DATA G HEAL SMARTER GUIDE COMPANION

Citations and Evidence Appendix, Colon Cancer

Step 1 and 2: Diagnosis and Standard of Care

CLAIM: *NCCN guidelines are the foundation of standard colon cancer care.*

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. nccn.org. Updated annually.

2. NCCN Guidelines for Patients: Colon Cancer. nccn.org/patients.

CLAIM: *BRAF V600E mutation in MSI-H tumors generally indicates sporadic rather than Lynch syndrome cancer.*

3. Toon CW, Walsh MD, Chou A, et al. BRAFV600E immunohistochemistry facilitates universal screening of colorectal cancers for Lynch syndrome. American Journal of Surgical Pathology. 2013;37(10):1592-1602. PMID: 23797718.

4. Parsons MT, Buchanan DD, Thompson B, et al. Correlation of tumour BRAF mutations and MLH1 methylation with germline mismatch repair (MMR) gene mutation status: a literature review assessing utility of tumour features for MMR variant classification. Journal of Medical Genetics. 2012;49(3):151-157.

5. StatPearls. A Review of Hereditary Colorectal Cancers. Updated 2025. ncbi.nlm.nih.gov/books/NBK538195/

Step 3: Give Yourself an Advantage

CLAIM: *Processed meat is a Group 1 carcinogen for colorectal cancer; red meat is Group 2A.*

6. International Agency for Research on Cancer (IARC). IARC Monographs evaluate consumption of red meat and processed meat. Press Release 240, October 2015. Each 50g daily portion of processed meat increases colorectal cancer risk by 18 percent. iarc.who.int

7. Bouvard V, Loomis D, Guyton KZ, et al. Carcinogenicity of consumption of red and processed meat. Lancet Oncology. 2015;16(16):1599-1600.

CLAIM: *Chronic stress measurably suppresses natural killer cell activity, which plays a role in anti-tumor immunity.*

8. Capellino S, Claus M, Watzl C. Regulation of natural killer cell activity by glucocorticoids, serotonin, dopamine, and epinephrine. Cellular & Molecular Immunology. 2020;17(7):705-711.

9. Dai S, Mo Y, Wang Y, et al. Chronic stress promotes cancer development. Frontiers in Oncology. 2020;10:1492.

10. Adam EK, Quinn ME, Tavernier R, et al. Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. Psychoneuroendocrinology. 2017;83:25-41.

Step 4: Predict What Treatments Will Work

CLAIM: *Pembrolizumab is first-line standard of care for MSI-H/dMMR metastatic colorectal cancer.*

11. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. New England Journal of Medicine. 2020;383(23):2207-2218. KEYNOTE-177 trial. Median PFS 16.5 months with pembrolizumab versus 8.2 months with chemotherapy.

12. Diaz LA Jr, Shiu KK, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis. Lancet Oncology. 2022;23(5):659-670.

13. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab versus chemotherapy in microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer: 5-year follow-up from the randomized phase III KEYNOTE-177 study. Annals of Oncology. 2024. 5-year OS 55% versus 44% despite 62% crossover.

14. Sinicrope FA, Ou FS, Arnold D, et al. Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair colon cancer (Alliance A021502; ATOMIC). Journal of Clinical Oncology. 2025;43(17 suppl):LBA1. ATOMIC trial. 3-year disease-free survival 86.4 percent with atezolizumab plus FOLFOX versus 76.6 percent with FOLFOX alone (HR 0.50).

CLAIM: *EGFR inhibitors (cetuximab, panitumumab) do not work in RAS-mutant colorectal cancer.*

15. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. New England Journal of Medicine. 2008;359(17):1757-1765.

16. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. New England Journal of Medicine. 2013;369(11):1023-1034.

CLAIM: *BRAF V600E plus encorafenib and cetuximab is approved for BRAF V600E-mutant metastatic colorectal cancer.*

17. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. New England Journal of Medicine. 2019;381(17):1632-1643. BEACON CRC trial.

18. Kopetz S, Yoshino T, Van Cutsem E, et al. Encorafenib, cetuximab, and mFOLFOX6 in BRAF V600E-mutated metastatic colorectal cancer (BREAKWATER). Nature Medicine. 2025;31(3):901-908. Phase 3 BREAKWATER trial. First-line encorafenib and cetuximab plus mFOLFOX6 significantly improved objective response rate, progression-free survival, and overall survival compared with standard chemotherapy in BRAF V600E metastatic disease

CLAIM: *DPYD testing before fluoropyrimidine therapy prevents severe and life-threatening toxicity.*

19. Henricks LM, Lunenburg CATC, de Man FM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. Lancet Oncology. 2018;19(11):1459-1467. Prospective study of 1,103 patients.

20. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clinical Pharmacology and Therapeutics. 2018;103(2):210-216.

CLAIM: *UGT1A1 testing reduces severe irinotecan toxicity risk.*

21. Innocenti F, Schilsky RL, Ramirez J, et al. Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the UGT1A1 genotype of patients with cancer. Journal of Clinical Oncology. 2014;32(22):2328-2334.

CLAIM: *Aspirin use may improve survival in patients with PIK3CA-mutant colorectal cancer.*

22. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. New England Journal of Medicine. 2012;367(17):1596-1606.

23. Paleari L, Puntoni M, Clavarezza M, et al. PIK3CA mutation, aspirin use after diagnosis and survival of colorectal cancer: a systematic review and meta-analysis of epidemiological studies. Clinical Oncology. 2016;28(5):317-326.

24. Martling A, Hed Myrberg I, Nilbert M, et al. Low-dose aspirin for PI3K-altered localized colorectal cancer. New England Journal of Medicine. 2025;393(11):1051-1064. ALASCCA trial. First randomized trial in PIK3CA or PI3K-pathway altered tumors: 3-year recurrence 7.7 percent with aspirin versus 14.1 percent with placebo.

CLAIM: *NTRK fusions, though rare, respond strongly to targeted TRK inhibitors.*

25. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. New England Journal of Medicine. 2018;378(8):731-739.

Step 5: Predict if Treatments Are Working

CLAIM: *CEA monitoring is part of standard colorectal cancer surveillance.*

26. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. Journal of Clinical Oncology. 2006;24(33):5313-5327.

27. Meyerhardt JA, Mangu PB, Flynn PJ, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer. ASCO clinical practice guideline endorsement. Journal of Clinical Oncology. 2013;31(35):4465-4470.

CLAIM: *ctDNA is a sensitive predictor of recurrence risk in resectable colorectal cancer.*

28. Kotani D, Oki E, Nakamura Y, et al. Molecular residual disease and efficacy of adjuvant chemotherapy in patients with colorectal cancer. Nature Medicine. 2023;29(1):127-134. CIRCULATE-Japan GALAXY trial.

29. Nakamura Y, Watanabe J, Akazawa N, et al. ctDNA-based molecular residual disease and survival in resectable colorectal cancer. Nature Medicine. 2024;30(11):3272-3283. Updated 23-month analysis: HR 11.99 for disease-free survival in ctDNA-positive patients.

30. Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. JAMA Oncology. 2019;5(8):1124-1131.

31. Tie J, Cohen JD, Lahouel K, et al. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer. New England Journal of Medicine. 2022;386(24):2261-2272. DYNAMIC trial. A ctDNA-guided approach cut adjuvant chemotherapy use by about half without compromising recurrence-free survival.

32. Kasi PM, Aushev VN, Ensor J, et al. Circulating tumor DNA for informing adjuvant chemotherapy in stage II and III colorectal cancer: interim analysis of the BESPOKE CRC study. 2024 ASCO Gastrointestinal Cancers Symposium. BESPOKE CRC registry (NCT04264702). Molecular residual disease was strongly prognostic for recurrence, and ctDNA-positive patients showed significant benefit from adjuvant chemotherapy.

Step 6: Why Did the Defense Systems Break Down?

CLAIM: *Gut microbiome composition influences both colorectal cancer development and immunotherapy response.*

33. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018;359(6371):91-97.

34. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97-103.

35. Wong SH, Yu J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nature Reviews Gastroenterology and Hepatology. 2019;16(11):690-704.

CLAIM: *Higher 25-hydroxyvitamin D levels are associated with better colorectal cancer outcomes.*

36. Wu G, Xue M, Zhao Y, et al. Low circulating 25-hydroxyvitamin D level is associated with increased colorectal cancer mortality: a systematic review and dose-response meta-analysis. Bioscience Reports. 2020;40(7). Each 20 nmol/L increase in 25(OH)D reduced CRC-specific mortality by 12 percent.

37. Maalmi H, Walter V, Jansen L, et al. Association between blood 25-hydroxyvitamin D levels and survival in colorectal cancer patients: an updated systematic review and meta-analysis. Nutrients. 2018;10(7):896.

CLAIM: *Chronic inflammation and inflammatory bowel disease are linked to colorectal cancer risk.*

38. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48(4):526-535.

39. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. New England Journal of Medicine. 2015;372(15):1441-1452.

CLAIM: *Insulin resistance and metabolic dysfunction increase colorectal cancer risk.*

40. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. Journal of Nutrition. 2001;131(11 Suppl):3109S-3120S.

CLAIM: *Higher fiber intake is associated with lower colorectal cancer risk.*

41. Aune D, Chan DSM, Lau R, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ. 2011;343:d6617.

Step 7: Monitor Your Body During Treatment

CLAIM: *Standard safety monitoring is required for each chemotherapy and targeted therapy regimen used in colon cancer.*

42. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Drug safety monitoring sections, updated annually. nccn.org

CLAIM: *EGFR inhibitors deplete magnesium and require electrolyte monitoring.*

43. Tejpar S, Piessevaux H, Claes K, et al. Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. Lancet Oncology. 2007;8(5):387-394.

CLAIM: *Oxaliplatin-induced peripheral neuropathy can be long-lasting and is dose-related.*

44. Beijers AJM, Mols F, Vreugdenhil G. A systematic review on chronic oxaliplatin-induced peripheral neuropathy and the relation with oxaliplatin administration. Supportive Care in Cancer. 2014;22(7):1999-2007.

Step 8: After No Evidence of Disease

CLAIM: *Active surveillance after curative-intent treatment improves outcomes by enabling early detection of recurrence.*

45. Pita-Fernandez S, Alhayek-Ai M, Gonzalez-Martin C, et al. Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. Annals of Oncology. 2015;26(4):644-656.

Step 9: Healing Instruments and Your Team

CLAIM: *Vitamin D, omega-3 fatty acids, curcumin, and certain other supplements have anti-inflammatory or anti-cancer evidence in colorectal cancer contexts.*

46. Song M, Lee IM, Manson JE, et al. Effect of supplemental vitamin D3 on colorectal adenoma recurrence (VITAL trial subgroup analyses). JAMA Network Open. 2022.

47. Cockbain AJ, Volpato M, Race AD, et al. Anticolorectal cancer activity of the omega-3 polyunsaturated fatty acid eicosapentaenoic acid. Gut. 2014;63(11):1760-1768.

48. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS Journal. 2013;15(1):195-218.

CLAIM: *Physical activity after colon cancer diagnosis is associated with improved survival.*

49. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. Journal of Clinical Oncology. 2006;24(22):3535-3541.

50. Brown JC, Ma C, Shi Q, et al. Physical activity in recurrent colon cancer: Cancer and Leukemia Group B/SWOG 80702 (Alliance). Cancer. 2023;129(23):3724-3734.

51. Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: a meta-analysis of prospective cohort studies. International Journal of Cancer. 2013;133(8):1905-1913.

52. Courneya KS, Vardy JL, O'Callaghan CJ, et al. Structured exercise after adjuvant chemotherapy for colon cancer. New England Journal of Medicine. 2025;393(1):13-25. CHALLENGE trial. A 3-year structured exercise program improved disease-free survival (HR 0.72), with 80 percent of the exercise group cancer-free at 5 years versus 74 percent, and a 37 percent lower risk of death.

CLAIM: *Mindfulness-based stress reduction shows measurable effects on cortisol and quality of life in cancer patients.*

53. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients. Psychosomatic Medicine. 2003;65(4):571-581.

Step 10: Maximize Joy and Be Your Own Champion

CLAIM: *Psychosocial support, social connection, and reduced isolation are associated with better cancer outcomes.*

54. Pinquart M, Duberstein PR. Associations of social networks with cancer mortality: A meta-analysis. Critical Reviews in Oncology/Hematology. 2010;75(2):122-137.

55. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Medicine. 2010;7(7):e1000316.

It's time to heal smarter.