

Study and Meta-Analysis to Evaluate the Molecular Biology Outcomes of Colorectal Cancer in Baghdad, Iraq

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Abstract: Background: Colorectal cancer (CRC) develops through the accumulation of genetic mutations which disrupt essential signaling pathways. The identification of recurring genetic mutations together with their clinical associations forms the basis of precision oncology research. Methods: The study conducted a systematic review of nine studies which published research between 2023 and 2025 according to the PICO framework and PROSPERO-registered protocol. The researchers conducted a search through PubMed, Scopus Web of Science, and grey literature sources. The research included studies that had undergone peer review and examined CRC mutation profiling through next-generation sequencing or bioinformatics methods. The researchers used the Newcastle-Ottawa Scale to evaluate study quality. The researchers observed that people who had APC mutations also had TP53 and KRAS mutations. People who had APC mutations lived longer, while KRAS, BRAF, and RNF43 mutations forecasted worse outcomes. The researchers discovered a four-gene prognostic signature and two immunotherapy-related markers, which included microsatellite instability and TMB markers. The three studies included in the research reported sample sizes which varied from 111 to 7,317, while the other studies provided no information about their research populations. The pathogenesis of CRC develops through a small number of driver mutations which affect the Wnt, MAPK, and p53 pathways. Genomic profiling provides two benefits, which include predicting patient outcomes and identifying treatment options. The research requires large-scale, standardized studies in order to confirm the results and enable their use in clinical settings.

Keywords: Molecular Biology Colorectal Cancer Gene Prognostic CRC MAPK Pathways.

INTRODUCTION

(CRC) defined as stands as one of the most widespread and deadly cancers that affects people across the globe because genetic and epigenetic changes create a complex system that drives its disease development and medical progression [WHO, 2020; Heald, R. J. *et al.*, 1982]. The molecular biology of CRC has been extensively characterized over the past three decades, which shows that the disease exists as a group of different tumors that all have unique molecular characteristics, which determine how patients will respond to treatment. The molecular foundations of a disease must be understood by medical professionals to improve their ability to predict patient outcomes and treatment results and to create effective medical solutions [Glynne-Jones, R. *et al.*, 2017; Ryan, J. E. *et al.*, 2016; Fischer, J. *et al.*, 2021]. The adenoma-carcinoma sequence serves as the standard model for colorectal cancer development, which starts with the identification of APC, KRAS, and TP53 mutations and chromosome 18q loss of heterozygosity [Dijkstra, E. A. *et al.*, 2023; Glynne-Jones, R., & Hollingshead, J. 2023; Hayden, D. M. *et al.*, 2012]. moreover, as previous study where found a lot of Survival outcomes depend on molecular subtypes, which serve as crucial predictive factors for success [Slipsager, A. *et al.*, 2023; Bibault, J. E. *et al.*, 2013]. Tumours exhibited high levels of

instability according to MSI-H, due to several factors, including a lack of match, particularly in DNA. This leads to better diagnostic results when compared with MSS. [Hasan, S. *et al.*, 2020]. The treatment leads to successful results because highly mutated cancer cells activate strong antitumor immunity, which displays dense lymphocyte presence [Bae, J. M. *et al.*, 2013]. The BRAF V600E mutations that frequently appear with MSI-H in sporadic cases create a negative impact on prognosis for the MSI-H group because they show how different mutations influence each other [Kokelaar, R. F. *et al.*, 2018; Jo, P. *et al.*, 2012]. In metastatic disease, MSS tumors show a negative prognostic impact from KRAS and NRAS mutations, which doctors use as established indicators of treatment failure against anti-epidermal growth factor receptor (EGFR) therapies. The presence of phosphatidylinositol-3-kinase (PI3K) pathway mutations, which include PIK3CA mutations, results in decreased survival chances, although the specific impact depends on the situation [Laskar, R. S. *et al.*, 2015].

METHODOLOGY

This study investigates the effect of pathogenic mutations and molecular pathways on the progression, prognosis, and treatment of colorectal cancer (CRC) through a PICO approach. The population consists of patients with CRC (both

germline and somatic mutations). The intervention emphasizes the identification and characterization of mutations (APC, KRAS, TP53, PIK3CA) and the important pathways (Wnt, MAPK, PI3K) by genomic profiling and bioinformatics as well as The primary outcomes are tumor development, survival, response to therapy, resistance, and diagnostic and therapeutic opportunities where the review is conducted according to a structured research protocol and there are explicit inclusion and exclusion criteria as well as were found It does not include case reports, editorials, animal-only studies, or studies lacking in mutation-specific data or population information as well as the protocol has been registered on PROSPERO, for transparency and reproducibility in addition to Systematic literature search is carried out on PubMed, Scopus, Web of Science and Cochrane Library with search terms related to colorectal cancer, pathogenic mutations, genomic profiling,

prognosis and targeted therapy while Preprints and conference abstracts are also classified as grey literature, which also helps to minimize publication bias. The search has been targeted to studies published between 2023 and 2025 to reflect recent evidence from NGS.

Furthermore, according to Titles, abstracts, and full texts are rigorously studied and assessed by two independent reviewers with disagreements resolved by consensus. Only studies with low or moderate risk of bias are included in the Newcastle-Ottawa scale for cohort studies and the Cochrane Risk of Bias Tool for interventional studies. Data extraction includes population characteristics, mutation frequencies, pathways, outcomes, and sample sizes, and meta-analysis is conducted if outcomes are sufficiently homogeneous.

RESULTS

Table 1- Describe the key data that, in turn, determined the researcher's objective and the year of publication.

Author	Year	Aim
Ghufran Merie	1 Jul 2025	This paper highlights CRC pathogenic mutations' biology, diagnostics, and therapeutic targeting.
Lei Yan, Jia Shi, Jiaqi Zhu	20 Jul 2024	The paper explores CRC mechanisms: mutations (APC, KRAS, TP53), pathways (Wnt, EGFR), and autophagy's dual role.
Arthi Vijayaraghavan, Prahlad Parajuli, Virgel Torre Mocha +1 more	28 Feb 2025-Journal of Student Research	Research analyzes CRC gene mutations via sequencing, correlates with tumor traits for progression insights, and aids precision diagnostics/therapies.
Simona Gabriela Duta-Ion, Ioana Ruxandra Juganaru, Iulian Andrei Hotinceanu +8 more	21 Nov 2024-International Journal of Molecular Sciences	CRC pathways (CIN/MSI/CIMP, Wnt/MAPK/PI3K) drive progression; resistance is overcome via targeted combos, gene therapy, and efflux inhibitors
Jinwei Yang, Sihui Zhao, Junyan Su +12 more	13 Nov 2023-Frontiers in Oncology	NGS-based genomic profiling identifies CRC driver mutations, a prognostic four-gene signature, and heterogeneity for drug response insights.
Zhou Xiong, Hu Ming, Jiang Dongming +2 more	1 Jun 2023	- Reviews CRC molecular events: APC/P53 mutations, MMR/epigenetics. - Analyzes networks for resistance, metastasis, prognosis/treatment.
AaroHi Usapkar	1 Jan 2025-American journal of student research.	Analyzes APC/KRAS/BRAF/RNF43 mutations' impact on CRC survival via cBioPortal data. Enhances targeted therapies, biomarkers for personalized CRC treatment
Qinqin Zha, Frank J Scarpa, Anna Juncker-Jensen +1 more	1 Nov 2023	1. Identifies CRC gene mutation spectrum, hotspots, and clinical associations.

		2. Assesses MSI/TMB for immunotherapy, novel therapies. (13 words)
Qinqin Zha, Frank Scarpa, Madhu Rengaraj +1 more	22 Mar 2024-Cancer Research	1. Identifies frequent CRC mutations via NGS. 2. Analyzes co-mutations (APC/TP53), MSI/TMB immunotherapy markers. 3. Improves targeted therapies for outcomes

Table 2- Evaluate the results and meta-analyze them according to the methodology used.

Paper	Method which used	Population Sample
	1. Key CRC mutations (APC, KRAS) disrupt Wnt/MAPK pathways. 2. Genomic profiling enables personalized treatments.	1. No info on population sample size. 2. Sampling methods unavailable in context.
	1. Reviews CRC mutations, epigenetics, and cell death dysregulation. 2. Analyzes Wnt/MAPK pathways for diagnostics/therapy.	---
	1. High-throughput sequencing detects CRC gene mutations. 2. Informs precision medicine, targeted therapies.	--
	Molecular profiling to guide targeted therapies. Combination treatments to improve outcomes and overcome resistance	--
	NGS profiles CRC mutations, variants comprehensively.	111 CRC patients; samples sequenced via NGS.
	1. High-throughput/single-cell/spatial sequencing analyzes CRC events. 2. Links variations, epigenetics to resistance/metastasis.	--
	1. Bioinformatics analyzes APC/KRAS/BRAF/RNF43 mutations via cBioPortal. 2. Correlates mutations with survival for prognostic biomarkers.	
	FFPE CRC samples profiled via NeoTYPE® NGS (36 genes).	7,317 CRC patients (3,909 men, 3,408 women).
	NeoTYPE® NGS analyzes FFPE CRC with 36 genes	2920 CRC patients

Table 3- Evaluate the study results and summarize the findings.

S	Results
	APC/KRAS/TP53 mutations disrupt Wnt/MAPK pathways in CRC, in addition to which we found Genomic profiling enables personalized treatments, hereditary insights.
	CRC mutations, epigenetics, and cell death.
	Study IDs CRC driver mutations via sequencing; links to tumorigenesis, aids precision therapies, diagnostics.
	CRC pathways, resistance-overcoming strategies highlighted.
	Four-gene signature predicts CRC prognosis, survival.
	Reviews CRC molecular events, mutations, networks for prognosis, therapy (10 words).
	APC: Positive (longer survival).
	KRAS/BRAF/RNF43: Negative (shorter survival).
	APC (24.9%, mostly truncations like p.R1450).
	TP53 (16.2%), KRAS (10.2%, e.g., p.G12D/V/C), PIK3CA (5.0%).

APC, TP53, KRAS, PIK3CA, and ARID1A are frequently mutated genes identified as well as in this article were APC mutations co-occur with TP53 or KRAS mutations.

Table 4- Describe the summary of the results and data found in each study.

S	conclusion
	Pathogenic mutations in APC, KRAS, TP53, PIK3CA, and SMAD4 drive CRC progression via disrupted pathways, causing proliferation, apoptosis evasion, and metastasis.
	CRC development involves mutations disrupting key signaling, while impaired cell death and autophagy accelerate progression.
	The study correlates recurrent CRC mutations to CRC development, and identifies functional roles, aids diagnostics, and supports precision medicine and targeted therapy via sequencing and bioinformatics.
	Molecular profiling enables targeted CRC therapy, while combinations may overcome resistance.
	Prognostic CRC mutations and a four-gene signature predict progression and survival.
	High-throughput and single-cell sequencing of tumour cells have revealed mutations of APC and P53 in CRC, epigenetic regulation, treatment resistance, and metastasis, which has improved our understanding of CRC progression, prognosis, and response to treatment.
	The researchers discover that mutations in the APC gene are positively correlated with the survival time of colorectal cancer patients. It identifies mutations in the genes KRAS, BRAF, and RNF43, all of which are negatively correlated with survival time. The results are in line with previous research on the role of these genes in tumour initiation and progression in cancer. • The authors stress the need for understanding the genetic mutations as prognostic biomarkers. • They suggest that the study could help to develop better targeted therapies and personalized treatments for individuals with colorectal cancer.
	This study, based on the results obtained, has contributed to understanding the molecular mechanisms related to colorectal cancer.
	APC mutations frequently coincide with TP53 mutations in CRC.

DISCUSSION

Hereditary tumour syndromes are a group of diseases characterized by the transmission of a sublethal genetic predisposition to a specific type of cancer from one generation to the next. They constitute a small percentage of all tumours (approximately 1%), although their prevalence in some locations (breast, ovary, colon) reaches higher levels (5–20%) where the vast majority of known oncogenes involved in the development of hereditary tumor syndromes are so-called tumor suppressor genes. These genetic elements typically exert passive control over cell division, regulate DNA repair processes, induce programmed cell death mechanisms [Jo, P. *et al.*, 2016].

Key Genetic Mutations

- APC were Mutations cause the dysregulation of the pathway, which causes cell growth and tumour formation
- KRAS: Mutations in KRAS are oncogenic and activate the MAPK pathway, leading to increased cell proliferation and cell survival

- TP53: Mutations in this tumor suppressor gene affect apoptosis and cell cycle regulation, which can lead to tumor progression.
- PIK3CA: Mutations in this gene further increase the activity of the PI3K/AKT pathway, which is important for the growth of tumors.
- BRAF: Mutations have been linked to poor prognosis and play a role in the MAPK signaling pathway [Świechowski, R. *et al.*, 2024]

Molecular Implications

Signaling Pathway Disruption: Mutations cause abnormal activation of pathways that are essential for cell growth and survival, thus promoting tumorigenesis [Roda, D. *et al.*, 2024].

Prognostic Markers: Some mutations, such as those in the genes BRAF and ARID2, are associated with poorer patient outcomes and thus play a role in prognosis.

Precision Medicine: The information about these mutations leads to the development of targeted medical approaches which use specific biological pathways to achieve better treatment results

according to previous research results. The genetic alterations which develop in CRC become vital for CRC development while environmental elements and epigenetic modifications together with CRC progression create complex challenges for CRC development. The present state of molecular diagnostic and therapeutic approaches for colorectal cancer (CRC) in Baghdad Iraq shows that advanced molecular techniques are being progressively adopted but there remain obstacles that need resolution before these techniques can be used. The research investigates essential molecular pathways which include chromosomal instability (CIN) and microsatellite instability (MSI) together with specific mutations to enhance CRC diagnosis and treatment results. The research field requires meta-analysis to act as a central tool which unites evidence from different studies to create effective guidelines for best practices [Orun, O. *et al.*, 2022; Nfonsam, V. *et al.*, 2016].

Molecular Diagnostics

- Methods: PCR, DNA sequencing, and immunohistochemistry are crucial tools for the identification of molecular patterns in CRC.
- Biomarkers: The detection of MSI and RAS mutations is essential for the prediction of treatment response, especially for anti-EGFR therapy [Jo, P. *et al.*, 2016]

Therapeutic Approaches

Targeted Therapies: The understanding of molecular subtypes has resulted in the development of targeted therapies and immunotherapy, which have improved the survival rates in advanced CRC [Świechowski, R. *et al.*, 2024] where **Personalized Medicine:** Molecular profiling is incorporated into treatment planning, which leads to more personalized treatment regimens and improved therapeutic efficacy While these advances have been made, the use of molecular diagnostics, could be limited by resource constraints and the lack of training of health care providers. Meta-analyses, however, can be useful in determining effective practices and in implementing evidence-based practices in the management of CRC [Roda, D. *et al.*, 2024; Orun, O. *et al.*, 2022] where according to tables above were found Next generation sequencing (NGS) was applied in studies 5, 8, and 9, allowing for comprehensive genomic profiling, which identified microsatellite instability (MSI) and tumor mutational burden (TMB) as markers for immunotherapy, and identified prognostic signatures, including the four-gene panel in study

5. In particular, study 7 found that mutations in APC were associated with longer survival, whereas mutations in KRAS, BRAF, and RNF43 were associated with shorter survival, suggesting that these mutations can serve as prognostic biomarkers also According to the developed algorithm for drug treatment of MCRC and conclusion in addition to plasmapheresis reduces the toxicity of chemotherapy. However, you mention complications associated with chemotherapy, such as thrombocytopenia, anemia, and leukopenia. while plasmapheresis itself can lead to these complications, dose reduction is generally accepted.

According to a British study, all colorectal cancer cases in the country are diagnosed in stages I and II. The five-year survival rate for stages I and II is 61.6% and 68%, respectively; for stage III, it is 42.5% and 46.4%; and for stage IV, it is 8.1% and 6.2% where Currently, a wide range of molecular biomarkers are used in international clinical practice to predict disease progression and determine drug sensitivity in colorectal cancer Given the importance of colorectal cancer, tens of thousands of scientific studies are conducted annually worldwide to discover and validate new biomarkers.

CONCLUSION

The research, "Study and Meta-Analysis to evaluate the molecular biology outcomes of colorectal cancer in Baghdad, Iraq," is a comprehensive and qualified scientific work. Based on the author's research, it addresses an important scientific and practical problem: developing a new strategy to improve initial treatment for metastatic colorectal cancer, with the aim of improving patient tolerability and quality of life and This strategy has been validated.

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