Economic Analysis of Germline Genetic Testing to Assess for Hereditary Colorectal Cancer: A Systematic Review

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OBJECTIVE

- The objective of this study was to evaluate the economic effects of germline genetic testing (GGT) among adults with colorectal cancer (CRC), those at increased risk of CRC, and healthy individuals, through the diagnosis of Lynch syndrome (LS) and other hereditary syndromes.

METHODS

- We conducted a systematic search for literature published after January 2013 that assessed clinical, economic, and humanistic outcomes in patients with CRC and those at elevated risk of CRC, using Embase (n = 8,317) and MEDLINE/PubMed (n = 4,520). The search strategy incorporated indexing terms (e.g., MeSH terms, Emtree terms) and keywords at the intersection of CRC, screening, and outcomes. The protocol was not registered.
- Following PRISMA guidelines, seven reviewers screened the title/abstract and full text according to predefined eligibility criteria. Each article was evaluated by two blinded reviewers. A third independent reviewer resolved any conflicts. We included studies if GGT was analyzed as a clinical scenario without the use of tumor screening or testing. Detailed eligibility criteria are presented in **Table 1**.
- Two reviewers evaluated the methodological quality of studies according to the CHEERS checklist. Conflicts were resolved by a third independent reviewer.

Table 1: *Eligibility criteria*

Inclusion Criteria	Exclusion Criteria
English language	Non-English publications
Peer-reviewed	Case studies, systematic reviews, meta-analyses, and clinical practice guidelines, conference abstracts
Individuals aged ≥18 years	Individuals aged <18 years
Individuals with CRC, LS, and/or familial polyposis	Individuals without CRC, LS, and/or familial polyposis
Outcomes based on GGT	Outcomes based on somatic/tumor testing
	Animal studies

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KEY FINDINGS

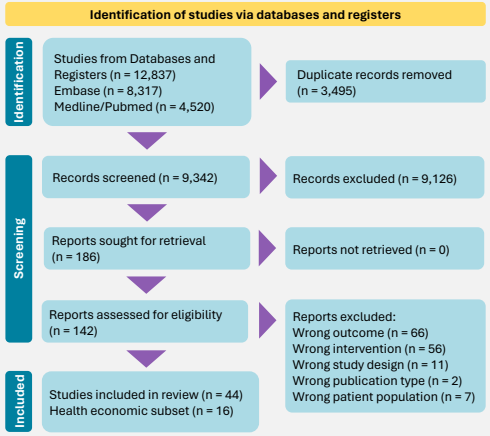
Despite the high level of heterogeneity among studies, the majority found germline genetic testing to be cost-effective. The identified literature was specific to colorectal cancer in the context of Lynch syndrome. Therefore, there is a need for further research to assess the potential value of panel testing to include other hereditary syndromes associated with colorectal cancer risk.

RESULTS

A PRISMA flow diagram (**Figure 1**) depicts the flow of information through the phases of review. Of 9,342 articles screened, 16 economic analysis articles were included in the review; eight were published prior to 2020. All articles described the impact of GGT on patients in the context of LS.

This analysis presents studies that included economic outcomes.

Figure 1: *PRISMA flowchart describing study selection and reasons for exclusion during full-text screening*



13 studies evaluated the cost-effectiveness of GGT using different willingness-to-pay (WTP) thresholds and assumptions for test cost, population, comparators, and whether family history and/or clinical criteria were used to define higher-risk groups.

- Ten out of 13 studies demonstrated at least one clinical scenario or screening strategy where the use of GGT was cost-effective based on a WTP threshold of $150,000.
- Three studies did not employ cost-effectiveness analysis (CEA) methods:
  - A cost-analysis to understand the economic burden of using GGT to identify individuals with LS.[3]
  - A survey of patients' WTP for GGT.[12]
  - A study to determine the lowest cost strategy to identify one case of LS.[10]
- **Table 2** summarizes clinical scenarios and strategies presented that were inclusive of GGT.
- Among US-based cost-effectiveness studies (n = 5), the base case cost of GGT alone varied widely over time, ranging from $4,000 in a 2014 article to $200 in a 2022 article.
- Ten of 13 CEA studies modeled a simulated population comprising patients with newly diagnosed CRC.
- The majority of studies used Markov models (n = 11) and adopted a healthcare system perspective (n = 7).

Abbreviation key:
CRC / colorectal cancer; CRCP / colorectal cancer polyposis; FDR / first-degree relative; GGT / germline genetic testing; LS / Lynch syndrome; LY / life year; QALY / quality-adjusted life year; SDR / second-degree relative; WTP / willingness-to-pay.

Citations/references can be found here:

Table 2: *Summary of cost-effectiveness articles*

Author (year) / country	Population	Referent strategy	GGT cost	GGT strategies	Cost per LY	Cost per QALY	Author's WTP threshold
Azardoost et al. (2018)[7] / Iran	CRC patients w/ cascade testing[b]	No screening	$8,727–$9,879	Amsterdam*, NGS	$12,043	$10,639	-
Barzi et al. (2015)[2] / USA	CRC patients w/ cascade testing[d]	No screening	$880 (base case)	MMRpro*, germline	$223,988	-	$50,000
				Up-front germline	$996,878	-	
			$685	MMRpro*, germline	$136,482	-	
				Up-front germline	$776,747	-	
			$490	MMRpro*, germline	$98,717	-	
				Up-front germline	$556,616	-	
			$295	MMRpro*, germline	$60,953	-	
				Up-front germline	$336,486	-	
			$100	MMRpro*, germline	$33,195	-	
				Up-front germline	$116,355	-	
Chen et al. (2016)[4] / Taiwan	CRC patients w/ cascade testing[b]	Existing screening pathway	$3,998	MMR gene sequencing (4 genes)	$145,110	-	$50,000
Gallego et al. (2015)[5] / USA	Patients referred to the clinic for evaluation of CRCP syndrome[a,b]	Existing screening pathway	$2,700	Panel 1: LS genes only	$122,316	$144,235	$100,000
				Panel 2: panel 1 + genes associated with autosomal dominant CRCP syndromes with high penetrance of CRC	$31,623	$37,467	
				Panel 3: panel 2 + genes associated with autosomal recessive CRCP syndromes with high penetrance of CRC	$30,813	$36,508	
				Panel 4: panel 3 + genes associated with autosomal dominant CRCP syndromes with low penetrance of CRC but not necessarily with other syndromes	$33,020	$39,112	
Gansen et al. (2019)[6] / Germany	CRC patients w/ cascade testing[c]	No screening	€21,444	Counseling, direct sequencing	€351,458	-	-
Gould et al. (2014)[7] / USA	CRC patients[a, b]	-	$4,000	MLH1, MSH2, MSH6 and PMS2 full gene sequencing	-	$132,200	ICER compared to least costly strategy
Guzauskas et al. (2022)[9] / USA	CRC patients[b]	Family history-based testing only	$200	LS screening at age 30 years	-	$132,200	$50,000, $100,000, $150,000
				LS screening at age 40 years	-	$123,900	
				LS screening at age 50 years	-	$140,400	
Guzauskas et al. (2023)[8] / USA	Age-based cohorts (20–60 years) of healthy adults w/ cascade testing[b]	No screening	$250 (base case)	Genomic screening using clinical sequencing with a restricted panel of high-evidence genes w/ cascade testing of FDRs	-	$68,600	$100,000
			$100		-	$39,700	
			$500		-	$116,800	
Kang et al. (2017)[11] / Australia	CRC patients w/ cascade testing[c]	No screening	AUD 1,200	Universal gene panel testing (no age limit, 1 year)	AUD 61,235	€1,682	AUD 30,000–50,000
Pastorino et al. (2020)[13] / Italy	CRC patients w/ cascade testing[b]	No screening	€250	MMR gene sequencing (4 genes)	-	€1,682	€30,000
Ramdzan et al. (2021)[14] / Malaysia	CRC patients[b]	No screening	$976	Genetic testing	$159	$196	-
Salikhanov et al. (2023)[15] / Switzerland	CRC patients w/ cascade testing[b]	Existing screening pathway	CHF 3,500	DNA sequencing + cascade testing of four or more FDRs and SDRs	-	CHF 65,058	CHF 100,000
Severin et al. (2015)[16] / Germany	CRC patients w/ cascade testing[c]	No screening	€120,050	Counseling, direct sequencing	€648,997	-	50,000

a Decision trees
b Health system perspective
c Payer perspective
d Societal perspective
* Clinical risk prediction model for LS