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Suboptimal Adherence to Germline Genetic Testing Guidelines: Insights from a Microsimulation Model

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Background

Hereditary colorectal cancer (CRC) syndromes account for a considerable proportion of preventable cancer cases. Germline genetic testing (GGT) of patients with cancer enables identification of pathogenic germline variants (PGV) that can guide cascade testing and risk-based screening of first-degree relatives (FDR).

Objective

This modeling study evaluated how adherence to GGT guidelines impacts detection of PGV among patients with CRC. We also assessed PGV identification and associated CRC outcomes among their first-degree relatives.

Methods

We developed a microsimulation model comprising two modules (GGT and CRC screening) and used it to compare real-world adherence to GGT with perfect adherence to GGT. Model parameters were informed by published data and expert validation.

The **GGT module** incorporated guideline-recommended testing pathways and modalities, including PREMM5 and MMR deficiency testing (IHC/MSI), to identify eligible candidates for testing and a targeted GGT panel for identifying Lynch syndrome.

Adherence to GGT was captured across four levels: eligibility for GGT, referral to genetic counseling, acceptance of counseling among those eligible, acceptance of GGT after counseling.

The **CRC screening module** adapted the published CRC-AIM model[1] to simulate disease progression, with three levels of risk-based CRC screening: average-risk screening, familial CRC screening, PGV-specific screening.



Click for references and information on testing pathways and key input parameters

Results



Per **10,000 probands with PGV**

Real-world adherence: **4,205** with PGV identified

Perfect adherence: **8,830** with PGV identified



Per **10,000 FDR**

Real-world adherence: **301** with PGV identified

Perfect adherence: **3,967** with PGV identified

CRC-associated outcomes in FDR

Measure	Real-world adherence	Perfect adherence
CRC cases (per 10,000)	1,567	1,196
CRC deaths (per 10,000)	648	476
Mean age at CRC diagnosis	46.7 years	45.8 years
Mean age at death	76.5 years	77.0 years

Key insights

Per 10,000 probands, perfect adherence resulted in the identification of 4,625 more carriers (a 110% relative increase) compared to real-world adherence. Per 10,000 FDR, perfect adherence identified 3,666 more PGV-positive FDR, equating to more than 12 times those identified based on real-world adherence.

For the CRC-associated outcomes among the full population of FDR, perfect adherence was associated with 371 fewer CRC cases and 172 fewer CRC deaths.

Survival metrics showed modest but favorable improvements, including earlier CRC diagnosis and increased life expectancy.

Conclusions

Our findings highlight substantial underuse of guideline-recommended GGT overall and demonstrate the huge potential to increase PGV identification and improve CRC outcomes among FDR by bettering adherence to established testing guidelines.

System-level strategies such as education, automated test eligibility identification, streamlined workflows, and enhanced cascade testing programs, represent high-value opportunities to reduce hereditary CRC burden.

Questions?
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Suboptimal Adherence to Germline Genetic Testing Guidelines: Insights from a Microsimulation Model (supplementary methods)

Genetic testing module

Probands

The GGT module incorporates guideline-recommended strategies and modalities for identifying Lynch syndrome in patients with CRC.

The proband population consisted of 10,000 individuals with PGVs in one of 16 genes: *APC*, *BMPR1A*, *EPCAM*, *GREM1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH* (biallelic), *NTHL1* (biallelic), *PMS2*, *POLD1*, *POLE*, *PTEN*, *SMAD4*, *STK11*, *TP53*.[2]

Adherence to GGT was captured across four levels:

1. Guideline-driven eligibity for GGT	
2. Referral to genetic counseling	0.621 probability[3]
3. Acceptance of genetic counseling among those eligible	0.794 probability[3]
4. Acceptance of genetic testing after counseling	0.966 probability[3]

FDR

Pedigrees were randomly generated for each proband based on real-world demographic data.[4,5]

Adherence to GGT in FDR was determined by completion of testing in siblings and children aged ≤ 40 (0.16 probability).[6]

Adherence to the following three screening strategies was calculated according to the values given in Table 1.

- Average-risk: colonoscopy every 10 years, from age 45 to 75
- Family-history screening: colonoscopy every 5 years, from age 40 to 85
- PGV-specific screening: colonoscopy initiation and interval dependent on PGV, ending at age 85

Table 1 Adherence to CRC screening among relatives of probands[7,8,9,10]

Case	No screening	Average-risk screening	Family history screening	PGV-specific screening
FDR did not receive GGT				
FDR was not offered GGT	15%	15%	70%	–
FDR was offered GGT but refused	15%	15%	70%	–
FDR received GGT				
No PGV detected	0%	100%	0%	–
PGV detected	0%	0%	19%	81%

CRC screening module

FDR

This module simulates CRC disease trajectories using the CRC-AIM model, a validated natural history model, which was adapted to capture the rates of adenoma and/or CRC associated with each PGV.[1]

The CRC screening population consisted of FDR of probands identified in the genetic testing module.

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