A counseling framework for moderate-penetrance colorectal cancer susceptibility genes

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The inclusion of moderate-penetrance cancer susceptibility genes in multigene panel testing poses challenges regarding the optimal management of individuals found to have pathogenic variants in these genes. A recently published counseling framework has provided evidence-based guidance for moderate-penetrance breast and ovarian cancer genes.[1] However, no such framework exists for moderate-penetrance colorectal cancer (CRC) susceptibility genes, including *CHEK2*, *APC**I1307K, and monoallelic *MUTYH*, which are among the most common multigene panel testing findings.[2] Currently the only recommendations to address this risk are from the National Comprehensive Cancer Network, which recommends that individuals who carry pathogenic *CHEK2* or *APC**I1307K variants irrespective of family history, or monoallelic *MUTYH* with a family history of CRC, undergo earlier and more frequent CRC screening, similar to individuals with a first-degree relative with CRC.[3] Whether early and increased CRC screening is truly justified for such carriers in the *absence of a family history* of CRC is unknown.

To better elucidate the appropriate timing of colonoscopy initiation, we calculated the cumulative lifetime risk (CLTR) of CRC as a multiple of the US Surveillance, Epidemiology, and End Results Program (SEER) estimates of ever developing CRC and the observed risk for selected genetic variants (*CHEK2* 1100delC, *CHEK2* I157K, *APC**I1307K, monoallelic *MUTYH*). Population age-specific incidence rates for CRCs were obtained from the 2010–2014 SEER cancer statistics for all races.[4] Average relative-risk multipliers were derived from a systematic meta-analysis.[5] We estimated 5-year and CLTR using previously described methods and applied the estimated odds ratio (OR) for each genetic variant to population age-specific incidence data.[6]

MODERATE-PENETRANCE CRC GENES

CHEK2

Pathogenic *CHEK2* variants are present in ~ 1% of Caucasians of European descent,[7] with evidence for CRC risk limited to the two most common founder mutations 1100delC and I157T. Although multiple reports demonstrated a nonsignificant CRC risk,[8] two meta-analyses reported a modestly increased CRC risk with ORs of 1.88 (95% confidence interval (CI), 1.29–2.73)[5] and 2.11 (95% CI, 1.41–3.16)[9] in *CHEK2* 1100delC carriers. However, given some irregularities in the analysis, the reported 2.11 OR[9] appears to have been an overestimation with adjusted data suggesting an OR of 1.8 (95% CI, 1.2–2.7),[10] similar to that in the report by Ma et al.[5] In comparison, the relative risk of CRC in individuals with a family history of CRC is reported as 2.25 (95% CI, 2.0–2.53).[11] For *CHEK2* I157T, a meta-analysis demonstrated an OR of 1.61 (95% CI, 1.40–1.87) for CRC,[12] similar to that in the meta-analysis by Ma et al.[5] (OR 1.56; 95% CI, 1.32–1.84). CRC risk may be increased in *CHEK2* carriers with a CRC family history, thereby implicating family history as a potentially important risk modifier.[12] However, there is no strong evidence that *CHEK2* is associated with CRC before age 50, nor an earlier age of CRC diagnosis.[8]

APC*I1307K

The *APC**I1307K founder germ line variant, present in 7% of Ashkenazi Jews, is associated with a 1.96 (95% CI, 1.37–2.79) OR for CRC risk in Ashkenazi Jews.[5,13] Age at CRC diagnosis in *APC**I1307K carriers is not different from that in noncarriers.[13] Association of *APC**I1307K with a family history is less clear with studies among CRC patients reporting a family history of CRC ranging from 0 to 28%.[13]

Monoallelic MUTYH

Monoallelic *MUTYH* mutations are among the more common germ line abnormalities discovered via multigene panel testing, regardless of the population being tested, with a ~ 2% prevalence.[2] CRC risk estimates associated with monoallelic *MUTYH* mutations are conflicting. The Colon Cancer Family Registry examined 223 monoallelic *MUTYH* carriers and their relatives estimating that such individuals had a cumulative 0.8% risk of CRC through age 50, regardless of CRC family history, versus 0.3% risk for noncarriers.[14]

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However, a large meta-analysis including > 25,000 MUTYH monoallelic carriers and > 18,000 controls reported only a very slight increase in CRC risk (OR 1.17; 95% CI, 1.01–1.34) that was based on weak overall evidence.[5]

MANAGING CRC RISK

Given uncertainties in the management of individuals with moderate-penetrance CRC gene variants, we estimated CRC risk associated with these variants to help better define possible CRC risk-reduction strategies. Estimated 5-year and CLTR of CRC for average-risk individuals and moderate-penetrance gene mutation carriers are shown in **Table 1**. For the average-risk individual, where current guidelines recommend initiating screening colonoscopy at age 50, a CLTR of CRC of 0.6% is reached by age 50–54.[3] However, for CHEK2 1100delC, CHEK2 I157T, and APC*I1307K carriers, this same level of CLTR of CRC is reached by age 45–49. Therefore, if initiation of CRC screening is based on the average-risk individual's CLTR of CRC, earlier initiation of screening colonoscopy in this timeframe in pathogenic CHEK2 and APC*I1307K carriers without a family history of CRC would seem reasonable (**Table 2**). Although our data is based on risk associated with CHEK2 1100delC and CHEK2 I157T, we would recommend considering all pathogenic CHEK2 mutation carriers equivalently given the current paucity of data on CRC risk associated with other CHEK2 variants. For monoallelic MUTYH carriers, cumulative risk of CRC is 0.7% by age 50–54, similar to individuals at average risk. Therefore, using similar reasoning, there does not appear to be an indication for earlier initiation of colonoscopy in monoallelic MUTYH carriers in the absence of a family history, consistent with current National Comprehensive Cancer Network recommendations.[3]

While such recommendations apply to patients with no family history of CRC, the presence of a family history increases risk, as individuals with a first-degree relative with

Table 2 Colonoscopy screening recommendations for individuals with moderate-penetrance mutations in selected genes

Gene	Family history of CRC	Age to start CRC screening	Screening interval if no adenomas
No mutation[a]	No	50	10 years
	Yes (≥1 FDR)	40[b]	5–10 years
	Yes (≥1 SDR <50 yo)	50	5–10 years
APC*I1307K	No	45	5 years
	Yes	45 or per FHx	5 years
CHEK2	No	45	5 years
	Yes	45 or per FHx	5 years
Monoallelic MUTYH	No	50	10 years
	Yes	50 or per FHx	5 years

CRC, colorectal cancer; FDR, first-degree relative; FHx, family history; SDR, second-degree relative.
[a]Recommendations based on guidelines from the National Comprehensive Cancer Network (ref. 3). [b]40 years old or 10 years earlier than the age of the youngest-onset CRC.

Table 1 Estimated 5-year and lifetime colon and rectal cancer risk for individuals with moderate-penetrance mutations in selected genes

Relative risk (95% CI)	Population (SEER 2010–2014)[a]		CHEK2 1100delC 1.88(1.29–2.73)[b]		CHEK2 I157T 1.56 (1.32–1.84)[b]		APC I1307K 1.96 (1.37–2.79)[b]		Monoallelic MUTYH 1.17 (1.01–1.34)[b]	
Age (years)	5-year (%)	Cumulative risk (%)	5-year (%)	Cumulative risk (%)	5-year (%)	Cumulative risk (%)	5-year (%)	Cumulative risk (%)	5-year (%)	Cumulative risk (%)
20–24	0.01	0.0	0.01	0.0	0.01	0.0	0.01	0.0	0.01	0.0
25–29	0.01	0.0	0.02	0.0	0.02	0.0	0.03	0.0	0.02	0.0
30–34	0.03	0.0	0.05	0.1	0.04	0.1	0.05	0.1	0.03	0.1
35–39	0.05	0.1	0.09	0.2	0.07	0.1	0.09	0.2	0.05	0.1
40–44	0.09	0.2	0.17	0.3	0.14	0.3	0.17	0.4	0.10	0.2
45–49	0.16	0.3	0.30	0.6	0.24	0.5	0.31	0.7	0.18	0.4
50–54	0.29	0.6	0.55	1.2	0.46	1.0	0.57	1.2	0.34	0.7
55–59	0.34	1.0	0.65	1.8	0.54	1.5	0.67	1.9	0.40	1.1
60–64	0.46	1.4	0.87	2.7	0.72	2.2	0.91	2.8	0.54	1.7
65–69	0.64	2.1	1.21	3.8	1.00	3.2	1.26	4.0	0.75	2.4
70–74	0.84	2.9	1.57	5.3	1.31	4.5	1.64	5.6	0.98	3.4
75–79	1.04	3.9	1.96	7.2	1.63	6.0	2.05	7.5	1.22	4.5
80–84	1.29	5.1	2.42	9.4	2.01	7.9	2.52	9.8	1.51	6.0
85+	1.41	6.4	2.66	11.8	2.20	9.9	2.77	12.2	1.65	7.5

Box shading reflects the cumulative colorectal cancer risk level reached at colonoscopy initiation based on SEER data (gray box), and age ranges at which similar cumulative risk thresholds are reached (dark green box) or almost reached (light green box) according to gene mutation status.
CI, confidence interval; SEER, US Surveillance, Epidemiology, and End Results Program.
[a]Based on SEER cancer statistics, age-specific rates of cancer of the colon and rectum (invasive), 2010–2014 (ref. 4). [b]Based on risk estimates in ref. 5.

CRC have a 2.25 (95% CI, 2.0–2.53) relative risk of CRC.[11] As such, earlier and more frequent colonoscopy is recommended for individuals with a family history of CRC based on the strength of the family history and the age of the CRC diagnoses (Table 2). Importantly, when assessing the CRC risk in moderate-penetrance CRC gene carriers, the screening age and interval should be based on the family history when a family history–based assessment results in earlier and/or more frequent screening recommendations than those dictated by consideration of the moderate-penetrance gene variant alone.

While our analysis has several limitations including risk estimates derived from a single meta-analysis, estimates based on limited studies resulting in wide confidence intervals, and the assumption that gene-associated risk is constant over lifetime, these estimates encompass a multitude of studies and are currently the most representative of actual population risk. The use of SEER estimates for absolute-risk calculations may not be applicable to other countries with different population-specific risks, or to populations such as African Americans, where absolute risk of CRC may be higher. Moreover, as SEER estimates are based on the inclusion of individuals at average risk as well as those at a higher risk of CRC, our derived risk estimates may reflect a slight overestimation of actual risk. Finally, our screening recommendations are based on the CRC CLTR threshold reached at initiation of screening colonoscopy at age 50 for the average-risk individual. Although it is conceivable that the age at which to initiate colonoscopy may be altered in the future, our risk-adapted screening strategy can be easily modified to meet such potential shifts in risk thresholds.

CASCADE TESTING

The utility of cascade testing is another important consideration with moderate-penetrance genes. As pathogenic *CHEK2* variants confer an increased risk of breast cancer[7] with enhanced breast cancer screening already recommended,[15] cascade testing in relatives of *CHEK2* carriers is reasonable based on breast cancer risk alone, although it may not alter breast screening management in the presence of a strong breast cancer family history. Given the modest CRC risk associated with *CHEK2* variants, and the resulting recommendation for more aggressive CRC screening, it also seems reasonable to offer cascade testing to relatives of *CHEK2* carriers based on CRC risk alone to allow for individualized CRC risk management. For *APC**I1307K carriers, there are currently no additional cancer risk-reduction strategies that would be employed other than enhanced CRC screening. Given the modest, but significantly increased, risk of CRC associated with *APC**I1307K, as well as the resulting recommendations for earlier CRC screening for this population, an argument could also be made for offering cascade testing for this variant solely for CRC risk stratification. As CRC risk associated with monoallelic *MUTYH* mutations does not appear to merit increased CRC screening, cascade testing for this purpose alone may not be justified. However, given the high prevalence of monoallelic *MUTYH* carriers,

cascade testing may be considered for family planning purposes, as recognition of carrier status in parents may help to identify offspring at risk for *MUTYH*-associated polyposis due to biallelic *MUTYH* mutations. Finally, as future research may provide more clarity regarding CRC and possibly other cancer risks, the decision of whether to pursue cascade testing will likely continue to evolve.

CONCLUSION

Increased uptake of multigene panel testing will continue to lead to the detection of germ line variants that confer a modest increase in cancer risk with questionable associated clinical significance. In hereditary breast cancer, emerging literature[16] suggests that many clinicians make inappropriately aggressive management recommendations for individuals with these variants. As CRC screening is not without its own risks, we advocate that a risk-adapted screening strategy be incorporated into the management of individuals with moderate-penetrance CRC susceptibility variants. For such germ line testing to truly translate into effective and rational risk reduction, larger studies will need to be performed, ideally with the inclusion of genetic and environmental modifiers (e.g., single-nucleotide polymorphisms, aspirin, etc.), to better quantify the risk associated with moderate-penetrance variants so that management recommendations can be more optimally tailored to the actual degree of CRC risk.

DISCLOSURE

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REFERENCES

1. Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol* 2016;13:581–588.
2. Yurgelun MB, Kulke MH, Fuchs CS, et al. Cancer susceptibility gene mutations in individuals with colorectal cancer. *J Clin Oncol* 2017;35:1086–1095.
3. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (version 2.2017) and Colorectal Cancer Screening (version 2.2017). https://www.nccn.org/. Accessed 1 November 2017.
4. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2014, National Cancer Institute. Bethesda, MD. https://seer.cancer.

gov/csr/1975_2014/. Based on November 2016 SEER data submission posted to the SEER website April 2017.

5. Ma X, Zhang B & Zheng W. Genetic variants associated with colorectal cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. *Gut* 2014;63:326–336.

6. Song H, Dicks E, Ramus SJ, et al. Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. *J Clin Oncol* 2015;33:2901–2907.

7. Meijers-Heijboer H, van den Ouweland A, Klijn J, et al. Low-penetrance susceptibility to breast cancer due to CHEK2(*)1100delC in noncarriers of *BRCA1* or *BRCA2* mutations. *Nat Genet* 2002;31:55–59.

8. de Jong MM, Nolte IM, Te Meerman GJ, et al. Colorectal cancer and the CHEK2 1100delC mutation. *Genes Chromosomes Cancer* 2005;43:377–382.

9. Xiang HP, Geng XP, Ge WW & Li H. Meta-analysis of CHEK2 1100delC variant and colorectal cancer susceptibility. *Eur J Cancer* 2011;47:2546–2551.

10. Katona BW & Yang YX. Colorectal cancer risk associated with the CHEK2 1100delC variant. *Eur J Cancer* 2017;83:103–105.

11. Johns LE & Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. *Am J Gastroenterol* 2001;96: 2992–3003.

12. Liu C, Wang QS & Wang YJ. The CHEK2 I157T variant and colorectal cancer susceptibility: a systematic review and meta-analysis. *Asian Pac J Cancer Prev* 2012;13:2051–2055.

13. Locker GY & Lynch HT. Genetic factors and colorectal cancer in Ashkenazi Jews. *Fam Cancer* 2004;3:215–221.

14. Win AK, Dowty JG, Cleary SP, et al. Risk of colorectal cancer for carriers of mutations in MUTYH, with and without a family history of cancer. *Gastroenterology* 2014;146:1208–1211.

15. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian (Version 2.2017). Available at: https://www.nccn.org/. Accessed November 1, 2017.

16. Kurian AW, Li Y, Hamilton AS, et al. Gaps in incorporating germline genetic testing into treatment decision-making for early-stage breast cancer. *J Clin Oncol* 2017;35:2232–2239.