recurrence (and for basing adjuvant chemotherapy decision making on this criterion) are not yet available.

Focusing on advanced colorectal cancer, in which validated and clinically useful predictive markers are widely used to select anti–epidermal growth factor receptor (EGFR) therapy, the absence of specific sensitivity/resistance patterns for infrequent mutant alleles in KRAS, NRAS, or BRAF genes should not prevent clinicians from ordering extended RAS testing to help tailor therapy. There are a number of justifications for this approach. First, in some prospective randomized trials, a detrimental effect has been observed with the addition of anti-EGFR agents to chemotherapy in patients whose tumors harbor mutations in KRAS beyond codons 12 and 13 or in NRAS.[4-6] Second, following advances in next-generation sequencing, the development of targeted agents for use in treating colorectal cancer is moving from the “one test–one drug” paradigm to a genomically stratified model.[7] Early clinical trials have shown that targeted therapies matched against KRAS, NRAS, or
BRAF mutations may offer promising treatment opportunities in colorectal cancer. Specifically for the BRAF V600 population, studies have shown that treatment with selective BRAF inhibitors in combination with other targeted agents (EGFR, mitogen-activated protein/extracellular signal-regulated kinase [MEK], and/or phosphatidylinositol 4,5-bisphosphate 3-kinase [PI3K] inhibitors) can lead to unprecedented response rates in highly chemo-refractory patients.[8,9] In summary, given the potentially detrimental effects of anti-EGFR therapies and the benefit demonstrated in early clinical trials with novel agents, the cost-effectiveness of extended RAS-BRAF mutation profiling needs to be reexamined.

The potential benefits of multiplexed genotyping platforms in individual patients with colorectal cancer have already been demonstrated, and the next logical step is to facilitate larger clinical trials with biomarker-driven therapies. However, there are many obstacles for implementation of next-generation sequencing in clinical practice:

- Unsolved biologic questions.
  - How to integrate and make biologic sense of the substantial amounts of genomic data?
  - How to distinguish a driver from a passenger genetic aberration?
  - How to deal with incidental findings?
  - How to define which mutations engender sensitivity to specific targeted agents?
  - How to select therapy in the case of multiple aberrations?
  - Should profiling be of primary tumor or of real-time biopsies of metastatic sites? Clonal evolution, selection pressure from prior therapies, and tumor heterogeneity may affect the results.
- Scientific concerns regarding platform selection and turnaround time: need for standardization in the collection, handling, and storage of specimens, and in bioinformatics pipelines.
- Logistical issues related to prescreening strategies: in whom, when, and where (local pathology lab or centralized lab?) to perform molecular profiling.
- Challenges in ethical and economic domains: setting up certified labs, costs of diagnostic tests and biopsies, off-label use of targeted therapies.

Moreover, to implement true personalized medicine, we should also consider the characteristics of the host-tumor relationship (tumor microenvironment and immune response) and host-drug relationship (metabolism genes and pharmacogenomics). As described by the authors, although many strategies have been developed for assessing dihydropyrimidine dehydrogenase (DPD) activity to guide 5-FU dosing, none has been properly validated for clinical utility. An alternative pharmacokinetically guided approach has indeed been proven to be cost-effective but is logistically more complex.[10] Uridine 5′-diphospho-glucuronosyltransferase 1A1 (UGT1A1) testing to guide irinotecan dosing is more promising, although the very low prevalence of the genetic variation linked to substantial hematologic toxicity at the standard doses used in the clinics largely compromises its utility. However, cost-effectiveness may change favorably when the test is used to identify a larger subpopulation that can tolerate higher doses of irinotecan, with increased response rates as seen in multiple phase I trials.[11-13] Larger phase II trials of genotype-directed tailored irinotecan dosing in advanced colorectal cancer are ongoing.

To conclude, we believe that the identification and characterization of gene signatures, driver events, and pharmacogenomics in molecularly homogeneous subsets of patients is likely to advance effective drug development strategies in colorectal cancer. Many challenges must be overcome before genomic-driven trials and personalized cancer medicine can become a reality and supplant currently accepted modalities. As costs decrease for next-generation sequencing and other high-throughput technologies, the clinical and economic impact of genomic tests in colorectal cancer will need to be revisited.

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