# **Economic Analysis of Germline Genetic Testing to Assess for Hereditary Colorectal Cancer:**

A Systematic Review Johnson, HA<sup>1</sup>, Hartzfeld, D<sup>1</sup>, Peters, ML<sup>2,3</sup>, Xiao, J<sup>4</sup>, Berksoy, E<sup>4</sup>, Kirshner C<sup>4</sup>, Sancar F<sup>1</sup>, Leach B<sup>1</sup>, Cox, H<sup>1</sup>, Thompson, G<sup>1</sup>, Kong, J<sup>1</sup>, Thakkar, S<sup>1</sup>, Cuyún Carter, G<sup>1</sup>

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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
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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

### **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 costeffectiveness 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.<sup>12</sup> A study to determine the lowest cost strategy to identify one case of LS.<sup>10</sup>
- 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:

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Author (year) / country	Population	Referent strategy	GGT cost	GGT strategies	Cost per LY	Cost per QALY	Author's WTP thre <u>shol</u>
Azardoost et al. (2018) <sup>1</sup> / Iran	CRC patients w/ cascade testing <sup>b</sup>	No screening	\$8,727- \$9,879	Amsterdam*, NGS	\$12,043	\$10,639	
Barzi et al. CRC patier (2015) <sup>°</sup> / USA cascade te			\$880	MMRpro*, germline	\$223,988	-	\$50,000
	CRC patients w/ cascade testing <sup>d</sup>	patients W/ de testing <sup>d</sup> No screening	(base case) \$685 \$490	Up-front germline	\$996,878	-	
				MMRpro*, germline	\$136,482	-	
				Up-front germline	\$776,747	-	
				MMRpro*, germline	\$98,717	-	
			\$400	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) <sup>4</sup> / Taiwan	CRC patients w/ cascade testing <sup>b</sup>	Existing screening pathway	\$3,998	MMR gene sequencing (4 genes)	\$145,110	-	\$50,000
				Panel 1: LS genes only	\$122,316	\$144,235	
Patients referred Gallego et al. to the clinic for Ex (2015) <sup>4</sup> / USA evaluation of scr CRCP syndrome <sup>3,3</sup> pa				Panel 2: panel 1 + genes			
				associated with autosomal dominant CRCP syndromes with high penetrance of CRC	\$31,623	\$37,467	
	Existing screening pathway	Existing screening \$2,700 pathway	Panel 3: panel 2 + genes associated with autosomal recessive CRCP syndromes with high penetrance of CRC	\$30,813	\$36,508	\$100,000	
			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) <sup>6</sup> / Germany	CRC patients w/ cascade testing <sup>c</sup>	No screening	€21,444	Counseling, direct sequencing	€351,458	-	-
Gould et al. (2014) <sup>7</sup> / USA	CRC patients <sup>a, b</sup>		\$4,000	MLH1, MSH2, MSH6 and PMS2 full gene sequencing	-	\$132,200	ICER compare to least costly strategy
Guzauskas et		Family history-based testing only	\$200	LS screening at age 30 years	-	\$132,200	\$50,000, \$100,000, \$150,000
al. (2022) <sup>9</sup> /	CRC patients <sup>b</sup>			LS screening at age 40 years	-	\$123,900	
USA				LS screening at age 50 years	-	\$140,400	
Guzauskas et al. (2023) <sup>8</sup> / USA Age-based cohorts (20–60 years) of healthy adults w/ cascade testing <sup>b</sup>	Age-based cohorts (20–60 years) of	No screening	\$250 (base case)	Genomic screening using clinical sequencing with a restricted panel	-	\$68,600	) \$100,000
	healthy adults w/		\$100	of high-evidence genes w/	-	\$39,700	
		\$500	cascade testing of FDRs	-	\$116,800		
Kang et al. (2017) <sup>11</sup> / Australia	CRC patients w/ cascade testing	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) <sup>13</sup> / Italy	CRC patients w/ cascade testing <sup>b</sup>	No screening	€250	MMR gene sequencing (4 genes)	-	€1,682	€30,000
Ramdzan et al. (2021) <sup>14</sup> / Malaysia	CRC patients <sup>b</sup>	No screening	\$976	Genetic testing	\$159	\$196	
Salikhanov et al. (2023) <sup>15</sup> / Switzerland	CRC patients w/ cascade testing <sup>b</sup>	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) <sup>16</sup> /	CRC patients w/ cascade testing <sup>6</sup>	No screening	€120,050	Counseling, direct sequencing	€648,997	-	50,000

