The use of molecular testing to personalize cancer treatment selection is on the rise and has been heralded as a panacea for patients diagnosed with cancer. In principle, the scenario for molecular testing is clearly positive: a relatively inexpensive test that identifies “responders” to expensive therapeutics can improve outcomes for those who receive it while sparing other patients (and society) the risk and expense of medicines that ultimately will not help and sometimes can harm. As with all major advancements in the treatment landscape, a fuller picture of molecular testing can only emerge through experience. That experience inevitably leads to a more nuanced understanding of molecular testing’s impact on outcomes, costs, and value for patients and populations.

A prime example of the evolution of knowledge from promise to reality can be seen with KRAS mutation testing in metastatic colorectal cancer (mCRC). KRAS, and to a lesser extent BRAF, mutation testing is used to identify mCRC patients who do not benefit from two costly anti–epidermal growth factor receptor (EGFR) therapies: cetuximab and panitumumab. The intent of testing is to avoid unnecessary drug exposure and the associated toxicity and cost for the 30% to 40% of mCRC patients who do not benefit from these drugs (ie, patients with tumors harboring KRAS mutations). Both the National Comprehensive Cancer Network and the American Society of Clinical Oncology clinical guidelines support the use of KRAS testing in clinical practice based on level 2 evidence from retrospective analyses of clinical trial data and other observational study designs (1,2). However, the real-world impact of screening for both KRAS and BRAF prior to treatment initiation is not yet fully understood. Simulation modeling can be a useful way to estimate the impact of molecular testing on population health outcomes, costs, and value, as well as to identify factors that fundamentally drive the benefits and drawbacks of molecular testing.

In this issue of the Journal, Behl et al. (3) report the results of a patient-level decision analytic model designed to compare four strategies involving KRAS and BRAF mutation testing to select treatments for patients diagnosed with metastatic colorectal cancer: 1) no anti-EGFR therapy (best supportive care); 2) anti-EGFR therapy without screening; 3) screening for KRAS mutations only (before providing anti-EGFR therapy); and 4) screening for KRAS and BRAF mutations (before providing anti-EGFR therapy). Best supportive care treatment could include all treatments other than anti-EGFR, such as chemotherapy, radiotherapy, anti–vascular endothelial growth factor (VEGF), and surgery. The authors considered clinical factors that were not accounted for in earlier evaluations, specifically the site of metastases (which influences the benefits of further therapies), cost of and impact of hepatic resection, and treatment patterns that are likely in real-world (vs trial-world) patients. They ran 10,000 simulations for 50,000 mCRC patients, generating average costs, outcomes, and uncertainty ranges around those averages. These estimates were then used to generate comparative results, including cost-effectiveness ratios for the different strategies.

Their study had two key findings. First, KRAS and BRAF testing are cost saving compared with treating all patients with anti-EGFR therapies. KRAS screening alone saves $7493 per patient. Adding BRAF testing may save an additional $1023 per patient. However, the population-level cost savings of approximately $103 million per year in the United States was not as dramatic as that of a previous analysis showing savings of $740 million per year (4). Although not explicitly stated, this difference is likely attributable to the attenuated cost-savings estimate from modeling a real-world vs trial population. The second key finding is that KRAS and BRAF testing do not improve survival compared with anti-EGFR therapy without testing; in fact, survival in the treat-all scenario is better, although the difference is negligible (approximately 1 day). The authors thus emphasize the primary benefit of KRAS/BRAF testing is the cost savings to patients and society, not survival.

Although the study provides a highly nuanced examination of the use of KRAS and BRAF testing in mCRC, it is subject to two important limitations, and the authors note that these issues may impact the study results and the conclusions. First, the analysis does not adjust for quality-of-life impacts and thus does not report quality-adjusted life years as an outcome. Quality-adjusted life years would capture the toxicity-sparring impacts of KRAS and BRAF testing. Including a quality-of-life adjustment to survival would likely show that testing improved outcomes (ie, it would have showed higher quality-adjusted life years for testing vs the no-testing strategies). Another limitation is that the analysis did not account for the cost of treating adverse events related to the drug therapies included. This will underestimate the cost savings, although given the relatively modest toxicity profile of cetuximab and panitumumab, the additional cost savings are unlikely to dramatically impact the conclusions.

We feel that this study highlights two important practical points about molecular testing that researchers and practitioners should keep in mind when translating results from clinical trials to the bedside or...
Hepatocellular Carcinoma

This long window of time provides an opportunity for investigating the development of HCC usually ranges from 10 to 30 years; to various etiologies (2). The latent period from the original disease of viral hepatitis (ie, hepatitis B and hepatitis C) and liver cirrhosis due to inflammation, a form of host immune defense. It is most obvious in the setting of viral hepatitis, especially hepatitis C viral infection. Hepatitis C virus is the major etiological factor for HCC in most developed countries. Hepatitis C virus has an ability to evade tent infection, resulting in lasting inflammatory response in the liver (3). Although the detailed molecular cascades are not entirely known, there is no doubt that inflammation can cause genetic and epigenetic dysregulation in hepatocytes and, eventually, cell transformation. Once cancer is established in the liver, the host’s innate and adaptive immune system still persistently attempts to eradicate or slow the cancer cell growth. Recent studies have demonstrated to populations. First, molecular testing is as much about generating cost savings by identifying nonresponders as it is about improving survival by identifying responders. In this context, highly accurate tests are needed to mitigate the potential negative survival impacts of classification. Second, molecular tests are probably not as good as they might first seem. Community practice is messy. Tests will be inconsistently applied and evaluated. Patients discontinue therapies more quickly than they do in registration studies. Distant metastases are much more difficult to manage than they are in clinical trials.

A good model will account for these issues because decision makers recognize they are part of the real world and want to know how they influence the results, even if those results become less favorable.

Even accounting for these issues, KRAS testing for mCRC proves to be a bit of a no-brainer; the test has sufficiently favorable sensitivity, specificity, and cost so that the clinical and economic rationale for its use is highly apparent. So what was the value of building a complex decision model for this problem? First, as we noted, it highlights the fact that real-world considerations attenuate the value of modern molecular tests, even those with high levels of analytical validity and clinical utility. Second, the authors have shown that the BRAF test, although it may have poorer performance characteristics than the KRAS test, can still save health resources without substantially sacrificing outcomes. Finally, and most importantly, this study of an unusually accurate test raises important issues that should be considered for other molecular tests in other settings. The “sacrifice” in life expectancy in the testing vs no-testing comparison is trivial because there are very few false-negative tests and because the targeted therapies are relatively safe and offer modest survival benefit when given to all patients regardless of their EGFR status. How would we consider a test that affords a similarly large savings in costs but also yields substantially fewer life years (or quality-adjusted life years) because of poorer test performance? What if the treatment offers a moderate benefit to all but a much higher benefit to a molecularly targeted minority? KRAS testing is here to stay, and these other molecular testing scenarios are surely on the horizon.

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Notes

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Current chemotherapy and radiation therapies for hepatocellular carcinoma (HCC), which causes 500,000 deaths per year worldwide, are not very effective. The recently approved multikinase inhibitor Sorafenib modestly improves survival by a few months in some patients with advanced cancer (1). Surgical resection and liver transplantation can be performed in less than 20% of patients. In the setting of viral hepatitis, especially hepatitis C viral infection. Hepatitis C virus is the major etiological factor for HCC in most developed countries. Hepatitis C virus has an ability to evade its host’s innate and adaptive immune system and establish persistent infection, resulting in lasting inflammatory response in the liver (3). Although the detailed molecular cascades are not entirely known, there is no doubt that inflammation can cause genetic and epigenetic dysregulation in hepatocytes and, eventually, cell transformation. Once cancer is established in the liver, the host’s innate and adaptive immune system still persistently attempts to eradicate or slow the cancer cell growth. Recent studies have demonstrated

Guardian and Selective Killer: The Versatile Functions of TLR3 in Hepatocellular Carcinoma

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To achieve this end, a better understanding of the mechanisms by which HCC develops and progresses is critically important. The common denominator underlying HCC carcinogenesis is inflammation, a form of host immune defense. It is most obvious in the setting of viral hepatitis, especially hepatitis C viral infection. Hepatitis C virus is the major etiological factor for HCC in most developed countries. Hepatitis C virus has an ability to evade its host’s innate and adaptive immune system and establish persistent infection, resulting in lasting inflammatory response in the liver (3). Although the detailed molecular cascades are not entirely known, there is no doubt that inflammation can cause genetic and epigenetic dysregulation in hepatocytes and, eventually, cell transformation. Once cancer is established in the liver, the host’s innate and adaptive immune system still persistently attempts to eradicate or slow the cancer cell growth. Recent studies have demonstrated