The 12-gene colon cancer assay validation and utility: summary of clinical evidence

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BACKGROUND

Clinical Necessity

- Worldwide, colorectal cancer is the third most common cancer in men and the second in women. In 2014, there will be an estimated 136,830 new colorectal cancer cases and 50,310 deaths in the United States.2
  - Approximately 30% of patients are diagnosed as stage II and 37% stage III.3
- Overall, 75–80% of patients with stage II colon cancers are cured with surgery alone.4
  - The addition of adjuvant therapy offers little absolute benefit.6–8 The current standard of care is to offer 5FU/LV adjuvant therapy to patients thought to be higher risk based on clinical and pathologic factors, despite little evidence that chemotherapy offers any clinical benefit.7
- Treatment decisions are based on the expectation that higher risk stage II patients derive larger absolute benefit with adjuvant chemotherapy.
- For patients with stage III colon cancer, current practice guidelines recommend 5-FU/LV + oxaliplatin for adjuvant therapy.7
  - However, oxaliplatin likely benefits only a minority of treated patients (6–7%),3,8–9 and comes with significant toxicity, including the prospect of long-term peripheral neuropathy.10–11
- For patients with early stage rectal cancer, despite decreasing local recurrence rates over the last two decades, the management of distant recurrence remains a challenge and the value of adjuvant chemotherapy remains controversial.12
- Across all colorectal disease states, conventional clinical and pathologic risk factors do not adequately discriminate risk and expected absolute benefit of chemotherapy to guide decision-making.

Objective

To describe the studies that meet an established definition of clinical validation and additional studies that support the utility of the assay

Figure 1: The 12-Gene Colon Cancer Assay

Table 1: Determination of Level of Evidence
(Simon J Natl Cancer Inst. 2009)

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Category</th>
<th>Study design</th>
<th>Validation studies available</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>Prospective</td>
<td>None required</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Prospective using archived samples</td>
<td>One or more with consistent results</td>
</tr>
<tr>
<td>II</td>
<td>B</td>
<td>Prospective using archived samples</td>
<td>None, or inconsistent results</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Prospective/observational</td>
<td>Two or more with consistent results</td>
</tr>
<tr>
<td>III</td>
<td>C</td>
<td>Prospective/observational</td>
<td>None, or one with consistent results, or inconsistent results</td>
</tr>
<tr>
<td>IV–V</td>
<td>D</td>
<td>Retrospective/observational</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

METHODS

- Simon et al.’s criteria for level of evidence were used to classify the clinical validation studies (Table 1).16

Genomic Profiling

- As the use of genomic assays increases, there is a need to clearly define appropriate clinical validation as the results are used for treatment decisions, recommendations by payers, and treatment guidelines.
- Tests must be “Fit for Purpose” with evidence relevant to that specific purpose. Consistent results across multiple well-designed studies are required to provide evidence for analytical performance, clinical validity, and clinical utility.15
- Here we summarize the studies that provide clinical validation and support the clinical utility of the 12-gene colon cancer assay.
- Studies that were conducted prospectively by pre-specifying the analyses and used archived samples with documented clinical outcomes were classified as validation studies for prognostic clinical outcomes and are considered to provide Level IB evidence.
- Additional studies that demonstrated the utility of the assay in a clinical setting were considered supportive.
**RESULTS**

**Figure 2: Development, Validation, and Utility of the 12-Gene Colon Cancer Assay**

<table>
<thead>
<tr>
<th>Development Studies (Surgery alone)²³</th>
<th>Development Studies (Surgery + 5FU+Lv)²³</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP C-01/C-02 (N=270)</td>
<td>NSABP C-04 (N=508)</td>
</tr>
<tr>
<td>Cleveland Clinic (N=765)</td>
<td>NSABP C-08 (N=508)</td>
</tr>
</tbody>
</table>

**Clinical Validation – Colon Cancer**

Stage II Colon Cancer
- QUASAR Surgery +/- 5FU (N=1,436)²³
- CALGB 9581 Surgery alone (N=690)²³

Stage III Colon Cancer
- NSABP C-07 5FU +/- Oxaliplatin (N=892)²⁶

**Clinical Validation – Rectal Cancer**

Stage III/IV Rectal Cancer
- TME Trial Total mesorectal excision alone (N=297)²¹

**Clinical Utility - Decision Impact Studies**

- PHAR Survey (N=92)²²
- Mayo Clinic Consortium (MCCRC) Prospective (N=141)²²
- Clalit Prospective (N=269)²⁶

**Table 2: Clinical Evidence**

<table>
<thead>
<tr>
<th>Author, Year / Trial / N patients</th>
<th>Risk of Recurrence: Primary Analysis</th>
<th>Risk of Recurrence: Analysis adjusted for covariates</th>
<th>Additional Endpoints</th>
<th>Evidence for Colon Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray, 2011 QUASAR N=1,436</td>
<td>HR: 1.58 (95% CI 1.16 to 2.15) per 25 units, p=0.004 Based on 711 patients treated with surgery alone No significant interaction with 5FU treatment (p=0.76)</td>
<td>HR: 1.83 (95% CI 1.15 to 2.20) per 25 units, p=0.006 Adjusted for T-stage, MMR status, number of nodes examined, tumor location, tumor grade, LVI² and age</td>
<td>DFS: HR: 1.42 (95% CI 1.09 to 1.84) per 25 units, p=0.010 OS: HR: 1.33 (1.01 to 1.76) per 25 units, p=0.041</td>
<td>Validation</td>
</tr>
<tr>
<td>Venook, 2013 CALGB 9581 N=892</td>
<td>HR: 1.52 (1.09 to 2.12) per 25 units, p=0.013</td>
<td>HR: 1.68 (1.18 to 2.38) per 25 units, p=0.004 Adjusted for T-stage, MMR status, number of nodes examined, grade, and LVI²</td>
<td>DFS: p=0.90 OS: p=0.89</td>
<td>Validation</td>
</tr>
<tr>
<td>Yoffers, 2013 NSABP C-07 N=892</td>
<td>HR: 1.96 (1.50-2.55) per 25 units, p=0.001 Adjusted for stage (II, IIIA/B, IIIC) and treatment (5FU vs 5FU+Ox) No significant interaction with stage (p=0.90) and oxaliplatin treatment (p=0.48)</td>
<td>HR: 1.97 (1.19 to 2.80) per 25 units, p&lt;0.001 Adjusted for stage (II, IIIA/B, IIIC), T-stage, MMR status, number of nodes examined, grade, and treatment</td>
<td>DFS: HR: 1.60 (1.28 to 1.99) per 25 units, p&lt;0.001 OS: HR: 1.89 (1.46 to 2.44) per 25 units, p=0.001 Adjusted for stage (II, IIIA/B, IIIC) and treatment (5FU vs 5FU+Ox)</td>
<td>Validation</td>
</tr>
<tr>
<td>Reimers, 2013 Dutch TME N=297</td>
<td>Stage II HR: 3.27 (1.52, 7.01), p&lt;0.001 Stage IIIA/B HR: 1.87 (1.18, 2.95), p=0.007 Stage IIIC p&lt;0.24 Adjusted for resection margin Significant interaction with stage (p=0.002)</td>
<td>Stage II HR: 3.40 (1.58, 7.30), p&lt;0.001 Stage IIIB/IIIC HR: 1.75 (1.11, 2.77), p=0.019 Stage IIIC p=0.12 Adjusted for T stage, grade, number of nodes examined, and resection margin</td>
<td>DFS: p=0.12 OS: p=0.11 Pre-specified main effect model adjusted for stage (II, IIIA/B, IIIC) and resection margin</td>
<td>Supportive</td>
</tr>
</tbody>
</table>

* This HR per 25 units is equivalent to HR per IQR: 1.38 (Gray, J Clin Oncol. 2011)
* This HR per 25 units is equivalent to HR per IQR: 1.43 (Gray, J Clin Oncol. 2011)
* Lymphovascular invasion
* Ratio of the hazards at the 75th and 25th percentiles of the Recurrence Score result

• Three studies of patients with stage II/III colon cancer demonstrated that the Recurrence Score result is significantly associated with risk of recurrence beyond the known prognostic factors and improves the ability to discriminate higher from lower recurrence risk patients

**Figure 3: Clinical Validation in Stage II Colon Cancer**

- QUASAR
- CALGB 9581
- NSABP C-07

**Figure 4: Clinical Validation Stage in II/III Colon Cancer 5FU +/- Oxaliplatin**

- Solid: 5FU
- Dashed: 5FU+Ox
Figure 6a. Patients’ responses post-assay “The results of the Oncotype DX Colon Cancer Assay influenced my treatment decisions.”

- 118 (85%) of 138 patients reported that the 12-gene assay influenced their treatment decisions.

Figure 6b. Physicians’ responses post-assay “The results of the Oncotype DX Colon Cancer Assay influenced my treatment recommendations.”

- In 103 (69%) of 150 cases physicians reported that the 12-gene assay influenced their treatment recommendations.

Figure 6c. Physicians’ responses post-assay “I am more confident in my treatment recommendation after ordering the Oncotype DX Colon Cancer Assay”

- In 126 (84%) of 150 cases physicians were more confident in their treatment recommendation after obtaining the Recurrence Score result.

Figure 6d. Physicians’ responses post-assay “The Oncotype DX Colon Cancer Assay results provided additional clinically relevant information”

- In 129 (86%) of 150 cases physicians agreed that the Recurrence Score result provided additional clinically relevant information.

Table 3: Clinical Utility Studies of the 12-Gene Colon Cancer Assay

<table>
<thead>
<tr>
<th>Study N pts in primary analysis</th>
<th>Country</th>
<th>Study Type</th>
<th>Patient Population</th>
<th>Overall Change in Treatment Recommendation</th>
<th>Decreased Intensity (LESS Treatment)</th>
<th>Increased Intensity (MORE Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartwright (N=92)</td>
<td>USA</td>
<td>Retrospective</td>
<td>Stage II colon cancer</td>
<td>29.3%</td>
<td>19.6%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Srivastava (N=141)</td>
<td>USA</td>
<td>Prospective</td>
<td>Stage II colon cancer (T3, MMR-P only)</td>
<td>44.7%</td>
<td>33.3%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Brenner (N=269)</td>
<td>Israel</td>
<td>Prospective</td>
<td>Stage II colon cancer (T3, MMR-P only)</td>
<td>37.9%</td>
<td>28.3%</td>
<td>9.7%</td>
</tr>
</tbody>
</table>

*Decreased intensity: changes to observation or to remove oxaliplatin from the adjuvant therapy
* Increased intensity: changes from observation or to add oxaliplatin to the adjuvant therapy
* Change from treatment recommendation to actual treatment received post-assay

Use of the Assay Influences Patient and Physician Confidence

- Studies of the clinical utility of the 12-gene assay show that use of the assay results in clinically meaningful changes in treatment recommendations.
- The changes in treatment recommendation resulted in an overall reduction in recommended adjuvant chemotherapy use, with a potential decrease in health care expenditure in this patient population.

Results (cont.)

Figure 5: Clinical Validation in Rectal Cancer
Risk profiles for patients with negative resection margins

- The Recurrence Score result has been validated as a predictor of recurrence risk in rectal cancer patients following TME surgery.

- Studies of the clinical utility of the 12-gene assay show that use of the assay results in clinically meaningful changes in treatment recommendations.
- The changes in treatment recommendation resulted in an overall reduction in recommended adjuvant chemotherapy use, with a potential decrease in health care expenditure in this patient population.
Use of the 12-Gene Colon Cancer Assay is Cost-Saving

• In a modeling study where use of the 12-gene colon cancer assay was compared to published patterns of care, use of the assay showed an average increase of 0.035 QALY and average decrease of $2,971 per patient in direct medical costs.26

• Using results of the prospective MCCRC decision impact study,27 a second modeling study showed that use of the assay:
  - increased quality-adjusted survival by 0.230 years due to avoidance of acute and long-term adverse events related to adjuvant chemotherapy,
  - was cost-saving:
    - overall medical costs decreased $1,683 per patient on average,
    - drugs and administration costs for adjuvant chemotherapy decreased by $3,978 per patient, and
  - costs for the management of adverse events decreased by $3,168 per patient (Figure 7).

• If the future cost of oxaliplatin is one-fourth of the current cost, use of the assay would save on average $546 per patient.

In 2011, the NCCN Task Force on Tumor Markers recognized the assay as having established clinical validation for patients with stage II colon cancer (Level 1B evidence).28

• Clinical utility of the 12-gene colon cancer assay is demonstrated by the impact of the Recurrence Score result on treatment recommendations. Treatment recommendations consistently changed >35%, demonstrating the value of the assay to clinical care.

• Three clinical utility studies with a combined total of 502 stage II colon cancer patients showed that 29-45% of initial treatment recommendations changed, resulting in a net reduction in use of adjuvant chemotherapy.

• The Recurrence Score result increased confidence in physician treatment recommendations in 126 (84%) cases and provided additional clinically relevant information in 129 (86%) cases. 129 (96%) of 135 post-assay definitive treatment decisions were concordant between patients and physicians compared to 49 (66%) of 74 definitive decisions pre-assay.

• Two separate modeling studies have shown that use of the assay in patient care is cost saving.

REFERENCES


