Cost-effectiveness of precision molecular diagnostic tests for stage II colorectal cancer

Vivek S. Chaudhari[1,2], Amalia M. Issa[1,2,3,4]^

[1]Personalized Precision Medicine & Targeted Therapeutics Institute, Springfield, PA, USA; [2]Department of Health Policy & Public Health, University of the Sciences in Philadelphia, Philadelphia, PA, USA; [3]Department of Pharmaceutical Sciences, University of the Sciences in Philadelphia, Philadelphia, PA, USA; [4]Department of Family Medicine, Faculty of Medicine & Health Sciences, McGill University, Montreal, QC, Canada

Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Amalia M. Issa, PhD, MPH. Founding Director, Personalized Precision Medicine & Targeted Therapeutics Institute, Springfield, PA, USA. Email: aissa.usciences@gmail.com.

Background: In colorectal cancer, inappropriate use of adjuvant chemotherapies may lead to significant increases in healthcare costs and harms to patients. Genome-based interventions are being increasingly used in the stratification of patients according to their risk profiles. However, earlier cost-effectiveness analyses of precision molecular diagnostics have indicated a paucity of data on comparative health economic outcomes. Our aim was to compare the cost-effectiveness of marketed genomic tests used in the prognosis of stage II colorectal cancer patients.

Methods: A Markov model was developed to compare the cost-effectiveness of treatment guided by any one of the following genomic tests: 12-gene assay or the 18-gene expression assay or the 482-gene signature or the Immunoscore assay in a hypothetical cohort of patients (n=1,000) with stage II colorectal cancer. Our study investigated outcomes in three health states: no recurrence, recurrence and death. This study was conducted from a societal perspective, and a 3% discount was applied to the costs and health outcomes. Sensitivity analyses were performed to assess the uncertainty of model parameters on the results.

Results: The cost of the Immunoscore assay strategy in stage II colorectal cancer patients was estimated to be US $23,564 with a gain of 3.903 quality-adjusted life years (QALYs) as compared with the 12-gene assay strategy at US $24,545 and 3.903 QALYs; the 18-gene assay strategy at US $28,374 and 3.623 QALYs; and the 482-gene signature treatment strategy at US $33,315 with 3.704 QALYs. Sensitivity analyses indicated that incremental cost-effectiveness ratio (ICER) values were sensitive to costs of genomic tests and adjuvant chemotherapies; and utilities related to patients in the no-recurrence health state.

Conclusions: Overall, the Immunoscore assay seems to be a dominant strategy at a threshold willingness-to-pay of $50,000 per QALY, but in the US other tests have been used for longer. Thus, the 12-gene assay may generate cost savings compared to the 18-gene expression assay. The findings of our study may provide useful information to policymakers regarding selection of the most appropriate genomic test, and resource allocation decisions.

Keywords: Cost-effectiveness; genomic tests; colorectal cancer; Markov model; adjuvant chemotherapy

Submitted Nov 07, 2022. Accepted for publication Nov 27, 2022.
doi: 10.21037/atm-2022-77
View this article at: https://dx.doi.org/10.21037/atm-2022-77

^ ORCID: 0000-0002-1667-3280.

Introduction

In colorectal cancer, there are no universally accepted guidelines for stage II patients to determine the future course of adjuvant chemotherapy after tumor resection (1-4). This uncertainty around the prognostic and predictive abilities of clinical biomarkers has underscored the need for assessment tools that can more precisely identify stage II patients who are at higher risk of recurrence and might derive benefit from adjuvant chemotherapy.

More recently, with advances in genomic medicine, precision molecular diagnostic tests have offered possibilities to predict disease relapse and guide adjuvant therapy decisions (5-10). Currently, there are four tests being marketed for clinical use in the United States (US): a 12-gene assay; an 18-gene expression assay, a 482-gene signature, and the Immunoscore assay. The 12-gene assay provides an individual recurrence score for patients with stage II colon cancer (5,11). The 18-gene expression assay provides a relapse risk assessment using clinical and pathologic factors such as T4-stage and microsatellite instability status (8,12). The 482-gene signature is a genomic assay used for the identification of stage II colon cancer patients who may have a risk of recurrence after initial surgery within five years (7). The Immunoscore assay is an *in vitro* diagnostic test that quantifies the densities of $CD3^+$ and cytotoxic $CD8^+$ T-cells at tumor sites using digital pathology. It provides a score for each patient to predict the risk of relapse for stage II colorectal cancer after resection (9,10).

Currently, there is a concern about rising medical costs in the US, as the utilization of health care services continues to increase along with the introduction of new health care technologies in clinical practice (13-15). Specifically, genome-based interventions, which have the potential to reduce adverse drug effects and patient readmissions by targeting at-risk individuals, have been entering the market rapidly, leading to the current availability of more than 150 personalized therapies on the market approved by the US Food and Drug Administration (16). However, high costs and inadequate evidence of the clinical utility of genomic tests may limit their coverage by health insurers and, consequently, their diffusion into clinical practice (17-19). A few cost-effectiveness studies have been performed separately for the 12-gene assay (20,21). However, there do not appear to be any studies that have compared the 12-gene assay, the 18-gene expression assay, the 482-gene signature, and the Immunoscore assay with respect to cost-effectiveness of treatment. Such comparative analyses may capture the upstream and downstream consequences of using novel precision molecular diagnostics and reflect the underlying clinical and economic evidence for improved outcomes, and uncertainties around the evidence (17,18,22). Therefore, it becomes even more essential to estimate total costs, potential cost savings, and health benefits associated with the use of new genomic tests to thereby guide resource allocation decisions. This study aims to evaluate the cost-effectiveness and quality of life associated with treatment decisions involving four different marketed genomic tests for stage II colorectal cancer patients by developing a decision analytic model. We present the following article in accordance with the CHEERS reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-2022-77/rc).

Methods

This economic modeling study was reviewed by the University of the Sciences Institutional Review Board (Protocol #1206794-1) and approved as a non-human subjects research. A hypothetical cohort of individuals aged older than 50 years who have been diagnosed with stage II colorectal cancer, who have undergone tumor resection, and who were waiting for treatment decisions based on marketed genomic tests were included in this study.

Interventions

The following four strategies were applied in the study population:

Strategy 1: the 12-gene assay followed by either adjuvant chemotherapy if patients were classified into the high-risk category or no chemotherapy if patients were classified into the low-risk category.

Strategy 2: the 18-gene expression assay followed by either adjuvant chemotherapy if patients were classified into the high-risk category or no chemotherapy if patients were classified into the low-risk category.

Strategy 3: the 482-gene signature followed by either adjuvant chemotherapy if patients were classified into the high-risk category or no chemotherapy if patients were classified into the low-risk category.

Strategy 4: the Immunoscore assay followed by either adjuvant chemotherapy if patients were classified into the high-risk category or no chemotherapy if patients were classified into the low-risk category.

Table 1 Clinical validity and risk classification of genomic tests

Genomic tests	Base case parameters		Sensitivity analysis range	Distribution	References
	Hazard ratio	Proportion of patients assessed			
12-gene assay	2.05	High-risk 0.14	1.64–2.46	Normal	(6)
		Low-risk 0.86			
18-gene expression assay	2.16	High-risk 0.37	1.59–2.66	Normal	(8)
		Low-risk 0.63			
482-gene signature	2.13	High-risk 0.45	1.62–2.70	Normal	(7)
		Low-risk 0.55			
Immunoscore assay	0.33	High-risk 0.27	0.24–0.41	Normal	(9)
		Low-risk 0.73			

Overview of the model

We developed a 5-year Markov model to estimate the costs and quality-adjusted life years (QALYs) associated with the implementation of four different marketed genomic tests (i.e., 12-gene assay, 18-gene expression assay, 482-gene signature, and Immunoscore assay) for stage II colorectal cancer treatment strategies. This study used the TreeAge software (TreeAge Software, Williamstown, MA, USA) to design a decision-analytic framework and compute incremental cost-effectiveness ratios (ICERs). Our study was conducted from a societal perspective. To consider the impact of time on the valuation of model parameters, the future costs and QALYs were discounted at 3% for the base-case analysis, as recommended by the Second Panel on Cost-effectiveness in Health and Medicine (22).

In the Markov model, we considered a simulation of 1,000 hypothetical patients with stage II colorectal cancer and compared four genomic test-guided treatment strategies. In each strategy, the patients were offered either the 12-gene assay or the 18-gene expression assay, or the 482-gene signature or the Immunoscore assay and then distributed into two risk categories, either high risk or low risk. This stratification of patients into the two risk categories of high and low was based on the recurrence score of the marketed genomic tests (5-10). Furthermore, the patients in the high-risk categories of the four genomic tests were assumed to be administered adjuvant chemotherapy, while the patients in the low-risk categories of the four genomic tests were assumed to be treated without adjuvant chemotherapy. The assumption regarding administration of adjuvant chemotherapy was based on the current standard of clinical practice, which considers the age of a colorectal cancer patient and impact of adverse effects associated with chemotherapy on the quality of life (23,24).

In this study, the outcomes of patients were investigated in three mutually exclusive health states: no recurrence, recurrence, and death. We assumed one year to be one cycle and performed the cohort simulation with a time horizon of five years. In every Markov cycle, we assumed that patients could only move towards a stage of recurrence and death from a no recurrence stage. They could not go back to a "no recurrence stage" from a recurrence stage but could remain in the same health state until they were deceased. We also assumed that patients may experience local or distant recurrence at an advanced stage of the disease.

Model parameters

We conducted a comprehensive review of the literature using specific search terms and different electronic databases (MEDLINE/PubMed, EMBASE, Web of Science, National Health Service Economic Evaluation Database (NHSEED), EconLit, CINAHL, and PROSPERO) from January 2006 to May 2019. The data relevant to the risk stratification of stage II colorectal cancer patients using genomic tests and the transition probabilities between health states of patients were obtained from the literature (*Tables 1*,*2*). In the model, adjuvant chemotherapy was assumed to be prescribed for high-risk patients and, therefore, a relative risk reduction of 0.18 was set for these patients to represent the benefit of chemotherapy (20). The transition probability of death was considered as zero.

For strategy 1, we considered a total of 247 patients

Table 2 Transition probabilities

Health states & year	Base case parameters	References
No recurrence to recurrence		
Year 1	0.02	(25)
Year 2	0.0714	
Year 3	0.0275	
Year 4	0.0282	
Year 5	0.0267	
No recurrence to death		
Year 1	0.0094	(25)
Year 2	0.0104	
Year 3	0.0114	
Year 4	0.0124	
Year 5	0.0134	
Recurrence to metastasis		
Year 1	0.1662	(26)
Year 2	0.1618	
Year 3	0.157	
Year 4	0.1521	
Year 5	0.1473	
Recurrence to no metastasis		
Year 1	0.0166	(26)
Year 2	0.0162	
Year 3	0.0157	
Year 4	0.0152	
Year 5	0.0147	
No metastasis to death		
Year 1	0.0391	(26)
Year 2	0.0444	
Year 3	0.0479	
Year 4	0.051	
Year 5	0.0538	
Metastasis to death		
Year 1	0.009	(26)
Year 2	0.0088	
Year 3	0.0085	
Year 4	0.0083	
Year 5	0.008	

as either high-risk, intermediate-risk or low-risk, and the recurrence score was determined using the 12-gene assay. We combined patients of the intermediate-risk group with those of the low-risk group, and it was assumed that patients in the high-risk group received adjuvant chemotherapy. Of 247 patients, 35 patients (14%) were categorized as high-risk, whereas 212 patients (86%) were categorized as low-risk using the 12-gene assay. For strategy 2, the recurrence score was calculated for a total of 416 patients using the 18-gene assay. It was determined that 153 (36.77%) patients were in the high-risk group and 263 (63.22%) patients were in the low-risk group. For strategy 3, of the 393 patients who were classified as either low-risk or high-risk, 177 patients (45.03%) were categorized into the former and 216 patients (54.96%) were categorized into the latter using the 482-gene signature. For strategy 4, 1,434 patients were classified using the Immunoscore assay. Of these patients, 1,045 patients (72.87%) were classified as low-risk and 389 patients (27.12%) were classified as high-risk.

Costs

The data related to the direct and indirect medical costs were identified from the published clinical and health economic studies (6-9,20-21,25-31). All costs were standardized to 2014 US dollars. The costs associated with adjuvant chemotherapy, administration, and adverse events were sourced from the literature. The costs of genomic tests were based on the list price and were obtained from publicly available resources (*Table 3*).

QALYs

In the model, we combined utility values with the amount of time a patient remained in that particular health state and derived QALYs. We referred to the literature to obtain the utility values for different health states, including no recurrence, recurrence, and productivity loss due to adjuvant chemotherapy. These values were in the range of 0 to 1, where 0= health equivalent to death and 1= best imaginable or perfect health.

Outcomes

The outcomes of the model included an estimation of total expected costs and QALYs for the 12-gene assay, the 18-gene expression assay, the 482-gene signature. and the Immunoscore assay. The ICER values of the four genomic

Table 3 Utilities, risk reduction and costs

Variables	Base case parameters	Sensitivity analysis range	Distribution	References
No recurrence	0.85	0.68–1.02	Beta	(20)
Recurrence	0.60	0.48–0.72	Beta	
Productivity loss due to chemotherapy	0.47	0.376–0.564	Beta	(27,28)
Relative risk reduction due to chemotherapy	0.18	0.144–0.216	Beta	(20)
Immunoscore assay	$3,000	2,400–3,600	Gamma	Communication with HalioDx, February 2019
12-gene assay	$4,420	3,536–5,304	Gamma	(29)
18-gene expression assay	$3,400	3,080–4,620	Gamma	(30)
482-gene signature	$3,850	2,720–4,080	Gamma	(31)
Adjuvant chemotherapy and administration	$7,746	6,196–9,296	Gamma	(21)
Adverse events	$23,589	18,871–28,307	Gamma	(21)

tests at a willingness to pay of $50,000 per QALY were calculated using the formula:

$$ICER = \frac{Cost_{(Strategy\ 1)} - Cost_{(Strategy\ 2)} - Cost_{(Strategy\ 3)} - Cost_{(Strategy\ 4)}}{Effects_{(Strategy\ 1)} - Effects_{(Strategy\ 2)} - Effects_{(Strategy\ 3)} - Effects_{(Strategy\ 4)}} \quad [1]$$

Sensitivity analyses

One-way sensitivity analyses were conducted on the model parameters and the robustness of the results was assessed. A Tornado diagram was employed to identify important parameters, which may have direct effects on the results of the model. In probabilistic sensitivity analysis, specific distribution was assigned to each parameter of the model, and 1,000 Monte-Carlo simulations were performed to assess the uncertainty of the model parameters on the results of the ICERs for the four genomic tests.

Results

Decision analytic framework

A decision analytic framework was designed for the evaluation of the costs and QALYs associated with genomic tests guided treatment strategies (*Figure 1*).

Base-case analysis

The Immunoscore assay *vs.* the 12-gene assay, the 18-gene assay, and the 482-gene signature

The cost of the Immunoscore guided treatment in stage II colorectal cancer patients was estimated to be $23,564 as compared with the 12-gene assay guided treatment at $24,545, the 18-gene assay guided treatment at $28,374, and the 482-gene signature guided treatment at $33,315. The use of treatment strategies guided by the Immunoscore assay, 12-gene assay, 18-gene assay, and 482-gene signature resulted in gains of 3.903, 3.623, 3.677, and 3.704 QALYs respectively. These results and ICER values indicate that the Immunoscore assay might be a more cost-effective strategy than the other three marketed tests at a threshold willingness-to-pay of $50,000 per QALY (*Table 4*).

The 12-gene assay *vs.* the 18-gene assay

The estimated cost of treatment for stage II colorectal cancer patients using the 12-gene assay was $24,545, with a gain of 3.623 QALYs, as compared with an estimated cost of $28,374 and a gain of 3.677 QALYs when the 18-gene expression assay was used. A cost savings of $3,829 was associated with the use of the 12-gene assay, whereas the 18-gene expression assay guided treatment was associated with a gain of 0.054 additional QALYs (*Table 5*).

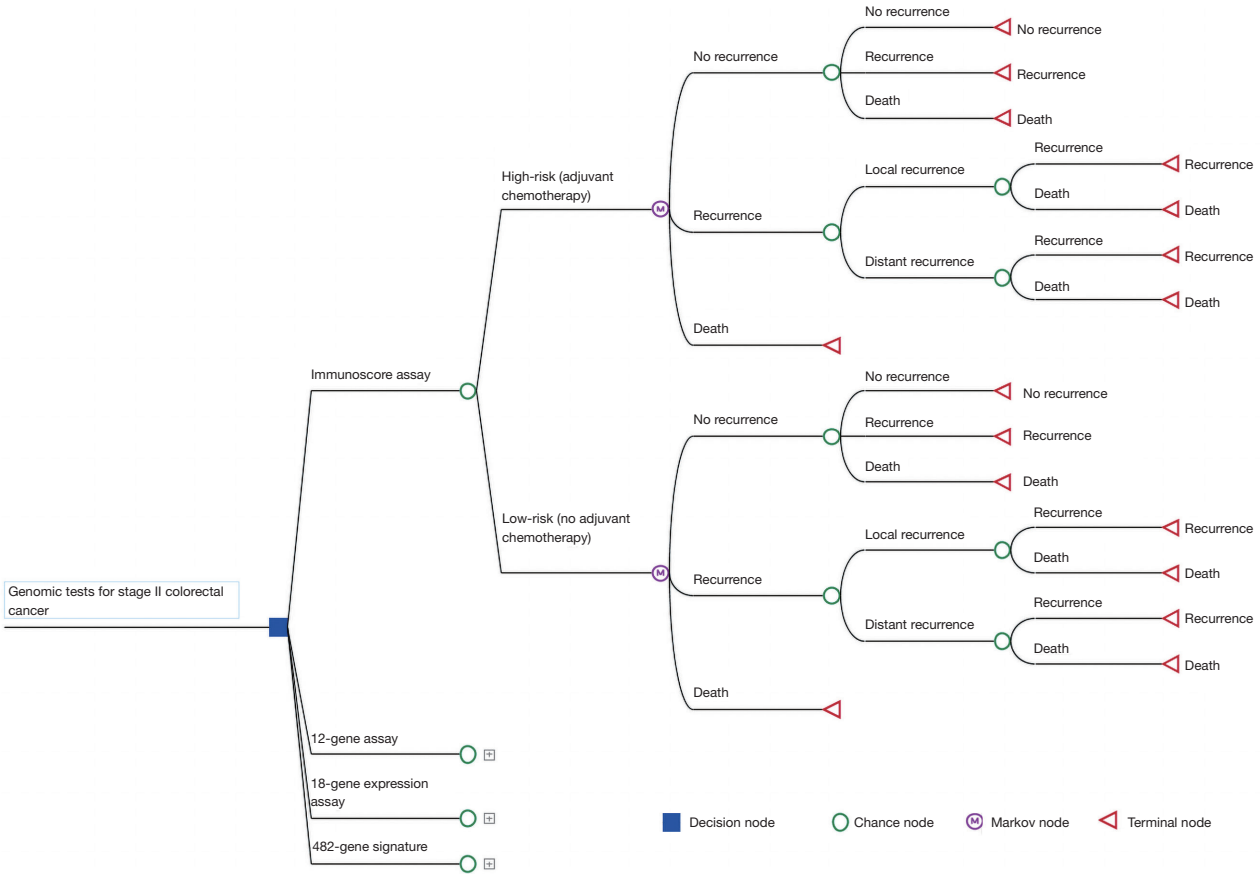

Figure 1 Decision analytic framework assumed a simulation of stage II colorectal cancer patients and compared four genomic test strategies. In each strategy, the patients were offered either 12-gene assay or 18-gene expression assay or 482-gene signature or Immunoscore assay and then, distributed into two risk categories. This stratification of patients into the two risk categories, high or low, was based on the recurrence score of genomic tests. The patients in the high-risk category classified by any of the genomic tests were assumed to receive adjuvant chemotherapy, while the patients in the low-risk category classified by any of the genomic tests were assumed to be treated without adjuvant chemotherapy.

Table 4 Incremental cost-effectiveness ratio for all marketed genomic tests

Genomic tests	Costs, $	Incremental, $	QALYs	Incremental QALYs	C/E, $/QALYs	ICER, $/QALYs
Immunoscore assay	23,564	–	3.903	–	6,037	–
12-gene assay	24,545	981	3.623	−0.28	6,774	Dominated
18-gene expression assay	28,374	4,810	3.677	−0.226	7,716	Dominated
482-gene signature	33,315	9,751	3.704	−0.199	8,994	Dominated

C/E, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life-years.

Table 5 Incremental cost-effectiveness ratio for 12-gene assay and 18-gene expression assay

Genomic tests	Costs, $	Incremental, $	QALYs	Incremental QALYs	C/E, $/QALYs	ICER, $/QALYs
12-gene assay	24,545	–	3.623	–	6,774	–
18-gene expression assay	28,374	3,829	3.677	0.054	7,716	Dominated

C/E, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life-years.

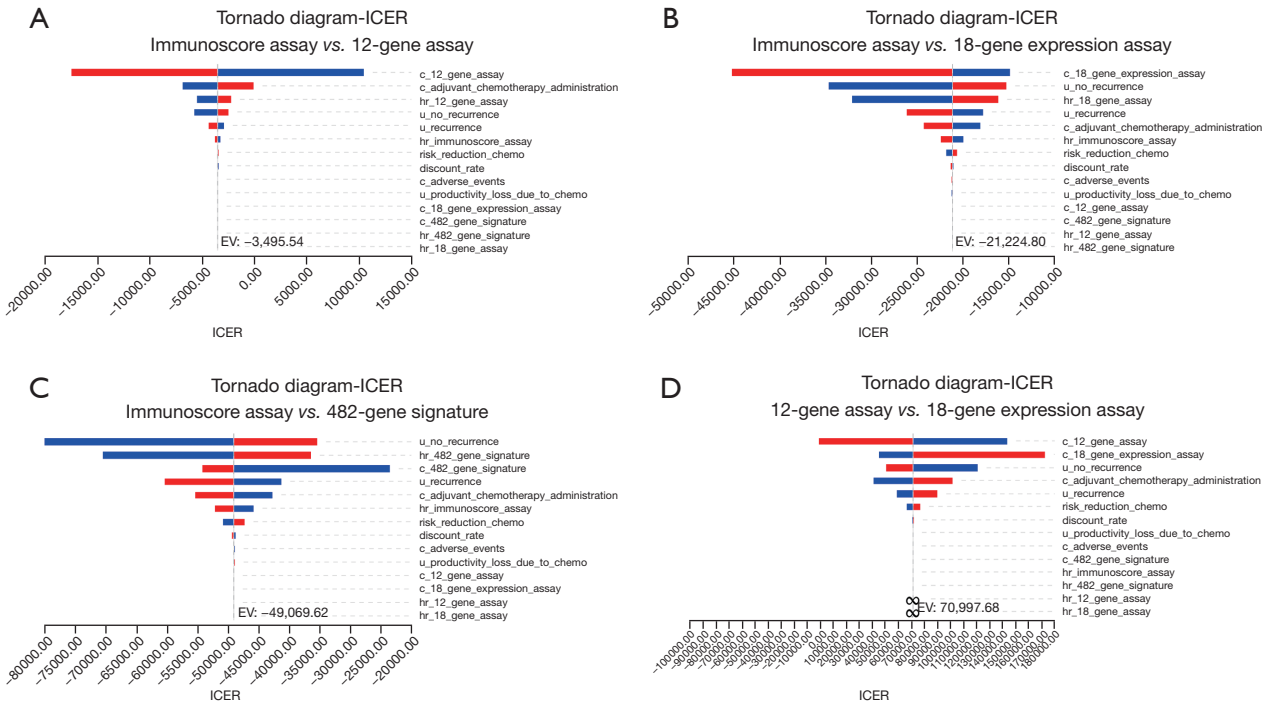

Figure 2 Tornado diagram of deterministic sensitivity analyses between different genomic test strategies. (A) Tornado diagram of Immunoscore assay versus 12-gene assay. (B) Tornado diagram of Immunoscore assay versus 18-gene expression assay. (C) Tornado diagram of Immunoscore assay versus 482-gene signature. (D) Tornado diagram of 12-gene assay versus 18-gene expression assay. These diagrams indicated the list parameters in the model in order of magnitude of influence on the ICER. Each bar, blue and red, represents a one-way sensitivity analysis performed at the selected node, for different precision molecular diagnostics tests that are being compared. ICER, incremental cost-effectiveness ratio; c, cost; u, utility; hr, hazard ratio; chemo, chemotherapy; EV, expected value.

Sensitivity analyses

One-way sensitivity analyses involving costs, utilities, hazard ratios, and probabilities were performed, where input values of all of the parameters across the ranges were varied. As shown in the Tornado diagram, the ICER values of the Immunoscore assay *vs.* the 12-gene assay or the 18-gene assay or the 482-gene signature were most sensitive to the costs of genomic tests and utilities related to patients in the no-recurrence health state (*Figure 2A-2D*).

In a probabilistic sensitivity analysis, we used the Immunoscore assay as a reference strategy versus the other genomic test strategies and performed 1,000 Monte-Carlo simulation trials. We constructed four scatterplots on the cost-effectiveness plane, where the incremental cost was on the vertical axis and incremental effectiveness was on the horizontal axis (*Figure 3A-3D*). These scatterplots provide a representation of each simulation trial specific ICER values. Each scatterplot is composed of four quadrants. The location of ICER values among these quadrants indicates whether the Immunoscore assay produces more effectiveness and more cost (northeast quadrant), more effectiveness and less cost (southeast quadrant), less effectiveness and less cost (southwest quadrant), or less effectiveness and more cost

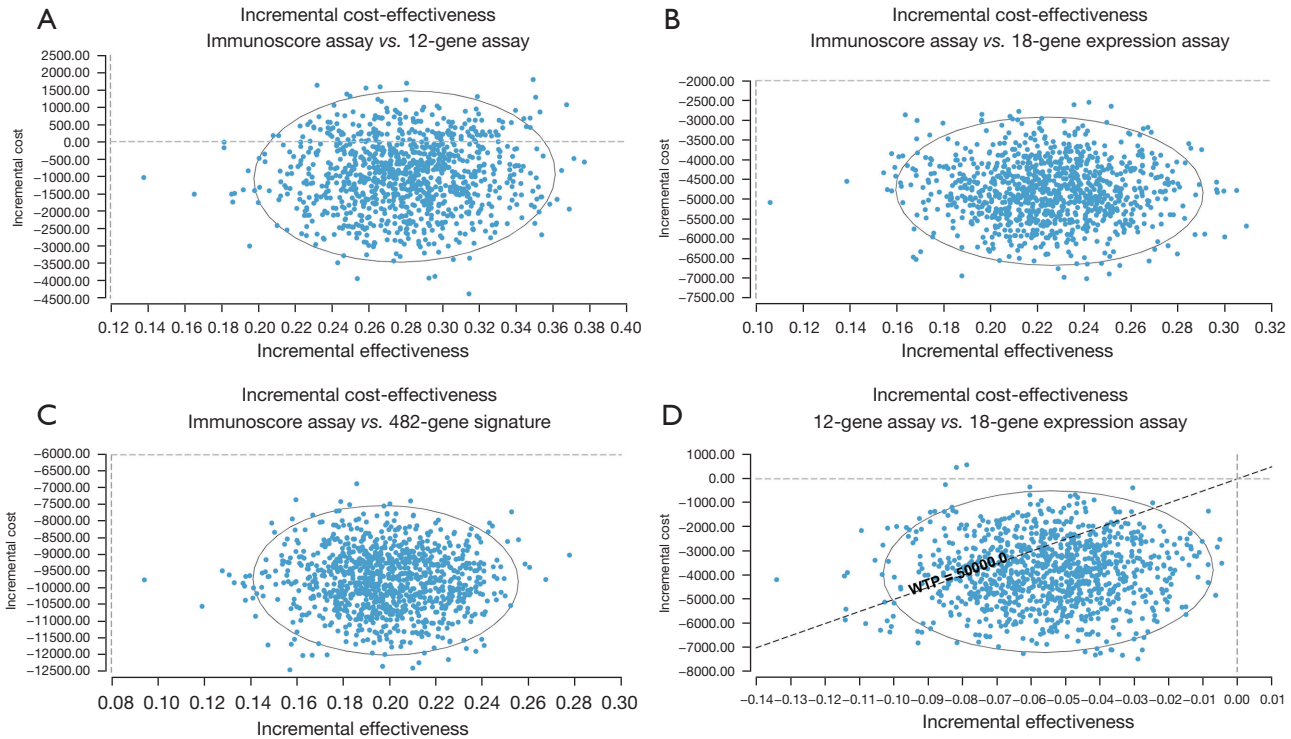

Figure 3 Incremental cost-effectiveness scatterplot between different treatment strategies. (A) Incremental cost-effectiveness scatterplot between Immunoscore assay versus 12-gene assay. (B) Immunoscore assay versus 18-gene expression assay. (C) Immunoscore assay versus 482-gene signature. Scatterplots showed that Immunoscore assay strategy generated more QALYs at lower costs in comparison with other three strategies. (D) Incremental cost-effectiveness scatteplot showed that 12-gene assay strategy gained less QALYs at lower costs in comparison with 18-gene expression assay strategy. WTP, willingness-to-pay; QALYs, quality adjusted life years.

(northwest quadrant) as compared with the other genomic test strategies.

In the scatterplot for the Immunoscore assay and the 12-gene assay, 83.20% of the total ICER values were in the southeast quadrant and 16.20% of total values were in the northeast quadrant. This suggests that the Immunoscore assay generated more QALYs at lower costs (*Figure 3A*). In comparison, in the scatterplots between the Immunoscore assay and the 18-gene expression assay or the 482-gene signature, 100% of the ICER values were in the southeast quadrant (*Figure 3B,3C*).

Overall, these scatterplots suggest that the Immunoscore assay might be the dominant strategy when willingness to pay was set at $50,000 per QALY. The scatterplot evaluating the 12-gene and the 18-gene expression assay showed 99.80% of total ICER values were located in the southwest quadrant (*Figure 3D*). This underscored that patients using the 12-gene assay gained less QALYs at lower costs in comparison with the patients who used the 18-gene assay-based treatment.

Discussion

Multiple genomic assays have been developed to identify high-risk subgroups in the heterogeneous population of stage II colorectal cancer patients that might benefit from adjuvant chemotherapy (5-10). Currently, four genomic tests (the 12-gene assay, an 18-gene expression assay, a 482-gene signature, and the Immunoscore assay) are available for clinical use in the US. Among these commercially available genomic tests, the clinical validity and utility of the 12-gene assay has been demonstrated in several studies to date (6,11,32-38), whereas the Immunoscore assay was made available to the US market on January 8, 2019 (39). The Immunoscore assay was validated in a prospective multicenter study with tissue samples from stage II colorectal cancer patients (9). This study measured the host immune response at the tumor site and demonstrated that it

could provide better prognostic value than the usual tumor risk parameters. The Immunoscore assay might identify a subgroup of high-risk stage II patients who may derive benefits from adjuvant chemotherapy, thereby contributing to the improvement of patient outcomes (9,10). In 2020, the European Society for Medical Oncology (ESMO) included the Immunoscore colon cancer test in its clinical practice guidelines for the diagnosis, treatment and follow-up of early-stage colon cancer (40). However, the Immunoscore assay has not yet been included in the NCCN clinical practice guidelines in the US (1).

In this study, we developed a decision analytic model and estimated costs, QALYs, and ICER values of treatment strategies based on using these 4 genomic tests. The base-case and probabilistic sensitivity analyses indicated that treating patients as guided by the Immunoscore assay was a dominant alternative in comparison with the three other genomic test–guided treatment strategies. Also, we investigated the cost-effectiveness of treatment strategies based on the 12-gene assay and the 18-gene expression assay, because these two tests have been available for clinical use in the US for several years. Earlier studies had compared the cost-effectiveness of the 12-gene assay with the current standard of care (20,21), but a direct comparison of cost-effectiveness with the 18-gene expression assay had not yet been performed to our knowledge. In the base-case analysis, our results demonstrated that differences between effectiveness (QALYs) were minimal across both groups, while the cost savings associated with the use of the 12-gene assay for the entire treatment were more than the list price of the 18-gene expression assay. These findings were consistent across a wide range of one-way and probabilistic sensitivity analyses.

To date, the 12-gene assay, the 18-gene expression assay, the 482-gene signature assay, and the Immunoscore assay have not been covered largely by major health insurers in the US due to a lack of sufficient evidence on their clinical utility (41-44). Such restrictions in the reimbursement of genomic tests highlight the gaps in the existing landscape of evidence. Our study compared and quantified the value of these marketed genomic tests, and generated new evidence related to both cost-effectiveness and quality of life for stage II colorectal patients. This information on costs and outcomes of patients may be helpful for policymakers to select the most appropriate genomic test and help inform their reimbursement decisions.

A key strength of the study is the consideration of local and distant recurrence as health states and the associated utility loss. In this study, we considered the treatment costs incurred for the first recurrence of colorectal cancer only. Because approximately 50% of colorectal cancer patients may develop metastases to their liver over the course of life (45-47), examining the costs for multiple recurrences in the model for all patients could skew the treatment strategies and falsely overestimate the costs. Therefore, estimated cost savings and gain in QALYs as demonstrated in our study are more reflective of real-world clinical settings than in earlier studies, which did not incorporate local or distant relapses of colorectal cancer into their models (20,21).

The ICER is considered to be a measure of value and approximately $50,000 per QALY is a standard threshold for cost-effectiveness of intervention in the US (22). Although our results showed that the implementation of genomic tests for colorectal cancer care may have high ICER values, previous studies on the use of the 12-gene assay to guide adjuvant chemotherapy decisions reduced direct medical costs and improved the quality of life of stage II colorectal cancer patients (20,21). Thus, based on our results, it is possible that the Immunoscore assay may reduce the costs associated with treatment in the longer time frame. Further, our results showed that the estimated total costs associated with use of the 12-gene assay versus the 18-gene assay-guided treatment may generate cost savings equivalent to $3,900. For example, if a hypothetical cohort of 1,000 stage II colorectal cancer patients is considered, the use of the 12-gene assay in comparison with the 18-gene expression assay may lead to savings in treatment costs that are nearly equivalent to $3,900,000, based on the average per patient cost savings of $3,900 achieved by the 12-gene assay. Such estimates on the reduction of total costs of clinical care at the population level may inform the resource allocation decisions of policymakers.

In sensitivity analyses of the Immunoscore assay versus the other three genomic tests, we found that there was a significant increase in the ICERs of the treatment strategies, specifically when a large proportion of patients received chemotherapy. This may be due to our assumptions in the economic models, which were heavily dependent on the costs and utilities associated with patients receiving chemotherapy. However, our assumptions were in accordance with clinical practice guidelines, where the use of chemotherapy is an integrated part of colorectal cancer care for patients with high-risk features (1).

It is noteworthy that, in one-way sensitivity analyses, hazard ratios of the 12-gene assay and 18-gene expression assay were not sensitive to their ICER values. This may

be due to negligible differences between their currently available hazard ratios. The robustness of our economic model might be more rigorously tested when the new parameters become available from the Prospective Study for the Assessment of Recurrence Risk in Stage II Colon Cancer Patients Using ColoPrint (PARSC) study (NCT00903565) (48).

The interpretations of the results of this study are limited by our assumptions in the decision analytic model. First, we relied on the published literature for model input parameters and considered publicly available data for the list price of genomic tests. Real-world evidence data on the effectiveness of genomic tests and targeted therapies may reflect a broad picture of the heterogeneous population in everyday clinical practice. Second, although utility values were used in economic analyses of this study, we did not incorporate patient preferences in the decision-making due to the unavailability of such data at the time. Such an inclusion of preference determination in the study might have guided a greater use of adjuvant chemotherapy and higher gain in QALYs. Third, our economic analysis assumed that all stage II colorectal cancer patients received genomic tests and, based on their recurrence risk score, they were either treated or not with the adjuvant chemotherapy. This pattern may change in a real-world clinical setting. Finally, our analysis provides information from a societal perspective in the United States and, therefore, these results may not be applicable in other health care systems.

In summary, we developed a health economic model for the comparison of four marketed genomic tests (a 12-gene assay, an 18-gene expression assay, a 482-gene signature and the Immunoscore assay) for the purpose of guiding treatment decisions about adjuvant chemotherapy in stage II colorectal cancer patients. Overall, the Immunoscore assay appears to be the dominant strategy as compared with the other three genomic tests at a threshold willingness-to-pay of $50,000 per QALY. Additionally, the 12-gene assay may generate cost savings for the treatment of stage II colorectal cancer patients as compared with the18-gene expression assay.

Conclusions

In this study, we quantified the additional costs and consequences of the currently marketed genomic tests and compared these with other competing alternatives. Overall, the Immunoscore assay appears to be a dominant strategy at a threshold willingness-to-pay of $50,000 per QALY, but when the duration of clinical use of genomic tests in the US is taken into consideration, we found that the 12-gene assay may generate cost savings compared to using the 18-gene expression assay for treatment decisions in stage II colorectal cancer patients. The findings of our study may provide useful information to policymakers regarding selection of the most appropriate genomic test, and resource allocation decisions.

Acknowledgments

We would like to thank Fabienne Hermitte, PhD (co-founder of HalioDX, now Veracyte) for early discussions and her insights about the Immunoscore® assay.

Funding: This work was partially supported by a grant from the Milton Lev Memorial Foundation to Dr. Amalia M. Issa. Vivek S. Chaudhari received the William H. Gano Memorial scholarship as a PhD student.

Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-2022-77/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-2022-77/dss

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-2022-77/coif). VSC received the William H. Gano Memorial scholarship as a PhD student. AMI reports that this work was partially supported by a grant from the Milton Lev Memorial Foundation to her. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This economic modeling study was reviewed by the University of the Sciences Institutional Review Board (Protocol # 1206794-1) and approved as a non-human subjects research.

References

1. Benson AB, Venook AP, Al-Hawary MM, et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:329-59.
2. Taieb J, Karoui M, Basile D. How I treat stage II colon cancer patients. ESMO Open 2021;6:100184.
3. Kannarkatt J, Joseph J, Kurniali PC, et al. Adjuvant Chemotherapy for Stage II Colon Cancer: A Clinical Dilemma. J Oncol Pract 2017;13:233-41.
4. Lee JJ, Chu E. Adjuvant Chemotherapy for Stage II Colon Cancer: The Debate Goes On. J Oncol Pract 2017;13:245-6.
5. Oki E, Watanabe J, Sato T, et al. Impact of the 12-gene recurrence score assay on deciding adjuvant chemotherapy for stage II and IIIA/B colon cancer: the SUNRISE-DI study. ESMO Open 2021;6:100146.
6. Yamanaka T, Oki E, Yamazaki K, et al. 12-Gene Recurrence Score Assay Stratifies the Recurrence Risk in Stage II/III Colon Cancer With Surgery Alone: The SUNRISE Study. J Clin Oncol 2016;34:2906-13.
7. Niedzwiecki D, Frankel WL, Venook AP, et al. Association Between Results of a Gene Expression Signature Assay and Recurrence-Free Interval in Patients With Stage II Colon Cancer in Cancer and Leukemia Group B 9581 (Alliance). J Clin Oncol 2016;34:3047-53.
8. Kopetz S, Tabernero J, Rosenberg R, et al. Genomic classifier ColoPrint predicts recurrence in stage II colorectal cancer patients more accurately than clinical factors. Oncologist 2015;20:127-33.
9. Pagès F, Mlecnik B, Marliot F, et al. International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. Lancet 2018;391:2128-39.
10. Kasi A, Dotan E, Poage GM, et al. Impact of Immunoscore on the Management of Stage II Colon Cancer Patients: A Physician Survey. Cancers (Basel) 2021;13:5467.
11. Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. J Clin Oncol 2011;29:4611-9.
12. Salazar R, Roepman P, Capella G, et al. Gene expression signature to improve prognosis prediction of stage II and III colorectal cancer. J Clin Oncol 2011;29:17-24.
13. Mariotto AB, Enewold L, Zhao J, et al. Medical Care Costs Associated with Cancer Survivorship in the United States. Cancer Epidemiol Biomarkers Prev 2020;29:1304-12.
14. Runyan A, Banks J, Bruni DS. Current and Future Oncology Management in the United States. J Manag Care Spec Pharm 2019;25:272-81.
15. Dieleman JL, Squires E, Bui AL, et al. Factors Associated With Increases in US Health Care Spending, 1996-2013. JAMA 2017;318:1668-78.
16. Personalized Medicine Coalition [Internet]. Washington DC: Personalized Medicine at FDA - The Scope & Significance of Progress in 2021 [Cited 2022 Jan 15]. Available online: https://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/Personalized_Medicine_at_FDA_The_Scope_Significance_of_Progress_in_2021.pdf
17. Keeling P, Clark J, Finucane S. Challenges in the clinical implementation of precision medicine companion diagnostics. Expert Rev Mol Diagn 2020;20:593-9.
18. Deverka PA, Douglas MP, Phillips KA. Use of Real-World Evidence in US Payer Coverage Decision-Making for Next-Generation Sequencing-Based Tests: Challenges, Opportunities, and Potential Solutions. Value Health 2020;23:540-50.
19. Phillips KA, Deverka PA, Trosman JR, et al. Payer coverage policies for multigene tests. Nat Biotechnol 2017;35:614-7.
20. Hornberger J, Lyman GH, Chien R, et al. A multigene prognostic assay for selection of adjuvant chemotherapy in patients with T3, stage II colon cancer: impact on quality-adjusted life expectancy and costs. Value Health 2012;15:1014-21.
21. Alberts SR, Yu TM, Behrens RJ, et al. Comparative economics of a 12-gene assay for predicting risk of recurrence in stage II colon cancer. Pharmacoeconomics 2014;32:1231-43.
22. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA 2016;316:1093-103.
23. Ejaz A, Casadaban L, Maker AV. Utilization and impact of adjuvant chemotherapy among patients with resected stage II colon cancer: a multi-institutional analysis. J Surg Res

2017;215:12-20.
24. Foo CC, Ku C, Wei R, et al. How does lymph node yield affect survival outcomes of stage I and II colon cancer? World J Surg Oncol 2020;18:22.
25. Ayvaci MU, Shi J, Alagoz O, et al. Cost-effectiveness of adjuvant FOLFOX and 5FU/LV chemotherapy for patients with stage II colon cancer. Med Decis Making 2013;33:521-32.
26. Joranger P, Nesbakken A, Hoff G, et al. Modeling and validating the cost and clinical pathway of colorectal cancer. Med Decis Making 2015;35:255-65.
27. Aballéa S, Chancellor JV, Raikou M, et al. Cost-effectiveness analysis of oxaliplatin compared with 5-fluorouracil/leucovorin in adjuvant treatment of stage III colon cancer in the US. Cancer 2007;109:1082-9.
28. Ness RM, Holmes AM, Klein R, et al. Utility valuations for outcome states of colorectal cancer. Am J Gastroenterol 1999;94:1650-7.
29. Genomic Health [Internet]. Redwood City: Annual Report 2016 [Cited 2021 December 15]. Available online: https://materials.proxyvote.com/default.aspx?docHostID=322481
30. Lopez NE, Weiss AC, Robles J, et al. A systematic review of clinically available gene expression profiling assays for stage II colorectal cancer: initial steps toward genetic staging. Am J Surg 2016;212:700-14.
31. Helomics [Internet]. Pittsburgh: Risk of recurrence gene signature, GeneFx [Cited 2021 December 15]. Available online: https://docs.wixstatic.com/ugd/18452a_af7512031d7446799f51c780a8764cb0.pdf
32. Renfro LA, Zhang N, Lopatin M, et al. Prospective Evaluation of a 12-Gene Assay on Patient Treatment Decisions and Physician Confidence in Mismatch Repair Proficient Stage IIA Colon Cancer. Clin Colorectal Cancer 2017;16:23-30.
33. Brenner B, Geva R, Rothney M, et al. Impact of the 12-Gene Colon Cancer Assay on Clinical Decision Making for Adjuvant Therapy in Stage II Colon Cancer Patients. Value Health 2016;19:82-7.
34. Reimers MS, Kuppen PJ, Lee M, et al. Validation of the 12-gene colon cancer recurrence score as a predictor of recurrence risk in stage II and III rectal cancer patients. J Natl Cancer Inst 2014;106:dju269.
35. Srivastava G, Renfro LA, Behrens RJ, et al. Prospective multicenter study of the impact of oncotype DX colon cancer assay results on treatment recommendations in stage II colon cancer patients. Oncologist 2014;19:492-7.
36. Cartwright T, Chao C, Lee M, et al. Effect of the 12-gene colon cancer assay results on adjuvant treatment recommendations in patients with stage II colon cancer. Curr Med Res Opin 2014;30:321-8.
37. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol 2011;29:3768-74.
38. Venook AP, Niedzwiecki D, Lopatin M, et al. Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581. J Clin Oncol 2013;31:1775-81.
39. HalioDx [Internet]. Richmond: HalioDx establishes us facilities in Richmond, Virginia and holds a CLIA certificate of registration for immunoscore®, 2019 [Cited 2022 February 26]. Available online: https://io.veracyte.com/press-releases/haliodx-establishes-us-facilities-in-richmond-virginia-and-holds-a-clia-certificate-of-registration-for-immunoscore/
40. Argilés G, Tabernero J, Labianca R, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1291-305.
41. BlueCross BlueShield of North Carolina [Internet]. Corporate Medical Policy, 2021 [Cited 2021 December 15] Available online: https://www.bluecrossnc.com/sites/default/files/document/attachment/services/public/pdfs/medicalpolicy/multigene_expression_assay_for_predicting_colon_cancer_recurrence.pdf
42. Wellmark [Internet]. Medical Policy, 2021 [Cited 2021 December 15]. Available online: https://www.wellmark.com/Provider/MedpoliciesAndAuthorizations/MedicalPolicies/policies/Genetic_Assays_Colon_Cancer.aspx
43. HealthLink [Internet]. Medical Policy, 2020 [Cited 2021 December 15]. Available online: https://www.anthem.com/dam/medpolicies/abc/active/policies/mp_pw_c128862.html
44. Johnson M [Internet]. HalioDx Opens US Lab, Expanding Access to Immunoscore in North America, 2019. Available online: https://www.360dx.com/cancer/haliodx-opens-us-lab-expanding-access-immunoscore-north-america#.XfGE2ZNKhE4
45. Zarour LR, Anand S, Billingsley KG, et al. Colorectal Cancer Liver Metastasis: Evolving Paradigms and Future Directions. Cell Mol Gastroenterol Hepatol 2017;3:163-73.
46. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol 2007;25:4575-80.
47. House MG, Kemeny NE, Gönen M, et al. Comparison of adjuvant systemic chemotherapy with or without hepatic

arterial infusional chemotherapy after hepatic resection for metastatic colorectal cancer. Ann Surg 2011;254:851-6.
48. ClinicalTrials.gov [Internet] Bethesda (MD): National Library of Medicine (US). 2019 Jan 09. Identifier: NCT00903565, A Prospective Study for the Assessment of Recurrence Risk in Stage II Colon Cancer Patients Using ColoPrint (PARSC), 2009, May 18 [Cited 2021 December 15]; Available online: https://clinicaltrials.gov/ct2/show/NCT00903565

Cite this article as: Chaudhari VS, Issa AM. Cost-effectiveness of precision molecular diagnostic tests for stage II colorectal cancer. Ann Transl Med 2022;10(23):1260. doi: 10.21037/atm-2022-77

