# Use of a multigene prognostic assay for selection of adjuvant chemotherapy in patients with stage II colon cancer: Impact on quality-adjusted life expectancy and costs

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## Background & Objective

- The absolute benefit of adjuvant therapy in stage II colon cancer is small. In unselected patients, survival is improved <5% with adjuvant treatment.[1]
- Patient selection for treatment is currently based on clinical factors and patient preferences.
- Expert guidelines panels have propose the following characteristics be considered in making treatment decisions:
  - Adequacy of lymph nodes (LN) sampling
  - Poor prognostic pathological features (T4 tumor, perforation, peritumoral lymphovascular involvement and poorly differentiated histology)
  - Patient's comorbidities and life expectancy
  - Mismatch Repair (MMR) status, if considering fluoropyrimidines-only therapy
- In 2009 Kerr et al. reported on the validation of a 12-gene expression Recurrence Score® assay (12-gene RS) that quantifies a patient's 3-year risk of recurrence on a continuous scale.[2]
  - Prospective-retrospective validation on archival samples from QUASAR trial
  - 2,146 stage II colon cancer patients randomized to surgery alone vs. 5-fluorouracil/ leucovorin (5-FU/LV)
  - The relative risk reduction (RRR) with 5-FU is consistent across RS risk levels (18%)

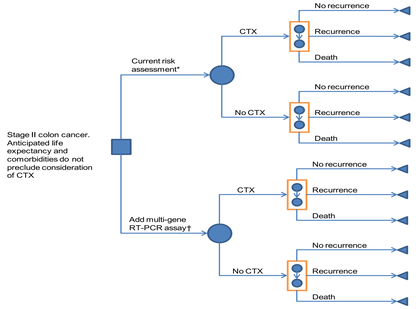
**Overall Objective**

- To determine the utility and cost-effectiveness of a multi-gene expression prognostic assay in guiding use of adjuvant therapy in patients with stage II colon cancer.
  - Endpoint 1: Impact on quality adjusted survival
  - Endpoint 2: Impact on cost from a societal perspective

## Methods

- A state-transition (Markov) model was developed to compute the utility and economic implications of assay adoption from a US societal perspective.
- A representative stage II colon cancer patient transitions between three health states: "no recurrence", "recurrence" and "death" (Figure 1).
- Model assumes the selection of adjuvant therapy when the quality adjusted life years (QALY) gained with treatment is greater than QALY loss associated with adjuvant chemotherapy.
- Other model assumptions:
  - T4 tumors (high risk) and dMMR (low risk) were omitted from model
  - Relative risk reduction of chemotherapy is 18% regardless of RS
  - Current propensity to use, and disutility of chemotherapy (0.5 years), based on published NCCN data (Earle et al. 2009)[3]

**Figure 1. Decision Tree**




Data sources:

- Risk of recurrence by RS was based on the QUASAR validation study.
- Risk of mortality and risk of recurrence were derived from US Vital Statistics and Surveillance Epidemiology and End Results, respectively.[4,5]
- Incidence of adverse events was derived from published trials.
- Costs of treatment were computed from Medicare Part B average sales price (April 1st, 2010);[6] costs of adverse events were obtained from literature and hospital utilization databases.
- Utilities for remission, relapse, and during treatment were derived from the literature.

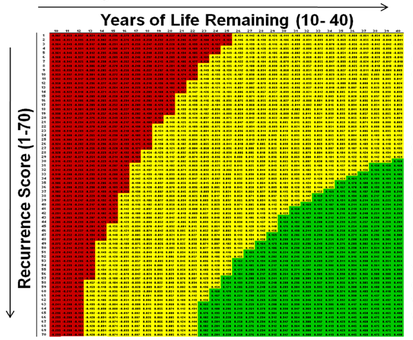
## Results

**Table 1. Comparison of RS use for treatment decisions based on clinico-pathologic factors alone**

| Model Endpoints | Values |
|---|---|
| Change in CTX use | -17% |
| QALY gained per patient | 0.035 |
| Net cost | -$2971 |
| Incremental cost-effectiveness ratio | Dominant |

*Abbreviations: CTX, chemotherapy; QALY, quality of life gained*

**Figure 2. QALYs gained or lost with adjuvant therapy, by RS and years of life remaining**




Red represents: No chemotherapy, where QALY loss during treatment is greater than overall gain

Green represents: Yes chemotherapy, where the QALY loss during treatment is less than overall gain

Yellow: Treatment decision dependent on individual patient's view of quality of life associated with chemotherapy

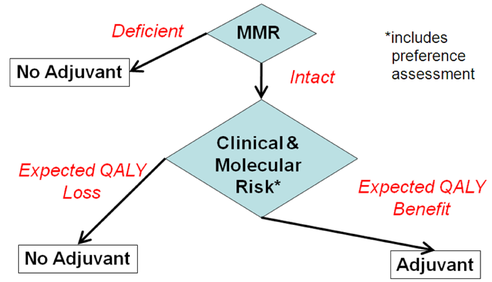
**Table 2. RS reduces chemotherapy use regardless of LN sampling or high-risk pathological features**

| | LVI or High Grade? | | |
|---|---|---|---|
| | **No (74%)** | **Yes (26%)** | **All** |
| **<12 LN (13%)** | | | |
| Change in CTX use | -35% | -56% | -40% |
| QALY gained | 0.063 | 0.104 | 0.073 |
| Net cost | -$9133 | -$16,402 | -$11,102 |
| ICER | Dominant | Dominant | Dominant |
| **>=12 (87%)** | | | |
| Change in CTX use | -11% | -27% | -14% |
| QALY gained | 0.027 | 0.049 | 0.031 |
| Net cost | -$851 | -$6245 | -$1710 |
| ICER | Dominant | Dominant | Dominant |

*Abbreviations: LN, lymph nodes; LVI, lymphovascular involvement; CTX, chemotherapy; QALY, quality adjusted life years, ICER, incremental cost-effectiveness ratio*

- Extensive 1-way sensitivity analyses show that cost-saving result was robust through a range of variables.
  - Results **NOT SENSITIVE** to: (1) cost of assay, (2) chemotherapy and complications, (3) type of chemotherapy and (4) frequency of complications
  - Results **SENSITIVE** to: (1) benefit of chemotherapy in patients >60 years of age and (2) utility loss from chemotherapy

## Proposed Future Stage II Algorithm




## Conclusion

- Clinical use of a 12-gene RS to assess risk of recurrence in T3 stage II colon cancers with intact MMR may improve quality-adjusted life expectancy and be cost-saving from a societal perspective.
- Patient age and disutility associated with chemotherapy are important considerations in adjuvant treatment decisions.
- Further research is required to develop tools for accurate prediction of disutility associated with adjuvant chemotherapy for individual patients. This would enable use of decision models such as the one presented to improve the outcome for patients and save costs.

## References

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