Quantifying the Impact of Adherence to Hereditary Cancer Testing on Colorectal Cancer Burden: A Microsimulation Model

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KEY POINTS

- Improving adherence to hereditary cancer testing is one of the most impactful and actionable steps to reduce the burden of colorectal cancer among at-risk individuals.
- Our clinically validated model provides a robust framework to evaluate and optimize germline genetic testing strategies for hereditary colorectal cancer syndromes in real-world clinical practice.

BACKGROUND

- Hereditary colorectal cancer (CRC) syndromes account for approximately 10% of all CRC cases, with Lynch syndrome being the most common.[1]
- Germline genetic testing (GGT) of newly diagnosed CRC patients enables detection of pathogenic germline variants (PGVs) and cascade testing to identify at-risk first-degree relatives (FDRs).
- The benefit of GGT is limited by generally low levels of adherence.[2,3]

OBJECTIVE

This study aimed to quantify the impact of adherence to GGT on PGV detection rates and downstream CRC outcomes among unaffected FDRs of CRC patients.

METHODS

Model Overview
A two-module microsimulation model was developed to evaluate the impact of GGT adherence on CRC outcomes among FDRs of newly diagnosed CRC patients.

Module 1: Genetic Testing
Applies the NCCN-recommended GGT strategy for identifying Lynch syndrome in newly diagnosed CRC patients (probands) and simulates cascade testing to FDRs.[4]

Module 2: CRC Screening
Simulates CRC disease trajectories using a validated natural history model, i.e., CRC-AIM,[5] extended to capture PGV-driven biological mechanisms of elevated CRC risk.

Proband Population and Adherence to GGT

- The proband population consisted of 500,000 carriers of one of 16 PGVs (Table) associated with elevated CRC risk and clinically actionable per guidelines.
- Proband receipt of GGT was contingent on four levels of adherence:

Eligibility for genetic testing
Based on guidelines[4]

Referral to genetic counseling among those eligible
62.1% probability[2]

Acceptance of genetic counseling among those referred
79.4% probability after referral[2]

Acceptance of genetic testing among those counseled
96.6% probability after counseling[2]

Table. PGV prevalence among PGV-positive CRC patients.[6]

PGV	Prevalence
APC (attenuated FAP)	13.02%
BMPR1A	0.94%
EPCAM	1.48%
GREM1	0.13%
MLH1	18.79%
MSH2	21.07%
MSH6	20.13%
MUTYH (biallelic)	4.97%
NTHL1 (biallelic)	0.13%
PMS2	15.03%
POLD1	0.13%
POLE	0.13%
PTEN	1.34%
SMAD4	0.94%
STK11	0.27%
TP53	1.48%

Cascade Testing and Screening Strategies

- For each proband, a pedigree of FDRs was randomly generated using real-world demographic data.[7,8]
- For each proband with a detected PGV, GGT was offered to each of their FDRs, who received GGT with an overall probability of 16%.[3]
- Each relative then adhered to one of three NCCN-recommended CRC screening strategies based on their perceived risk:

Average-Risk Screening
Colonoscopy every 10 years (ages 45–75 years)

Family-History Screening
Colonoscopy every 5 years (ages 40–85 years)

PGV-Specific Screening
Start age and interval dependent on PGV (ending at age 85 years)

Natural History Model and Evaluated Scenarios
A validated natural history model (CRC-AIM)[5] was extended to capture PGV-driven mechanisms—including increased adenoma generation at earlier ages and accelerated adenoma-to-CRC transition—and calibrated to real-world data for each PGV.

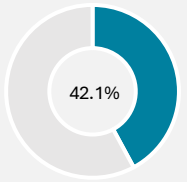
No GGT
No GGT; real-world adherence to CRC screening

Real-World GGT
Real-world adherence to both GGT (among those eligible) and CRC screening

Perfect GGT
Perfect adherence to GGT (among those eligible); real-world adherence to CRC screening

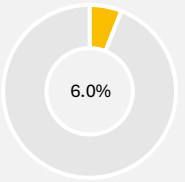
RESULTS

PGV Detection Rates Among Probands



(2-fold increase)

PGV Detection Rates Among PGV+ FDRs



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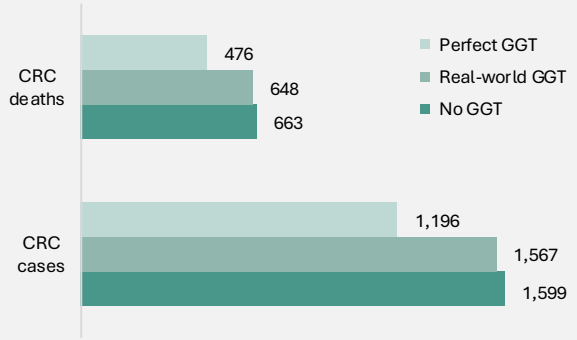
Lifetime CRC Cases and Deaths per 10,000 FDRs



Compared to No GGT

- Real-world adherence to GGT yielded only minimal reductions in CRC cases (1,599 → 1,567) and deaths (663 → 648) per 10,000 FDRs.
- Perfect adherence to GGT produced substantial reductions: 25% fewer CRC cases (1,599 → 1,196) and 28% fewer CRC deaths (663 → 476) per 10,000 FDRs.

Mean Age at CRC Diagnosis

No GGT	Real-world GGT	Perfect GGT
46.8 years	46.7 years	45.8 years

Mean Age at Death

No GGT	Real-world GGT	Perfect GGT
76.4 yrs	76.5 yrs	77.0 yrs

Compared to No GGT

- Real-world adherence to GGT did not meaningfully alter either outcome.
- Perfect adherence to GGT shifted CRC diagnosis earlier, enabling more effective intervention, while simultaneously extending mean lifespan by 0.6 years.

CONCLUSIONS

- **Unidentified At-Risk Relatives**
  Current real-world adherence to GGT leaves most at-risk FDRs unidentified, severely limiting CRC prevention potential.
- **Substantial Gains from Better Adherence**
  Improving adherence could substantially increase PGV detection rates and avert meaningful numbers of CRC cases and deaths. Clinical studies should further explore the impact on CRC outcomes among FDRs with a detected PGV.
- **Clinical Decision Support**
  This clinically-validated microsimulation model can support evaluation of strategies to optimize GGT for hereditary CRC syndromes in clinical practice.

REFERENCES

1. Chen et al. Hereditary Colorectal Cancer Syndromes: Molecular Genetics and Precision Medicine. *Biomedicines*. 2022;10(12):3207.
2. Sye et al. Referral, Uptake, and Outcome of Genetic Counseling and Testing in Patients With Early-Onset CRC. *J Natl Compr Canc Netw*. 2023;21(11):1156–1163.
3. Uson et al. Germline Cancer Susceptibility Gene Testing in Unselected Patients With CRC. *Clin Gastroenterol Hepatol*. 2022;20(3):e508–e528.
4. NCCN Guidelines® Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1.2024 — August 8, 2024.
5. Vahdat et al. Calibration and Validation of the CRC-AIM Microsimulation Model Using Deep Neural Networks. *Med Decis Making*. 2023;43(6):719–736.
6. Coughlin et al. Multigene Panel Testing Yields High Rates of Clinically Actionable Variants Among CRC Patients. *JCO Precis Oncol*. 2022;6:e2005017.
7. U.S. Census Bureau. Fertility of Women in the United States: 2024.
8. Brown et al. Trends in Mean Age of Mothers in the United States, 2016–2023. *Natl Vital Stat Rep*. 2025;74(9):1–6.

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