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Is Universal Genetic Testing Cost-Effective to Detect and Manage Lynch Syndrome in Singapore?

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Background

- Universal genetic testing in colorectal cancer (CRC) patients coupled with cascade testing among family members has been proposed as a public health strategy to reduce Lynch Syndrome (LS)-related cancer burden.
- This study aims to evaluate the cost-effectiveness of different strategies in terms of early detection and treatment of LS in CRC patients and their family members in Singapore.

Methods

Study Design: A model-based cost-utility analysis.
Model: A decision analytic model combining a decision tree with Markov models.
Perspective & Time Horizon*:* Healthcare payers' perspective, lifetime horizon of proband and first-degree relatives (FDRs).
Target population: Incident CRC patients; FDRs of those with LS.
Reference & Candidate Testing Strategies:

1) No testing;
2) Universal tumor testing strategies or universal germline testing (GT) for LS.

Primary Outcomes: Total cost, effectiveness in Quality-Adjusted Life Years (QALYs), incremental cost-effectiveness ratio (ICER), cancer cases avoided, and cancer-specific deaths averted.
Discount Rate: Costs (SGD) & QALYs discounted annually at 3% to the year 2024.
Willingness To Pay Threshold: 45,000 SGD/QALY.
Key Assumptions: Probands develop up to two cancers (second cancer can be either CRC, gastric (GC) or endometrial cancer (EC)), while FDRs could develop CRC, EC, or GC as their first cancer. We assumed 100% compliance with recommended surveillance programs

Results

Table 1: Diagnostic yield from different testing strategies from the decision tree analyses.

Strat. #	Diagnostic strategies to identify LS probands	Sensitivity (Range)*
1	No test	0
2	GT|IHC MMR$^-$	95.72% (68.71-99.6)
3	GT|BRAF600E$^-$|IHC MLH1$^-$ ***Or*** GT|IHC MSH2/MSH6/PMS2$^-$	94.49 % (59.91-99.28)
4	GT|MLH1 methylation$^-$|IHC MLH1$^-$ ***Or*** GT|IHC MSH2/MSH6/PMS2$^-$	93.88% (64.09-98.96)
5	GT|MSI-High	90.84% (42.17-99.3)
6	GT|BRAF600E$^-$|MSI-High	89.68% (36.78-98.98)
7	Universal GT	99.50% (99.00-100)

IHC=Immunohistochemistry, MSI= Microsatellite instability, GT=Germline testing.
***Specificity is 100% for all strategies.**

Table 2: Base-case cost-effectiveness results of undominated LS diagnosis strategies.

Strat. #	Cost (SGD)	Incr. Cost	Eff. (QALY)	Incr. Eff (QALY)	ICER vs No testing	ICER vs Previous strategy
No testing	17,687	-	136.480	-	-	-
Strat. 4	19,457	1,770	136.635	0.155	11,392	11,392
Strat. 2	19,523	67	136.638	0.003	11,593	21,873
Strat. 7	20,089	565	136.645	0.006	14,586	90,367
Long term outcomes of FDRs only						
No testing	12,833	-	126.434	-	-	-
Strat. 4	16,350	3,516	126.562	0.128	27,392	27,392
Strat. 2	16,556	206	126.565	0.003	28,439	81,928
Strat. 7	18,822	2,266	126.570	0.005	44,015	438,322

Results (continued)

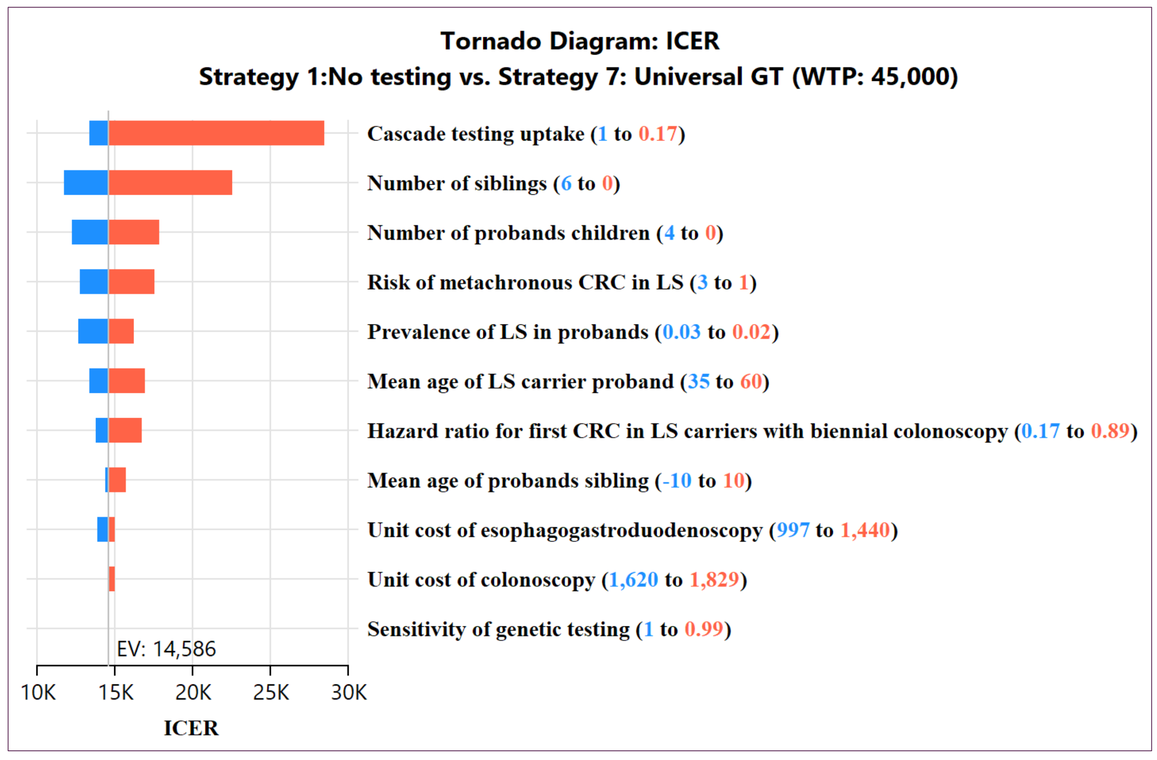

Figure 1: Main drivers for cost-effectiveness of universal GT relative to the reference strategy (no Testing), identified in sensitivity analysis (WTP: S$45,000).
Color bars: Blue indicate lower ICER values (more cost-effective), orange indicate higher ICER values (less cost-effective). Parameter ranges shown in parentheses: blue value reduces ICER, orange value increases ICER

Table 3: Lifetime benefits of LS-specific surveillance compared to routine surveillance in LS carrier FDRs.

	Cancer cases avoided	Cancer specific deaths averted	Additional life years gained
Male	0.0007	0.42	0.014
Female	0.0016	0.30	0.013

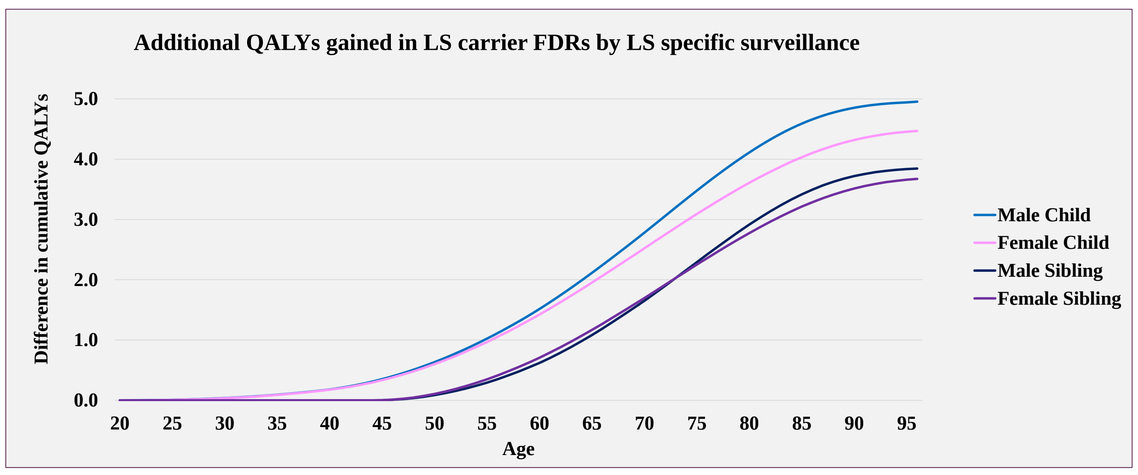

Figure 2: Additional QALYs gained over lifetime by LS carrier FDRs undergoing LS specific surveillance compared to routine surveillance.
The mean age of long-term model entry for siblings and children of LS carrier probands was 45 and 20 years, respectively.

Discussion & Conclusion

Given the prevalence of 2.2% of LS in newly diagnosed CRC patients and ~4 FDRs per proband:

- Universal GT (strategy 7) is likely cost-effective for LS screening in incident CRC patients compared to no testing (strategy 1) but not compared to IHC-guided GT strategies (with/without MLH1 hypermethylation testing).
- In incremental analyses using a WTP threshold of S$ 45,000/QALY, both strategy 2 and 4 were cost-effective. However, due to higher effectiveness, strategy 2 would be the optimal strategy (ICER of 21,873/QALY).
- Universal GT is the most effective strategy, detecting the most LS cases and yielding the highest QALYs, but requires a higher WTP to be cost-effective.
- The cost-effectiveness of Universal GT is expected to improve with increased cascade testing uptake, first-degree relatives per proband, metachronous CRC risk in LS carriers, and LS prevalence.
- Implementation of LS-specific management in LS carrier FDRs is expected to prevent 2.4 LS-associated cancers/1,000 individuals and reduce cancer related deaths by 72% compared to routine surveillance.

References:

1. Li, Shao-Tzu, et al. "Impact of subsidies on cancer genetic testing uptake in Singapore." Journal of Medical Genetics 54.4 (2017): 254-259.
2. Wang, Vivian Wei, et al. "Predictive genetic testing of first degree relatives of mutation carriers is a cost-effective strategy in preventing hereditary non-polyposis colorectal cancer in Singapore." Familial Cancer 11 (2012): 279-289.

Supplementary Materials