Anticipating the Clinical Use of Prognostic Gene Expression–Based Tests for Colon Cancer Stage II and III: Is Godot Finally Arriving?

Anita Sveen, Arild Nesbakken, Trude H. Ågesen, Marianne G. Guren, Kjell M. Tveit, Rolf I. Skotheim, and Ragnhild A. Lothe

Abstract

Purpose: According to current recommendations for adjuvant treatment, patients with colon cancer stage II are not routinely offered chemotherapy, unless considered to have a high risk of relapse based on specific clinicopathological parameters. Following these criteria, it is challenging to identify the subgroup of patients that will benefit the most from adjuvant treatment. Contrarily, patients with colon cancer stage III are routinely offered chemotherapy, but due to expected adverse effects and frailty, elderly patients are often excluded from standard protocols. Colon cancer is a disease of the elderly and accordingly, there is a large subgroup of patients for which guidelines for adjuvant treatment remain less clear. In these two clinical settings, improved risk stratification has great potential impact on patient care, anticipating that high-risk patients will benefit from chemotherapy. However, microsatellite instability is the only molecular prognostic marker recommended for clinical use.

Experimental Design: In this perspective, we provide an updated view on the status and clinical potential of the many proposed prognostic gene expression–based tests for colon cancer stage II and III.

Results: The main limitation for clinical implementation is lack of prospective validation. For patients with stage II, highly promising tests have been identified and clinical trials are ongoing. For elderly patients with stage III, the value of such tests has received less focus, but promising early results have been shown.

Conclusion: Although awaiting results from prospective trials, improved risk assessment for patients with stage II and III is likely to be achieved in the foreseeable future.

Introduction

The question of whether to treat patients with colon cancer stage II with adjuvant chemotherapy remains among the most challenging questions in oncology (1). Although approximately 20% of patients with stage II relapse after surgery, improvements in survival upon treatment with chemotherapy is very low for this patient group as a whole, and adjuvant therapy is not recommended as standard of care (2–6). Rather, the choice of adjuvant therapy for the individual patient with colon cancer stage II is based on clinicopathological high-risk factors, including stage pT4 (invasion of serosal surface or adjacent organs), poor differentiation, lymphatic or vascular invasion, bowel obstruction or perforation, emergency surgery, incomplete tumor resection, and inadequate number of lymph nodes sampled (<12; 7). In a recent study by O’Connor and colleagues, reporting on a representative population of almost 25,000 patients with stage II (ages 65 years or older), as many as 75% of the patients were categorized with at least one poor prognostic feature (8). No survival benefit from adjuvant treatment was found for this high-risk patient group. Furthermore, there was only a 2% difference in the frequency of use of adjuvant therapy between the high- and low-risk groups (8). Accordingly, improvements to risk stratification continue to have great potential benefit for patient care in colon cancer stage II.

In contrast, adjuvant treatment of patients with colon cancer stage III is considered one of the greater success stories of gastrointestinal oncology (9). This is due to a more than 10% absolute improvement in survival for patients receiving fluorouracil-based treatment, and another 4% by addition of oxaliplatin (3, 10–13). However, although standard protocols recommend adjuvant chemotherapy for all medically fit patients with stage III disease (6, 7), only a little more than half of the patients reported by

Keywords: Prognostic gene expression–based tests, colon cancer stage II, colon cancer stage III, adjuvant chemotherapy.
Translational Relevance

Identification of patients with colon cancer stage II and III who will benefit from adjuvant treatment is a major clinical challenge. A significant proportion of patients treated with surgery alone experiences relapse, whereas some patients receiving chemotherapy would be cured with surgery alone. The use of gene expression–based tests, in conjunction with clinicopathological parameters, has clear potential for improved treatment decisions based on risk assessment. Several prognostic gene expression–based tests have been proposed for this purpose. However, clinical implementation is awaiting prospective validation. For colon cancer stage II, clinical trials are underway and this prospect has never been closer. For colon cancer stage III, clinical relevance is limited to patients that are not routinely offered adjuvant chemotherapy, in particular elderly patients. Promising results are emerging also for this patient subgroup.

O'Connor and colleagues (57% of 18,185 patients with stage III) actually did receive such treatment (8). This is consistent with previous reports of underuse of adjuvant chemotherapy (14). In particular, the use of chemotherapy decreases with increasing patient age and comorbidity (8, 15). Elderly patients are often underrepresented in clinical trials, hence there is little data on the trade-off between efficacy and toxicity (16). However, it was recently reported that patients older than 75 years have a similar magnitude of survival benefit from fluorouracil-based treatment as younger patients (17, 18). The high age of patients with colon cancer (40% are older than 75 years at the time of diagnosis) and the increasing life expectancy in general, therefore emphasize the importance of guidance of treatment options by improved risk stratification also for this patient group (16).

Overview of gene expression–based prognostic tests

In contrast with anticipations, with the pioneering success in breast cancer (reviewed in ref. 19), and despite the large number of proposed gene expression–based assays (overview in Table 1), clinical guidelines for colon cancer explicitly express that no multigene assays are currently recommended for use in risk assessment and determination of adjuvant treatment (6, 7). This is a natural consequence of the lack of large prospective trials designed to evaluate their clinical value. Such trials are still considered the gold standard for evaluation of biomarkers, albeit with suggested alternatives to the conventional setting with randomized, controlled trials (20–22). As evident from Table 1 and several previous reviews (23–27), the main limitations of the proposed assays are small sample sizes and unsatisfactory or lacking validation in independent patient series. However, changes are on the horizon. To our knowledge, five tests have now been launched, including OncoType DX Colon Cancer (Genomic Health, Inc.); ColoPrintPRS (Signal Genetics LLC); ColoPrint (Agendia NV); GeneFx Colon (Precision Therapeutics, Inc.); and OncoDefender-CRC (Eveirst Genomics, Inc.). All these tests have been shown to have prognostic value in independent patient series, although the designs and sample numbers of the validation analyses have varied (Table 1; see also previous reviews of ColoPrint, OncoType DX Colon Cancer, and GeneFx Colon; refs. 25, 28, 29). In addition, we have recently published two new tests, ColoGuideEx (30) and ColoGuidePro (31), performing development and successful validation in three independent patient series across populations and micro-array platforms (Table 1).

Currently, OncoType DX Colon Cancer is the only test that is available outside of research settings, although it has not yet been recommended for clinical use (32). This is the test for which prognostic potential has been most thoroughly validated (Table 1; refs. 33–35). Furthermore, for evaluation of ColoPrint, patients are being recruited to the Prospective Analysis of Risk Stratification by ColoPrint (PARSC) prospective trial (NCT00903563) to assess the performance in estimating 3-year relapse rates for colon cancer stage II (36). This is the first trial that has been specifically designed to assess the prognostic value of a gene expression signature in colon cancer. The trial has been designed as an observational rather than a randomized, controlled study. Although this is regarded to yield lower levels of evidence of clinical value, it exemplifies an agreement between feasibility and clinical relevance that can provide an adequate foundation for recommendations of clinical implementation (37).

Clinical potential

Gene expression signatures are likely to be implemented in the clinic as supplemental rather than individual prognostic tests (19). In stage II and III colon cancer, important factors to consider in this respect are the conventional clinicopathological prognostic markers, primarily the previously mentioned high-risk factors for stage II disease. Also, molecular subtypes should be taken into consideration. Following validation of prognostic potential in several studies (38–40), microsatellite instability (MSI) status of the tumor is now suggested for clinical use in stage II (7, 41). Patients whose tumors have a high level of MSI have a favorable prognosis and improved outcome seems to be confined to patients with stage II disease (42). Gene expression–based tests for stage II colon cancer should provide prognostic information independent of these factors.

Most of the proposed prognostic gene expression signatures for colon cancer have focused on stage II, due to the unambiguous clinical potential for improved selection of patients with a high risk of relapse and higher expected benefit from adjuvant chemotherapy (Fig. 1). GeneFxColon, OncoDefender-CRC, and ColoGuideEx have been developed specifically to identify patients with stage II and a high risk of relapse (30, 43, 44). OncoType DX Colon Cancer was developed also for patients with stage III disease (34), but validation analyses have been restricted to patients with stage II (retrospective analysis of 711 and 690 selected...
Table 1. Proposed gene expression signatures for prognostic assessment of colorectal cancer stage II and III

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of markers in signature</th>
<th>Cancer type</th>
<th>Tumor stage</th>
<th>Test development</th>
<th>Validation (independent samples)</th>
<th>Sample type</th>
<th>Assay for clinical testing</th>
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<tbody>
<tr>
<td>Bertucci and colleagues (49)</td>
<td>235</td>
<td>CRC</td>
<td>II and III</td>
<td>9</td>
<td></td>
<td>FF</td>
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<tr>
<td>Kwon and colleagues (50)</td>
<td>60</td>
<td>CRC</td>
<td>II and III</td>
<td>12</td>
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<td>FF</td>
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<tr>
<td>Wang and colleagues (51)</td>
<td>23</td>
<td>CC</td>
<td>III</td>
<td>38</td>
<td>(a) 36</td>
<td>FF</td>
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<td>(b) 50 (separate study; Barrier and colleagues [57])</td>
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<td>(c) 123 (separate study; Jiang and colleagues [63])</td>
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<tr>
<td>Eschrich and colleagues (52)</td>
<td>43</td>
<td>CRC</td>
<td>II and III</td>
<td>45</td>
<td>95</td>
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<tr>
<td>Arango and colleagues (53)</td>
<td>17</td>
<td>CRC</td>
<td>III</td>
<td>25</td>
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<tr>
<td>Barrier and colleagues (54)</td>
<td>30</td>
<td>CC</td>
<td>II and III</td>
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<tr>
<td>Barrier and colleagues (55)</td>
<td>47</td>
<td>CC</td>
<td>II and III</td>
<td>12^c</td>
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<td>FF</td>
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<tr>
<td>D’Arrigo and colleagues (56)</td>
<td>29</td>
<td>CRC</td>
<td>II and IV</td>
<td>20</td>
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<tr>
<td>Barrier and colleagues (57)</td>
<td>30</td>
<td>CC</td>
<td>III</td>
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<tr>
<td>Bandres and colleagues (58)</td>
<td>8</td>
<td>CC</td>
<td>III</td>
<td>16</td>
<td>27 (stage II and III; qPCR of 5 genes^d)</td>
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<tr>
<td>Barrier and colleagues (59)</td>
<td>70</td>
<td>CC</td>
<td>III</td>
<td>24^e</td>
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<td>Cavalieri and colleagues (60)</td>
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<td>CRC</td>
<td>III and IV</td>
<td>19</td>
<td>55 (stage I–IV; qPCR of 2 genes^d)</td>
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<tr>
<td>Yamasaki and colleagues (61)</td>
<td>119</td>
<td>CRC</td>
<td>I–IV</td>
<td>58</td>
<td>28 (stage II and III)</td>
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<tr>
<td>Lin and colleagues (62)</td>
<td>22</td>
<td>CRC</td>
<td>I–IV</td>
<td>1–49</td>
<td>Reciprocal validation between gene signatures and patient cohorts</td>
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<td>7^e</td>
<td>CC</td>
<td>II</td>
<td>123</td>
<td>110 (qPCR)</td>
<td>FF and FFPE</td>
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<tr>
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<td>36</td>
<td>CC</td>
<td>I–IV</td>
<td>145</td>
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<td>FF</td>
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<td>Watanebe and colleagues (65)</td>
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<td>III</td>
<td>36</td>
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<tr>
<td>Staub and colleagues (66)</td>
<td>112</td>
<td>CRC</td>
<td>I–IV</td>
<td>62</td>
<td></td>
<td>FF</td>
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<tr>
<td>Jonissen and colleagues (67)</td>
<td>128</td>
<td>CRC</td>
<td>II and III</td>
<td>188</td>
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<td></td>
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<td>(a) 79 (selected patients; restricted gene signature)</td>
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<td>(b) 37 (separate study; not satisfactory results; Thorsteinsson and colleagues [71])</td>
<td>FF</td>
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<tr>
<td>Smith and colleagues (68)</td>
<td>34</td>
<td>CC</td>
<td>I–IV</td>
<td>55</td>
<td>177 (successfully also for stage II and III independently)</td>
<td>FF</td>
<td></td>
</tr>
<tr>
<td>Matsuyama and colleagues (69)</td>
<td>27</td>
<td>CRC</td>
<td>I–IV</td>
<td>77</td>
<td>73 (stage II and III; qPCR of 1 gene)</td>
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<th>Validation (independent samples)</th>
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<tbody>
<tr>
<td>Peng and colleagues (70)</td>
<td>8§</td>
<td>CRC</td>
<td>II and III</td>
<td>95</td>
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<td>FF</td>
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<tr>
<td>Salazar and colleagues (48)</td>
<td>18</td>
<td>CRC</td>
<td>I–IV</td>
<td>188</td>
<td>(a) 206 (stage I–III; successfully also for stage II and III independently)</td>
<td>FF</td>
<td>ColoPrint</td>
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<td>Kennedy and colleagues (43)</td>
<td>634</td>
<td>CC</td>
<td>III</td>
<td>215</td>
<td>144</td>
<td>FFPE GenoFx Colon</td>
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<tr>
<td>Ageisen and colleagues (33)</td>
<td>13§</td>
<td>CRC</td>
<td>II</td>
<td>44</td>
<td>(a) 52 (data from Jorissen and colleagues [67] and Smith and colleagues [68])</td>
<td>FF</td>
<td>ColoGuideEx</td>
</tr>
<tr>
<td>Sveen and colleagues (31)</td>
<td>7§</td>
<td>CRC</td>
<td>II and III</td>
<td>172</td>
<td>215 (successfully also for stage III independently; data from Jorissen and colleagues [67] and Smith and colleagues [68])</td>
<td>FF</td>
<td>ColoGuidePro</td>
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<td>qPCR-based tests (preselected genes)</td>
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<tr>
<td>Schetter and colleagues (72)</td>
<td>9</td>
<td>CC</td>
<td>I–IV</td>
<td>113</td>
<td>73</td>
<td>FF</td>
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<td>Pillaire and colleagues (73)</td>
<td>7</td>
<td>CRC</td>
<td>I–IV</td>
<td>75</td>
<td>—</td>
<td>FF</td>
<td>—</td>
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<tr>
<td>O’Connell and colleagues (34)</td>
<td>12</td>
<td>CC</td>
<td>II and III</td>
<td>1,861</td>
<td>(a) 711 (stage II; separate study; Gray and colleagues [33]) (b) 690 (stage II; separate study; Venook and colleagues [35])</td>
<td>FFPE OncoType DX Colon Cancer</td>
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</tr>
<tr>
<td>Carvalho and colleagues (74)</td>
<td>1</td>
<td>CRC</td>
<td>III</td>
<td>52</td>
<td>—</td>
<td>FF</td>
<td>—</td>
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<tr>
<td>Graidez and colleagues (75)</td>
<td>2</td>
<td>CC</td>
<td>II and III</td>
<td>228</td>
<td>—</td>
<td>FFPE GeneFx Colon</td>
<td></td>
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<tr>
<td>Lenahan and colleagues (44)</td>
<td>5</td>
<td>CRC</td>
<td>I and II</td>
<td>74</td>
<td>264</td>
<td>FFPE OncoDefender-CRC</td>
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Tests developed from publically available gene expression data:

<table>
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<tr>
<th>Study</th>
<th>Number of markers in signature</th>
<th>Cancer type</th>
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<th>Test development</th>
<th>Validation (independent samples)</th>
<th>Sample type</th>
<th>Assay for clinical testing</th>
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</thead>
<tbody>
<tr>
<td>van Laar (76)</td>
<td>163</td>
<td>CC</td>
<td>I–IV</td>
<td>232 (data from Smith and colleagues [68])</td>
<td>60 (data from stage II and III; Jorissen and colleagues [67])</td>
<td>—</td>
<td>ColonPRS</td>
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<tr>
<td>Merlos-Suarez and colleagues (77)</td>
<td>71</td>
<td>CRC</td>
<td>I–IV</td>
<td>345 (data from Jorissen and colleagues [67]; Smith and colleagues [68])</td>
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<th>Number of markers in signature</th>
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<th>Test development</th>
<th>Validation (independent samples)</th>
<th>Sample type</th>
<th>Assay for clinical testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oh and colleagues (78)</td>
<td>114</td>
<td>CRC</td>
<td>I-IV</td>
<td>177 (data from Smith and colleagues [68])</td>
<td>(a) 117 (subset of 80 probes; data from Staub and colleagues [66]; and Smith and colleagues [68])</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>(b) 96 (stage I-III; unsuccessfully for the subset of 80 probes; data from Jorissen and colleagues [67])</td>
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<tr>
<td>Shi and colleagues (79)</td>
<td>487</td>
<td>CRC</td>
<td>II and III</td>
<td>111 (data from Smith and colleagues [68])</td>
<td>67 (data from Jorissen and colleagues [67])</td>
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</tbody>
</table>

Abbreviations: CC, colon cancer; CRC, colorectal cancer; FF, fresh frozen.

*Non-neoplastic colonic mucosa adjacent to tumors.

*bUnivariate prognostic associations.

cRefinement of previously reported signature (Wang and colleagues [51]).

dcDNA mediated annealing, selection, extension and ligation (DASL) assay of 502 genes.

eIdentified using exon resolution microarrays.

fMeta-analysis.
patients from two clinical trials; refs. 33, 35). Similarly, the primary objective of the PARSC trial is to assess the value of ColoPrint for patients with stage II ($n = 575$; ref. 36), and the test has been launched for this patient group only (45). Prognostic potential independent of many of the high-risk factors of stage II colon cancer has been shown retrospectively for these tests by multivariate validation analyses. Also, independence of MSI status has been validated for Oncotype DX Colon Cancer (33, 35) and ColoPrint (46, 47).

Importantly, among the secondary objectives of the PARSC trial is comparison of risk assessment according to ColoPrint and the American Society of Clinical Oncology high-risk criteria (2).

The more ambiguous clinical potential of prognostic gene expression signatures for patients with colon cancer stage III has limited the number of studies with this focus. Considering that almost half the patients will be cured with surgery alone, it is clear that current adjuvant treatment standards result in substantial overtreatment (3). Still, clinical implementation of gene expression signatures to identify stage III patients that can safely be treated by surgery alone, has been deemed unlikely (29). This will depend on confident identification of patients with low risk of relapse. Accordingly, clinical relevance is limited to subgroups of patients for which standard protocols do not apply, for example to elderly patients (Fig. 1). Colon cancer stage III presents with lymph node metastases (right) and these patients are routinely offered adjuvant treatment. However, elderly and frail patients are less commonly treated with chemotherapy. For patients older than 75 years, clinical guidelines are less clear, and improved prognostic assessment could aid in the decision to treat. This patient group has received less focus, and no prognostic gene expression–based tests have been thoroughly validated for elderly patients alone. However, ColoGuidePro has been shown to have potential from analyses of a small patient series. For patients with stage III in general, prognostic potential has been shown also for ColoPrint.

Additional issues to consider for the clinical utility of prognostic gene expression signatures are technical issues about sampling procedures and methodologies for measuring gene expression. These technical issues have been a source of some variation among the proposed tests (Table 1). Applicability to formalin-fixed, paraffin-embedded (FFPE) samples is in agreement with current hospital
routines for sample processing. Tests that are applicable to FFPE samples, for example the Oncotype DX Colon Cancer assay, also have the advantage of availability of archived material for collection of large patient cohorts for retrospective analyses (33–35). However, FFPE material commonly contains partially degraded RNA, producing less reliable gene expression measures compared with fresh-frozen tissue (26). Furthermore, the technology used for gene expression analysis has alternated between microarray- and quantitative PCR (qPCR)–based analysis (Table 1). The former has allowed for genome-wide analyses and the latter has been limited to preselected sets of genes. The diagnostic use of both technologies has been successfully established for prognostic assessment of breast cancer. Finally, pricing is also an important issue for clinical implementation. The cost of the Oncotype DX Colon Cancer assay is arguably high at $3,200. Still, cost-effective analyses have indicated cost benefit for patients with pT3 stage II colon cancer, when taking into account the concomitant reduction in use of adjuvant chemotherapy (48).

In conclusion, several promising gene expression–based tests have been proposed for risk assessment of stage II colon cancer. The clinical implementation of these tests is still detained by insufficient validation, but this prospect has never been closer. Results from clinical trials are anticipated to provide the answer to which tests may aid in the persistent clinical challenge of identifying patients at high risk of relapse and accordingly, have expected larger benefit from chemotherapy. For stage III colon cancer, the decision against adjuvant treatment of patients with good prognosis is an ethically challenging implication of risk stratification. However, the use of gene expression–based signatures to determine the risk of relapse in elderly and frail patients, who are more vulnerable to chemotherapy, may present a valuable clinical advance. Also emerging as a likely scenario from the ongoing genome sequencing efforts is the combined forces of prognostication and companion diagnostics, to identify patients with high-risk stage II and III disease who may benefit also from targeted therapy.

Disclosure of Potential Conflicts of Interest
A. Sveen, A. Nesbakken, T.H. Ågensen, and R.A. Lothe have ownership interest (including patents) in patent application for ColoGuideEx and ColoGuidePro. R.I. Skotheim has ownership interest (including patents) in patent application. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions
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Writing, review, and/or revision of the manuscript: A. Sveen, A. Nesbakken, T.H. Ågensen, M.G. Curen, K.M. Tveit, R.I. Skotheim, R.A. Lothe

Grant Support
This study was supported by the South-Eastern Norway Health Authority (Research Grant "Genome Medicine of Colorectal Cancer," project number 2011024, to R.A. Lothe, supports A. Sveen as post doc).

Received June 28, 2013; revised September 30, 2013; accepted October 2, 2013; published OnlineFirst October 28, 2013.

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www.aacrjournals.org

Published OnlineFirst October 28, 2013; DOI: 10.1158/1078-0432.CCR-13-1769

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