For the first time we are aware of, Jang et al have used novel genetic mutation biomarkers instead of clinicopathologic features to estimate the most cost-effective treatment with the greatest added quality-adjusted life years (QALYs) among patients with stage T1 colorectal cancer (CRC). One QALY equates to 1 year in perfect health. The incremental cost-effectiveness ratio was used to summarize the cost-effectiveness of the health care intervention per QALY.

Current approaches to therapy selection are based on estimates of nodal disease risk using pathologic features, such as depth of submucosal invasion (ie, >2000 μm), lymphovascular invasion, histologic grade, or tumor budding after endoscopic polypectomy. The higher the risk of nodal metastasis, the greater the need for surgical intervention (ie, laparoscopic or open). Initial attempts at endoscopic resection (eg, endoscopic mucosal resection, endoscopic submucosal dissection) have no adverse effects on long-term outcomes.

In the study by Jang et al, the authors chose to use genetic features of cancers to assign the best therapy. A total of 6 gene variant subgroups were used to stratify CRC prognosis; 5 subgroups for microsatellite stable tumors were defined by combinations of 1 or 2 APC (OMIM 611731) nonsense variants, a nonsynonymous TP53 (OMIM 191170) variant, and 1 of 5 nonsynonymous KRAS (OMIM 190070) variants. Microsatellite instability–high tumors with BRAFV600E (OMIM 164757) variants were also studied. Using $100 000 per QALY to determine cost-effectiveness, Jang et al determined that the least expensive procedure, endoscopic therapy, was cost-effective for all 6 subgroups.

We applaud the authors for the novelty of basing their findings on biological data (ie, somatic variants) rather than simply pathologic data. The use of genetic data raises the hope that, with future research, nodal status could be more accurately predicted, reducing the chances of recurrent disease (and its associated costs) when only a local therapy is administered. A critical issue in treating stage T1 CRC is the ability to accurately predict nodal metastasis, which worsens prognosis and drives the need for adjuvant chemotherapy. The risk of nodal metastasis is estimated to be between approximately 6% and 16% in stage T1 CRC. A Surveillance, Epidemiology, and End Results Program of the National Cancer Institute database review of patients with stage TINOMO CRCs demonstrated higher 1-year (92% vs 88%) and 5-year (75% vs 62%) survival among patients who underwent surgical resection vs polypectomy, but the survival was similar in both cohorts after accounting for age, comorbidities, and propensity quintile. Thus, with proper genetic and pathologic selection, it may be possible to reduce the risk of recurrence (and the associated costs of treating recurrence), thereby personalizing therapy for this subset of patients with CRC.

Notably, the expected life span was close to normal for all subgroups described in the study by Jang et al and summarized earlier. Consequently, it is not that surprising that the least expensive therapy emerged as the most cost-effective. The costs for endoscopic therapy were estimated to range from $41 000 to $78 000 across the 6 subgroups. The additional costs for the most expensive therapy (ie, open colectomy) were between $10 000 and $14 000 higher in 4 subgroups and at most $28 000 higher. Given the modest increase in cost, some patients might elect to receive the more aggressive therapy, owing to the potential life span gains. For example, for the most aggressive subgroup (ie, APC(2)/KRAS/TP53), those who received laparoscopic therapy were expected to live 0.55 years longer (QALY time was only 0.21 years). Moreover, the gains will vary by patient, and the modeling itself is imperfect. Additionally, adding genetics to predicting the stage of an endoscopically
resected T1 cancer may be more accurate than pathologic assessment alone, and this accuracy might translate to reduced costs over time, favoring the less aggressive procedure.

A 2016 study by Schell et al\(^5\) identified variable prognosis with variants in APC, TPS3, KRAS, and BRAF distributed in 6 classes. Given the recent advances in next-generation sequencing technology, most polyps could be biopsied and/or resected and submitted for targeted somatic sequencing. Jang et al\(^1\) have demonstrated the ability to incorporate genetic testing into the therapeutic algorithm to individualize therapy. The addition of genetic testing to clinicopathologic features (ie, the current standard of care) may provide a new means of determining the most cost-effective, highest-quality approach for this early stage of disease. A prospective comparison of genetic vs pathologic staging in predicting surgical pathologic staging will be necessary to determine whether genetic assessment can improve accuracy and lower costs when a less aggressive procedure is deemed appropriate. These approaches are consistent with the emerging population health model for sustainable and affordable health care.