

Abstract

OBJECTIVES

Colorectal cancer (CRC) is a fatal disease with an increasing incidence in Asian countries. one of the most important risk factors for this disease is lynch syndrome. Identifying Lynch syndrome (LS) in patients with colorectal cancer (CRC) and monitoring their relatives can increase the life expectancy of their close relatives. The aim of this study is to analyze the cost-effectiveness of five molecular testing strategies to screen LS among the patients with newly diagnosed CRC and conducting preventive surveillance in their first-degree relatives.

METHODS

A decision tree model was designed to identify the number of LS mutations and related costs in CRC patients. In doing this, five strategies were modeled i.e. Amsterdam II criteria, microsatellite instability (MSI) testing, immunohistochemistry (IHC) and next-generation sequencing (NGS). A Marko model was used to estimate the long term outcome of monitoring (including colonoscopy and taking aspirin) among the relative of those patients with CRC who carry LS. Costs from a health system perspective and Quality-adjusted life years (QALYs) and life-years gained in relatives were estimated over a lifetime horizon and discounted at 3% per annum.

RESULTS

All strategies were cost-effective when compared with no testing. The two most cost-effective strategies were strategy 2 (IHC testing followed by NGS testing) and strategy 4 (MSI testing, followed by NGS testing) with ICER of 4,604 \$ and 4,748 \$ per QALY, respectively.

CONCLUSIONS

Our finding suggested that from an Iranian health care system perspective, IHC testing followed by NGS testing is the most cost-effective strategy compared to the other strategies. These results will be useful for offering to screen LS in newly diagnosed CRC patients.

Introduction

- Colorectal cancer (CRC) is a fatal and prevalent disease.
- About 6% of CRC cases are related to the Hereditary factors and positive family history in terms of incidence and prevalence; so, it would be curable in the early stages of the disease.
- Lynch syndrome (LS) is the most common inherited cancer disorder with an autosomal dominant inheritance caused by a germline mutation in one of the DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6 and PMS2).
- The molecular testing of the CRC patients at the risk of LS and their subsequent monitoring could lead to the early diagnosis of the disease, reducing the cost of the future treatment and ensuring longer life expectancy and better quality of life in the individuals who are prone to this disease.
- The molecular testing techniques, such as IHC and MSI, are performed on the tumor tissue specimens and their adjacent healthy tissues; they have a high power to screen the defective genes. Meanwhile, in the genetic NGS testing, the blood DNA samples are usually used to detect the germline mutations in one of the MMR genes.
- We evaluated the cost-effectiveness of different possible screening methods for diagnosing LS in a population with CRC.

Methodology

- This study was a model-based economic evaluation.
- A decision tree model was accordingly designed to calculate the number of cases of LS detected in each strategy and the related costs.
- The decision tree model started with an assumptive cohort of 10,000 CRC cases.
- Markov model was used to estimate the short and long-term costs and CRC-related effects associated with colorectal cancer in the first-degree relatives.
- The time horizon considered in this study was up to the age of 90 or the time of passing away.
- The effectiveness in terms of QALYs and LYG in relatives was estimated over a lifetime horizon.
- To evaluate the validity of the Markov model, One-way sensitivity analyses were carried out for all parameters considered in this study.

Fig 1. Molecular screening strategies for lynch syndrome

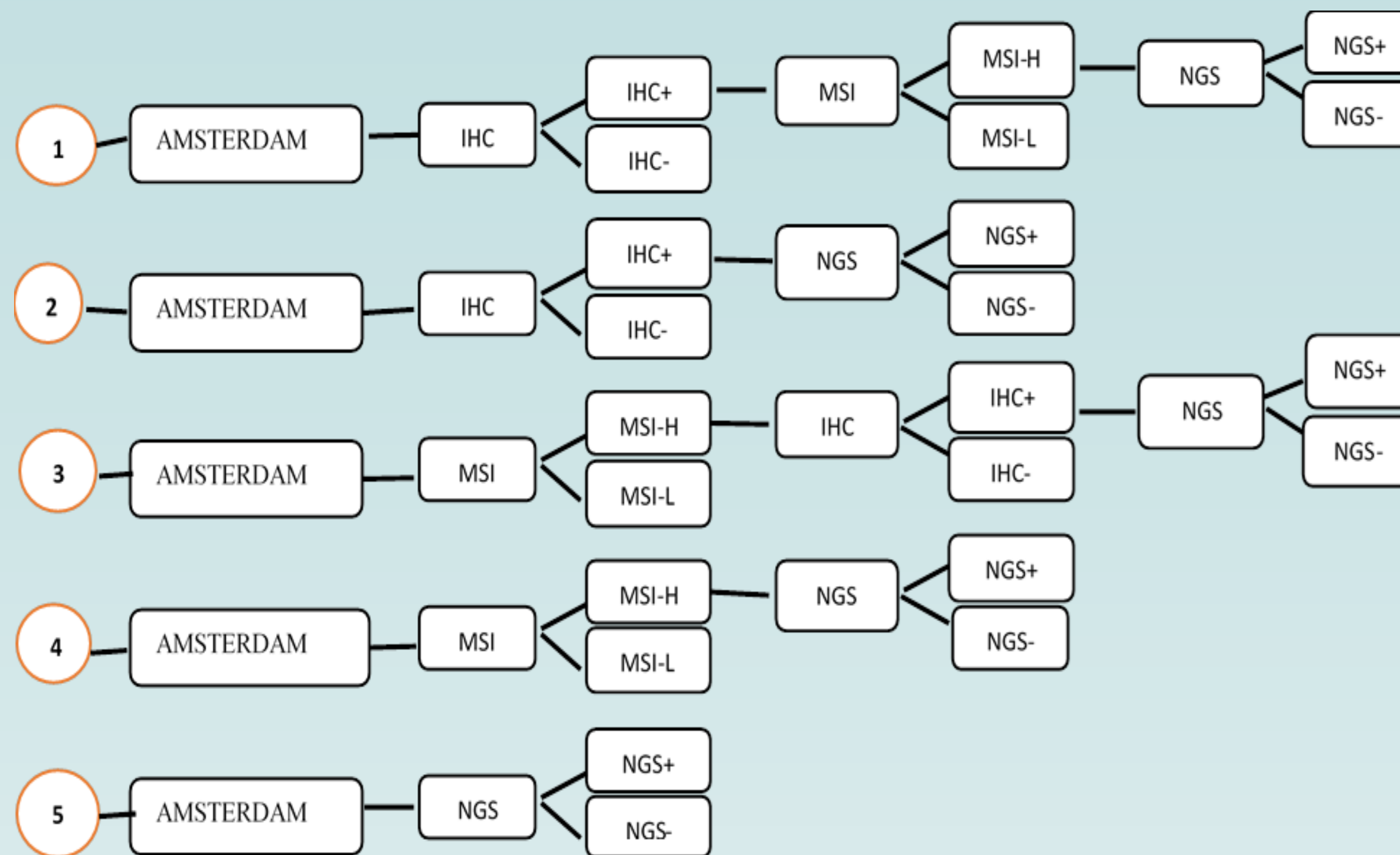
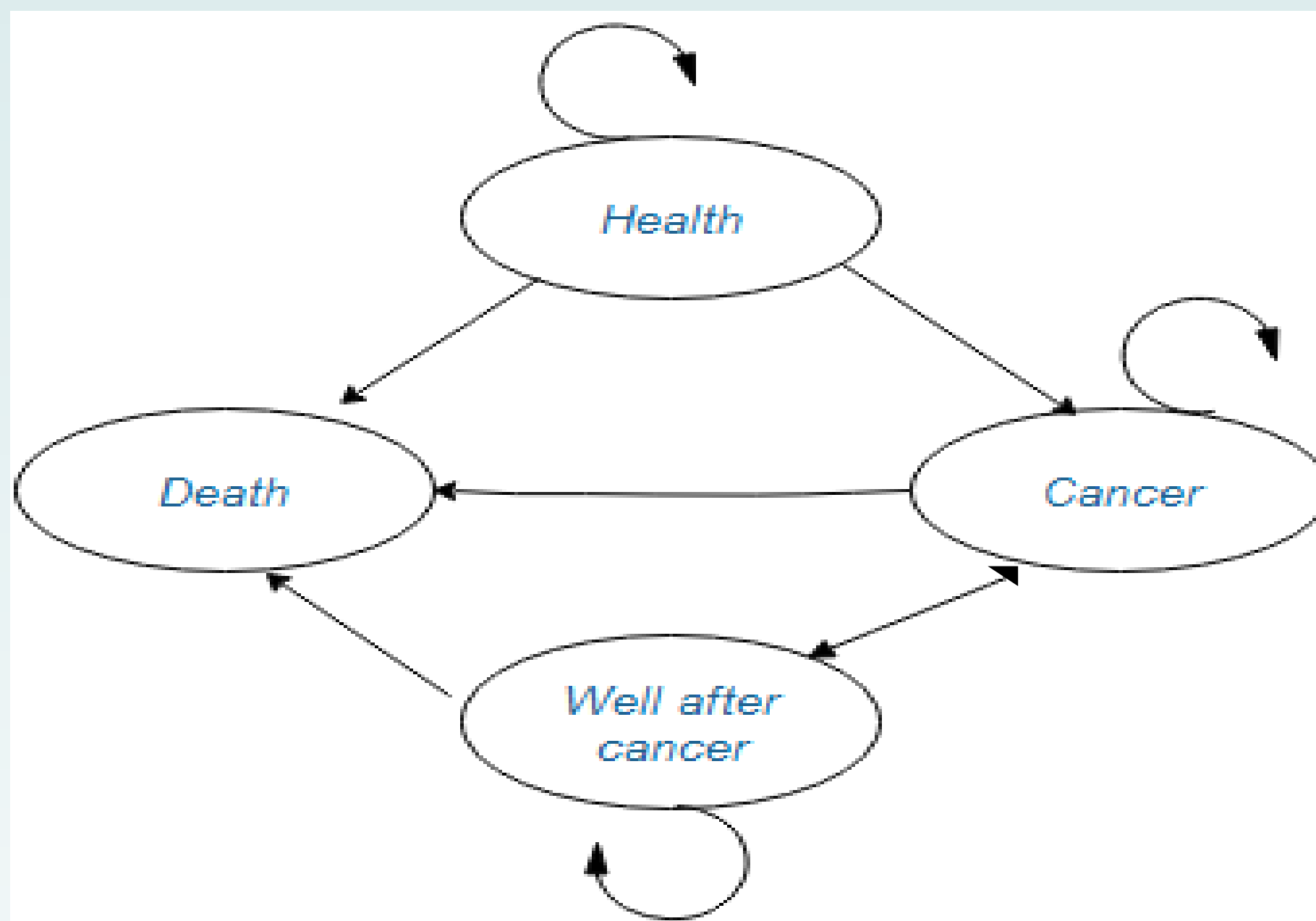


Fig 2. Markov Algorithm



- The time horizon considered in this study was up to the age of 90 or the time of passing away.
- The analysis was carried out using the Excel Software and all costs and outcomes were discounted at 3% per annum.
- The effectiveness in terms of QALYs and LYG in relatives was estimated over a lifetime horizon.
- We calculated the QALYs by the utility of a health state multiplied by the period of time corresponding to that state.
- To evaluate the validity of the Markov model, One-way sensitivity analyses were carried out through a 20% decrease and increase were applied to all parameters except the discount rate and years of colonoscopy.

Results

- All screening strategies could reduce cancer incidence and death and yield more life-years, as compared with the no-screening strategy. Table 1 displays the incremental costs, incremental effects, and incremental cost-effectiveness ratios (ICERs (QALY) and ICERs (LYG)) in the five screening strategies.
- the cost of identifying LS in the first-degree relatives in strategies 1 to 5 was 5,770, 4,400, 6,569, 4,669 and 16,439 \$ per FDR, respectively.
- Comparison of the costs and outcomes in different strategies showed that strategy 5 could be ruled out because it was strongly dominated by the strategy 2 (strategy 2 had less cost and better outcomes in comparison to the strategy 5).

- Strategies 1, 3 and 4 were dominated by strategy 2, because they were less effective and had a higher ICER.
- the strategy 2 was both the most effective and the least costly strategy, with a lower ICER, as compared to the other strategies.

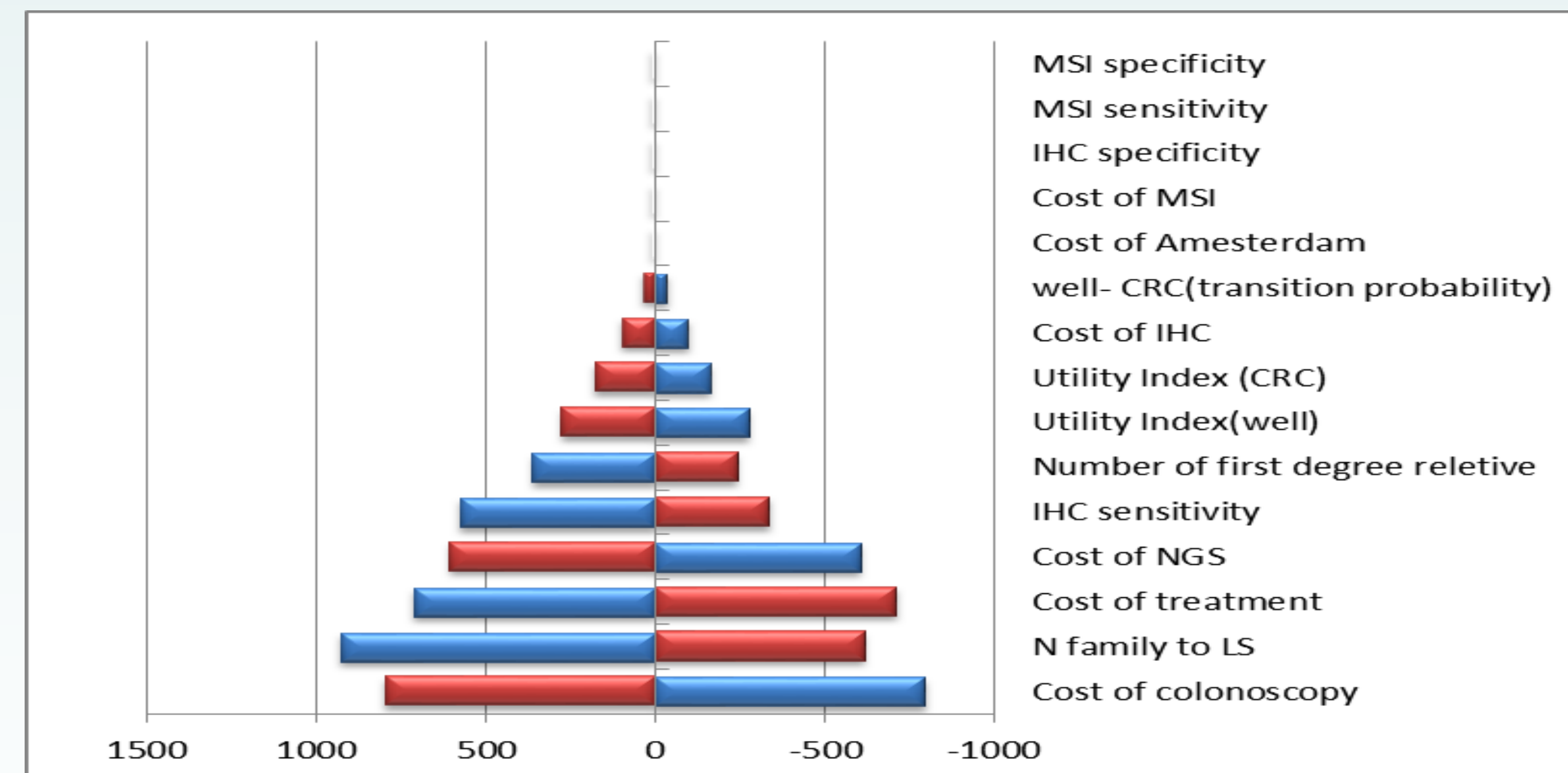
Table 1. Incremental cost-effectiveness ratios for screening strategies

Strategy	incremental cost \$	incremental QALY	LYG	ICER1 (QALY)	ICER (LYG)
strategy 1	1,427,775	268	237	5,337	6,029
strategy 2	2,054,928	446	395	4,604	5,202
strategy 3	1,340,024	233	206	5,763	6,511
strategy 4	1,966,129	414	367	4,748	5,364
strategy 5	2,645,799	249	220	10,639	12,043

LYG, life-year gain. QALY. quality-adjusted life year

- Based on one-way sensitivity analysis, in strategies 1 to 3, IHC sensitivity, the cost of colonoscopy and MSI sensitivity had the most effect on the results. The same was true for the strategies 4 and 5 with regard to the number of families who inherited LS.
- in the strategy 2, which was the most cost-effective, a 20 percent decrease and increase in the variables related to the cost of colonoscopy, the number of families who had inherited LS, the cost of treatment and the cost of NGS led to an ICER range of 1593\$, 1543\$, 1420\$ and 1212\$ per QALY respectively.
- The results of one-way sensitivity analysis are shown in Fig. 3 using the Tornado Chart.

Fig 3. One-way sensitivity analysis



Conclusion

- All strategies were cost-effective, as compared to non-screening, from the perspective of the Iran health care system.
- Strategies that began with the Amsterdam criteria and they were followed by IHC or MSI tests, alongside the NGS test, were the most cost-effective, as compared to non-screening; in fact, the strategy 2 was the most cost-effective one.
- The cost-effectiveness ratio achieved through the use of NGS testing for the CRC patients without any other molecular testing was close to the upper cost-effective threshold and therefore, had the least cost effectiveness. The screening would also have many clinical benefits for first-degree relatives of patients.