Review Article

Steps toward Molecular Diagnostics in Early Detection of Familial Colorectal Cancer: Insights and Emerging Clinical Applications for Hospitals

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ABSTRACT

Colorectal cancer (CRC) ranks among those leading causes of cancer-related deaths worldwide, with up to 85% of cases attributed to sporadic mutations. This review research article investigates the molecular characteristics of early detection in CRC familial cases, particularly within hospitals in Medina. The study principally reviews genetic markers, such as; *APC*, *MLH1*, and *MSH2*, which are associated with hereditary CRC syndromes like Lynch syndrome and familial adenomatous polyposis (FAP). However, germ-line (hereditary) CRC syndromes account for only about 5 % of all cases, whereas non-syndrome familial cases, where a family history is present but no single pathogenic mutation is identified, this make up roughly 20–25%. The research also explores the implication of sporadic CRC, which represents the majority of cases and often occurs before the age of 50 due to somatic mutations. Advanced techniques for molecular screening in use such as circulating tumor DNA (ctDNA) analysis, methylation specific PCR (MSP), and miRNA assays are assessed for their effectiveness in early detection of the disease. These methods offer non-invasive and highly sensitive screening choices, particularly for detecting CRC in high-risk subjects. Although this review focuses on genetic mutations, it's crucial to underline the importance of detecting sporadic mutations, as they are the foremost and pose a growing challenge. The findings emphasized an urgent need for localized screening programs in Medina intended to our local focused population. Screening agendas should integrate molecular diagnostics for both hereditary and sporadic CRC. Our main recommendations include the employment of genetic testing for high-risk families and further surveys into the genetic and environmental factors explicit to our local population in Medina, Saudi Arabia.

INTRODUCTION

Colorectal cancer (CRC) ranks as the third most often diagnosed cancer among men and women, and it is the second leading cause of cancer incidence globally [1], accompanied by significant morbidity and mortality rates [2, 3]. It primarily comprises the malignant proliferation of neoplastic cells beginning in the large intestine and rectum, thus frequently begins with the emergence of polypoid masses that have the potential to become cancerous over time. CRC shows diverse incidence rates globally, with most industrialized nations exhibiting high prevalence due to lifestyle factors such as a high-fat diet, lack of physical activity, and obesity [3]. With regard to the growing CRC incidence rate in Saudi Arabia, this type of cancer is the prevalent amongst gastrointestinal cancers in the area [4]. CRC raises major health worries, Saudi Arabia reflecting a part of worldwide patterns of rising incidence rates [5]. National health initiatives in Saudi Arabia as other countries are centered on this issue by promoting early detection and screening programs, demonstrating a proactive strategy to lessen the burden of CRC in the country. In a particular matter, the local epidemiology on CRC and the wider healthcare response to this condition is crucial specifically in Madinah.

Indeed, it is vital to identify the symptoms of colorectal cancer at its early stages, as this would lead to improve survival rates, a reduction in cancer-related fatalities, and the availability of non-aggressive treatment options [6]. Patients with localized CRC have a 5-year relative survival rate of approximately 90%, while over 15% of those with advanced- stage cancer survive for five years[7]. Some methods commonly used for conventional screening include colonoscopy, fecal occult blood testing (FOBT), and imaging. However, many of these techniques have drawbacks, such as being painful, costly, and having low sensitivity particularly in the case of early malignant or less differentiated lesions [8]. Advancements in molecular biology have created new possibilities for the early diagnosis of CRC through the identification of genetic and epigenetic alterations pertinent to cancer development. At the earliest stage of CRC, molecular diagnostics like the analysis of circulating tumor DNA (ctDNA), RNA, and protein markers may offer noninvasive cancer screening methods with ultrahigh sensitivity [9, 10]. When there is a family history of colorectal carcinoma, identifying genetic factors like APC, MLH1, and MSH2 mutations is crucial for implementing gene-targeted screening [4, 11].

In areas such as Medina, where genetic and environmental factors contribute to cancer risk, individuals from high-risk familial groups can be diagnosed with Colorectal Cancer (CRC) at an early stage relatively easily. However, familial colorectal cancer is a serious condition found in families that is linked to hereditary syndromes like Lynch syndrome or familial adenomatous polyposis [12, 13] and accounts for around 20-25% of all instances of CRC [14]. A considerable family history of CRC entails a heightened carcinogenic risk, making it essential to implement a rapid and effective early detection strategy for these populations [15]. Cancer is often treated only after it has been detected at an advanced stage. However, in Medina, there is an opportunity to incorporate molecular studies into clinical practices that can aid in the early detection of colorectal cancer within families. This would enhance patients' well-being and help lower health system costs.

The pertinent literature seems to be especially deficient in local molecular investigations of familial colorectal cancer in Medina, and the current screening programs might not take into account the specific needs of families at high risk. This reference research tackles this challenge by examining the current molecular knowledge in this field and its potential application for early diagnosis in Medina's hospitals. This approach will assist in achieving the goals of identifying the most effective molecular biomarkers and their associated diagnostic techniques for early diagnosis among familial colorectal cancer patients in Medina, as well as methods for implementing these techniques [3].

This study aimed to provide a scientific piece of work to be a guide and source for future molecular studies into familial CRC in Medina. Thus, building a molecular profile of family cases at risk of CRC for Medina and the Saudi population. Furthermore, it enables the screening of high-risk community members and promotes the elimination of biomarker candidates and ways for early detection.

METHODS

Literature Search Strategy and Selection Criteria

The primary goal of this reference research is to compile and evaluate molecular studies on early detection of colorectal cancer (CRC) in familial cases, particularly focusing on those relevant to high-risk populations who are residents of Medina. The strategy for searching was devised to systematically find peer-reviewed studies that addressed genetic markers, molecular screening techniques, and familial risk factors related to early CRC detection.

Databases

Relevant literature was gathered using three key databases: PubMed, Scopus, and Google Scholar. The selection of these databases was based on their thorough coverage of biomedical, clinical, and molecular research. While clinical trials and review articles were primarily accessed through PubMed, Scopus and Google Scholar were used to obtain broader interdisciplinary research, including studies in molecular genetics and bioinformatics.

Keywords

A set of specific keywords and search strings was developed to ensure a thorough search. Keywords included combinations such as; "Colorectal cancer" AND "early detection", "Molecular screening", "non-invasive testing", "colorectal cancer incidence". "Familial risk factors", "Medina"

Selection Criteria

The selection of relevant literature involved multiple steps:

• **Title and Abstract Screening** : Initially, articles were assessed based on their titles and abstracts. At this stage, studies that did not cover molecular aspects of colorectal cancer or familial risk factors were excluded. As an example, studies that concentrate solely on non-genetic risk factors like diet or lifestyle were eliminated.

• **Full- Text Review** : After the initial screening, the complete texts of chosen articles were examined to verify their compliance with the inclusion criteria. Studies that performed molecular diagnostics, addressed genetic mutations pertinent to familial CRC, and employed advanced screening methods like ctDNA analysis or DNA methylation assays were prioritized.

• **Relevant Journals** : Particular attention was paid to high- impact journals such as *Nature Reviews Clinical Oncology*, *The Lancet*, *International Journal of Molecular Sciences*, *Journal of Clinical Oncology*, and *World Journal of Gastrointestinal Oncology*.

• **Grey Literature**: Alongside peer-reviewed studies, grey literature—including technical reports, conference proceedings, and clinical guidelines — was examined. This was essential for pinpointing regional studies and unpublished research related to Medina or the Middle East that may not have been published in mainstream journals.

Inclusion/Exclusion Criteria

Inclusion Criteria

• **Study Type** : Only original research articles, systematic reviews, clinical trials, and meta-analyses were considered for inclusion. Research concentrating on molecular genetics, screening methods, and familial risk factors particular to CRC was given priority.

• **Period**: Only studies published from 2019 to 2024 were taken into account, as they reflect the latest advancements in colorectal cancer detection.

• **Geographical Relevance**: Global studies were included, but special focus was directed towards those with findings related to the population of Medina, Saudi Arabia, or the wider Middle Eastern context. This played a vital role in investigating the use of molecular techniques for familial colorectal cancer cases in this region.

• **Familial Focus** : Only studies that explicitly dealt with familial colorectal cancer, genetic predisposition, or hereditary syndromes such as Lynch syndrome or familial adenomatous polyposis (FAP) were included [4].

• **Molecular Markers and Screening** : Studies focused on genetic markers (e.g., *APC, MLH1, MSH2*), molecular screening techniques (e.g., liquid biopsy, ctDNA, methylation- specific PCR), and innovative diagnostic methods were included [9].

Exclusion Criteria

• **Non- Familial Cases** : Studies that dealt with sporadic CRC without focusing on familial or hereditary risk factors were excluded.

• **Non-Molecular Approaches**: Research that relied solely on traditional screening methods such as colonoscopy or fecal occult blood testing (FOBT) without incorporating molecular techniques was excluded [16].

• **Late-Stage CRC**: Studies focusing solely on late-stage colorectal cancer were excluded, as this research emphasized early detection in high-risk familial cases [17].

• **Irrelevant Populations** : Research focusing on populations that were not geographically or genetically relevant to Medina or familial CRC was excluded. For instance, studies on colorectal cancer in populations with distinct genetic profiles, such as those in Western or East Asian countries, were excluded unless they provided insights transferable to the Middle Eastern context [3].

Data Extraction

Data extraction was conducted in a structured manner to ensure that relevant information was systematically captured from the selected studies. A detailed data extraction form was designed, which included fields for key information such as:

Study Characteristics

• **Study Design**: Whether the study was a clinical trial, observational study, systematic review, or meta-analysis.

• **Population** : Description of the study population, including the number of participants, their demographic characteristics, and familial CRC history.

• **Genetic Markers** : The specific genetic markers or mutations examined (e.g., *APC* , *MLH1* , *MSH2*).

• **Screening Techniques** : The molecular screening methods used, such as ctDNA analysis, methylation-specific PCR, or miRNA assays [18].

• **Outcomes**: The key outcomes of the study, such as the sensitivity and specificity of molecular markers for early CRC detection, or the identification of new genetic mutations.

• **Coding Method** : Data were coded into categories related to the key themes of the study: genetic markers, screening techniques, and familial risk factors. Each category was further subdivided into specific markers (e.g., *APC*, *KRAS*), screening methods (e.g., liquid biopsy, fecal DNA testing), and familial risk syndromes (e.g., Lynch syndrome, FAP) [12]. This structured approach facilitated cross- study comparisons and the synthesis of findings across different research papers.

• **Data Synthesis Tool** : Mendeley reference management software was used to organize and manage the large volume of studies and citations. The tool helped in storing full-text articles, generating in-text citations, and categorizing studies by thematic relevance.

Analysis

The data analysis process involved synthesizing the findings from the selected studies to extract meaningful insights into early detection of familial colorectal cancer through molecular approaches.

Thematic Analysis

Genetic Markers: Studies were analyzed to identify common genetic mutations linked to familial CRC. Thematic analysis focused on exploring the frequency and clinical relevance of markers like *APC*, *MLH1*, *MSH2*, and their implications for early detection [9]. Additionally, emerging markers like DNA methylation profiles and miRNA signatures were evaluated.

Screening Techniques: Molecular screening techniques such as ctDNA analysis, liquid biopsy, and methylation-specific PCR were thematically grouped based on their efficacy in early CRC detection [16]. Studies that reported on the sensitivity, specificity, and clinical application of these methods were synthesized.

Familial Risk Factors: The analysis focused on the familial clustering of CRC, examining studies that addressed hereditary syndromes like Lynch syndrome and FAP. Specific attention was given to studies that investigated the relationship between familial genetic mutations and the development of colorectal cancer [18].

Meta-Analysis: Although a full meta-analysis was not feasible due to the heterogeneity in study designs, populations, and outcome measures, elements of the meta-analysis were incorporated where possible. For example, studies that provided statistical data on the diagnostic accuracy of molecular markers were quantitatively compared to assess the overall sensitivity and specificity of different molecular approaches [17]. Results were presented as weighted averages of sensitivity and specificity across studies, when appropriate.

Synthesis of Findings: The findings were synthesized to identify trends in the literature regarding the most effective molecular markers and screening techniques for early detection of familial CRC. These findings from studies reviewed here were further analyzed in the context of their applicability to Medina, given its wide relavent genetic and environmental profile in those studied populations [3]. Certainly, studies that discussed the implementation of ctDNA testing in clinical practice were evaluated for their aplicablity and relevance to Medina's healthcare infrastructure.

Gap Analysis: A key part of our analysis involved identifying gaps in the literature, particularly in the context of familial colorectal cancer in Medina. It was remarked that there are not enough local studies on genetic markers that are specific to Medina or the Middle Eastern population. Also emphasizing that advanced molecular screening techniques like liquid biopsy have not been widely adopted in clinical practice in Medina [18].

Summary of Findings

This reference study aims to integrate literature regarding the timing of colorectal cancer (CRC) diagnosis in relation to families, emphasizing molecular markers, screening methods employed, and family history. Several papers published between 2019 and 2024 provide insights into the importance of molecular diagnostics in the early stages of colorectal cancer (CRC) among high-risk individuals and their relatives.

DISCUSSION

Genetic Markers

All types of cancer, particularly CRC, require a prompt and accurate diagnosis for a successful patient’s disease management. Genetic markers are being employed for the stratification of personalized cancer medicine. Furthermore, the possibility of disease inheritance of specific mutations that intensify the chances of developing cancer in one’s life. Several major genetic

markers have been discovered which are mainly associated with specific genetic dispositions such as lynch syndrome and Familial adenomatous polyposis (FAP) syndromes. Among the most frequent genes reported in CRC are *APC, MLH1,* and *MSH2* Genes[19-21].

In the Indian community, where colorectal cancer incidence is somewhat lower but still affects 5– 10% of patients, Bhai's 2022 study concentrated on inherited colorectal cancer syndromes. 36 families were studied, which involved genetic testing of 19 patients with possible inherited cancer susceptibility syndromes. A range of pathogenic variations, including cases of Cowden syndrome, FAP, and HNPCC were identified. Bhai's work enhances our knowledge of inherited colorectal cancer predispositions in India and worldwide by emphasizing the importance of genetic testing, counseling, and inclusive management approaches [21].

In Abdul Murad's (2012) study, primary aim was to analyze mutations in key genes (*MLH1, MSH2, KRAS,* and *APC*) associated with colorectal cancer (CRC). Of the 76 patients studied, 38 had 17 identified missense mutations, as some deemed harmful. The research underscored the significance of mutation screening as an early detection approach to potentially reduce CRC-related mortality rates, while also pointing out the genetic diversity among CRC patients [22].

Hereditary colorectal cancer (CRC) syndromes associated with high penetrance mutations, which contribute significantly to early-onset cases, are the focus of Olkinuora's 2021 study. A significant percentage of familial and early- onset cases lack molecular characterization, requiring additional research to completely understand CRC susceptibility genetics, even if many of these mutations are well- understood and used in diagnostics and patient management. Numerous susceptibility loci have been discovered by next- generation sequencing, and their validity is still being confirmed. For those with cancer- predisposing mutations, current management entails lifelong surveillance; however, new medicines, such as cancer vaccines, may change this strategy [23].

• The *APC* gene:

Is closely associated with mutations in genes of the APC family mutations[24], constituting familial adenomatous polyposis (FAP) [25], which, in turn, markedly enhances the risk of developing colorectal carcinoma. This form of familial adenomatous polyposis is characterized by the emergence of hundreds to thousands of adenomatous polyps in the colon and rectum, which if not treated can predispose the individual to malignancy [12]. Conversely, such alteration of the gene has been linked with a mutation in persons with a high risk of Lynch syndrome, which is the most common inherited colorectal cancer [9]. Lynch syndrome not only predisposes a person to CRC at younger ages but also involves errors in the MMR system. The finding of mutations in these genes permits possible human intervention, which is a need of the hour such that the morbidity and mortality rates of high-risk individuals are reduced [4].

The importance of APC gene mutations in colorectal cancer is the main topic of Fodde's 2002 study. In addition to causing familial adenomatous polyposis (FAP), these mutations are essential for the majority of sporadic colorectal malignancies. The 'adenoma- carcinoma' sequence, is a series of histological changes caused by loss of APC gene function. Cells gain a selective advantage for clonal growth and genetic instability through APC inactivation two processes critical for tumor development. By activating the Wnt pathway beside inducing the chromosomal instability in intestinal tumor cells, mutated APC is vital to the onset and propagation of colorectal cancer [26].

Aitchison's 2020 study investigates the rise in early-onset colorectal cancer (EOCRC) cases, contrasting with the declining trend in global colorectal cancer (CRC) rates. Although mutations of the APC gene are characteristic of early-stage CRC, patients with EOCRC are less likely to have such mutations compared to older patients. The study utilizes a novel sequencing technique aimed at crucial gene regions to assess the APC mutation status in a sample of EOCRC patients from New Zealand[27].The results indicate that the proportion of APC mutations in EOCRC patients is greater than the prior assumption of 72%. Furthermore, these mutations are spread throughout the gene rather than concentrated in hotspots, which is characteristic of random mutations in older patients.

Sequencing plans for these individuals are influenced by the incidence of mutations within hotspots, which is consistent with previous EOCRC observations. The study finds a relatively

high rate of APC promoter methylation (40%) but modest rates of loss of heterozygosity and microsatellite instability, which may be related to young people's increased exposure to pro-oncogenic lifestyle variables[27].

DNA Methylation Markers

DNA methylation which is an epigenetic modification is another significant marker for early colorectal carcinoma (CRC) [28]. Hypermethylation of Tumor suppressor genes, for instance, *MGMT and MLH1* have been recorded in CRC patients and contributes to the disease by shutting down these genes [17] Citing previous works, it is evident that analysis of methylation made the ctDNA approach a novel and non-invasive form of cancer detection [16]. Methylation markers for example SEPT9 have been successfully utilized in developing diagnostic kits for CRC in asymptomatic cases in the early stages of patients [18, 28].

Kim's 2010 study explores the connection between DNA methylation indicators and family colorectal cancer. Genetic and epigenetic alterations in colonic cells cause colorectal cancer to develop. By altering particular oncogenic pathways, aberrant DNA methylation, also known as "epigenomic instability," that takes place in nearby normal mucosa aids in the development of colon cancer. The *CpG* island methylator phenotype is a subtype of colon cancer that is defined by hypermethylation of gene clusters. These DNA methylation patterns can be used as indicators of aggressive or metastatic illness, as well as biomarkers for early detection and surveillance of colorectal cancer. The purpose of the project is to investigate how DNA methylation contributes to colorectal neoplasia and its growing importance as a molecular marker in therapeutic settings[29].

The usefulness of DNA methylation as a biomarker in the diagnosis, prognosis, and response to treatment of colorectal cancer is investigated in Müller's 2022 study. The study explores novel potential markers from a variety of sample sources after outlining recognized diagnostic biomarkers such as *SEPT9* and the *NDRG4/ BMP3* combo. These indicators are linked to the development of tumors and include SDC2, VIM, APC, and others. Even though numerous studies find methylation alterations specific to tumors, repeatability is severely limited by the absence of independent sample validation. To solve this problem, genome-wide methylation analysis, or methylome, is suggested[30].

In order to identify distantly recurrent or metastatic colorectal cancer in plasma, Xie's 2021 study investigates colorectal cancer-associated methylation DNA markers (*MDMs*) in primary and metastatic colorectal cancer. By examining a panel of *MDMs* in primary and metastatic tissues, prior to testing plasma samples, the study demonstrates a high concordance between primary and metastatic tissue *MDMs*. By employing these *MDMs*, the research develops a predictive algorithm that shows the plasma assay of novel *MDMs* associated with colorectal cancer can identify primary and distant recurrences of colorectal cancer with high accuracy, surpassing traditional markers like carcinoembryonic antigen. This opens up a possible clinical use of plasma *MDMs* in identifying both initial and recurrent colorectal cancer [31]. Furthermore, studies conducted by Xie (2021)[32], Müller (2022)[30], collectively investigated the role of DNA methylation indicators in colorectal cancer research. Kim's study emphasizes the impact of irregular DNA methylation on colon carcinogenesis and proposes that methylation patterns could function as an early detection markers. Müller's research examines methylation-based biomarkers, prominence the need for genome wide analysis to ensure clinical reliability and addressing uncertainties regarding reproducibility. Xie's study focuses on DNA methylation markers associated with colorectal cancer, signifying their effectiveness in identifying primary and recurrent cases of the disease in plasma samples. Considering all of these findings together, they emphasize the significance of DNA methylation indicators for detecting and monitoring colorectal cancer and suggest that these indicators could be useful in improving patient outcomes.

Circulating Tumor DNA (ctDNA)

ctDNA analysis has established into a method with high sensitivity for both demographic and therapeutic assessment of colorectal carcinoma. DNA is released from the tumor cell into the circulation and can be detected in the blood by liquid biopsy. Genetic alterations in KRAS, TP53, or APC genes, detectable in ctDNA, can aid in CRC surveillance and diagnosis [33]. Since they do not require invasive procedures and can be performed numerous times, liquid biopsies are very

valuable and practical tools for patients at high risk due to family history, making regular testing necessary [34].

Circulating tumor DNA (ctDNA) is a promising method for classifying and tracking familial colorectal cancer (CRC)[35]. This technique, which is non-invasive and highly precise with the potential for early detection, examines DNA fragments in the blood that are resultant from tumors. For familial colorectal cancer cases, ctDNA analysis shows valuable for monitoring family members at high risk, detecting cancer in those without symptoms but with a family history, and screening for well-known hereditary mutations. Various ctDNA markers, including copy number modifications, gene mutation assessments, and methylation markers like *SEPT9 and BMP3*, have shown potential for identifying colorectal cancer.

Collectively, the study findings of Brenne (2023) [36], Li (2019) [35], and Bach (2019) [37] illuminate the potential of circulating tumor DNA (ctDNA) in the identification and treatment of colorectal cancer in families. Brenne's study proved the potential for detecting colorectal cancer (CRC) using methylation ctDNA markers in an unselected sample resembling a screening situation, up to two years prior to clinical diagnosis. The study's documentation of specific markers, like *BMP3 and FLI1* , which showed that a panel of these markers had moderate sensitivity and high specificity for CRC detection, supported the concept that incorporating ctDNA detection into screening programs could lead to early diagnoses[36].

Li's research explored the wider clinical applications of ctDNA in colorectal cancer (CRC), stressing its role in early detection, screening, therapy recommendations, and monitoring disease progression. The research highlighted the predictive utility and potential of ctDNA as a non-invasive diagnostic instrument in the realm of personalized medicine for colorectal cancer patients, highlighting its benefits compared to traditional tissue biopsies. To demonstrate the utility of ctDNA in tumor surveillance and oncotherapy, the study underlined its ability to identify actionable genetic changes, monitor treatment responses, and predict disease progression prior to clinical validation [35].

Generally, many studies have confirmed that these indicators display strong sensitivity and specificity. However, it remains difficult to standardize methods, boost the sensitivity of early detection, and determine optimal screening intervals for patients at high risk. As research and technology progress, ctDNA based tests could become an important component of CRC screening programs, especially for individuals with a familial history of the disease. This approach serves as a valuable asset in the fight against familial colorectal cancer, offering a less invasive alternative to conventional screening methods and having the potential to detect CRC up to two years prior to clinical diagnosis in certain cases.

MicroRNA (miRNA) Signatures

miRNAs, are small non- coding RNAs, manage gene expression and contribute to the development of cancer. The diagnostic potential of miRNA crosses in CRC has been highlighted by various studies[38-40]. Specific *miRNAs*, such as *miR-21 and miR-31*, are overexpressed in colorectal tumors and can be detected in blood samples [3]. miRNA-based assays provide a reliable and non-invasive approach to the early detection of CRC, particularly for those with a familial tendency to the disease.

MicroRNA (miRNA) molecules are becoming a more promising approach for identifying familial colorectal cancer (CRC). These small non- coding RNA molecules, are crucial for gene parameters, have shown potential as biomarkers for risk assessment and early detection of CRC. Certain miRNA panels, like the combination of *miRNA-29a, miRNA-125b, and miRNA-145*, have been identified in numerous studies as holding high sensitivity and improved diagnostic accuracy for colorectal cancer. MiRNA signatures offer numerous advantages for identifying familial colorectal cancer, such as the ability to screen non-invasively with only blood samples, potential for early detection, and high sensitivity and specificity, alongside prognostic relevance [41, 43]. For individuals with a familial disease history, miRNA-based detection can be employed to screen family members whom at high risk, deliver regular monitoring, and serve as an adjunct to standard genetic testing for hereditary CRC conditions. Although most studies have focused on sporadic CRC, the principles of miRNA-based detection are likely relevant to familial cases as well. However, challenges remain, including the need for thorough validation studies, standardization of protocols, and alignment with existing screening methods. As research

progresses, miRNA signatures could become central in CRC screening programs, especially for individuals with a familial disease. This might lead to earlier diagnoses and enhanced outcomes for patients with familial CRC [43].

Screening Techniques

Screening methods significantly promote the early detection of familial colorectal cancer (CRC) [44]. A diversity of strategies has been established and indorsed for individuals with a family history of colorectal cancer, owing to their heightened risk relative to the general population. Colonoscopy remains the gold standard for screening in high-risk groups, including those with a family history of colorectal cancer [45]. Precancerous lesions can be found and removed with its help. According to guidelines from a number of organizations, such as the American Society for Gastrointestinal Endoscopy (ASGE) [46], and the American College of Gastroenterology (ACG) [47], screening for colonoscopy should start at the age of 40 or ten years prior to the earliest CRC diagnosis in that family, contingent on which comes first. Screening can take place every five to ten years, conditional on the specific family history.

A fecal occult blood test (FOBT) is another well-known screening method that can reduce death rates from colorectal cancer [48]. Although, it is generally considered to be less effective for high-risk groups, it is also less invasive than colonoscopies. However, it may still be used in screening plans, especially when combined with other techniques. It has also been shown that sigmoidoscopy can reduce CRC mortality, whether used alone or alongside FOBT. It may be an option for those who cannot or do not want to undergo a complete colonoscopy [49]. Recent studies have emphasized the increased incidence of advanced adenomas among first-degree relatives (FDRs) of colorectal cancer patients. A Taiwanese study found that FDRs had a 2.5-fold increase in the likelihood of developing adenoma and a 4.5-fold increase for advanced adenoma compared to controls with no family history. This underlines the importance of targeted screening for this demographic [44, 49].

Screening methods involving the Fecal Immunochemical Test (FIT) are crucial for early detection and precautionary efforts related to familial colorectal cancer (CRC). The FIT test, which is non-invasive, can detect concealed blood in the stool. This may serve as an early sign of colon cancer or precancerous polyps. For individuals with a family history of colorectal cancer, screening typically begins 10 years prior to the diagnosis of the youngest affected member, which is earlier than in the general population. Research has shown that FIT is effective in reducing colorectal cancer (CRC) mortality rates, with a 33% decrease in the general risk of CRC-related death and a 42% reduction for deaths from left-sided colon and rectal tumors [50]. The test's advantages include its high sensitivity, non-invasive nature, absence of dietary restrictions, and frequent applicability. A positive FIT result imposes a follow-up examination, and individuals with a significant family history of colorectal cancer may require more comprehensive screening methods, such as a colonoscopy. In certain cases of familial CRC, it may also be recommended to carry out genetic testing to identify specific hereditary conditions. To find the best screening method, it is vital to frequently consult healthcare professionals and modify the specific screening protocol to each individual's risk level, considering their family history and other risk factors.

Overall, over the past few years, advanced molecular screening techniques have emerged to allow more precise detection of colorectal cancer at early stages with less invasive procedures. These techniques tend to work best with families at high risk, where there is an opportunity to detect the disease earlier on and pause its progression.

Liquid Biopsies

Liquid biopsies, which detect ctDNA and other tumor-derived components in the bloodstream, have revolutionized CRC screening [16]. These tests can identify mutations associated with colorectal cancer long before symptoms appear, making them ideal for early detection[51-53]. One of the most well-known liquid biopsy tests is that detects methylated *SEPT9* DNA in blood samples. Some studies have shown that this test has a recognized sensitivity and specificity, making it as a valuable tool for population-wide screening and monitoring of familial CRC cases if these findings confirmed by other researchers, is the field [18].

Fecal DNA Testing

Stool-based testing for DNA includes the examination of the stool for abnormal markers of colorectal tumors: these are the Cologuard tests [9]. These tests seem to be more sensitive and can facilitate diagnosis at early-stage CRC than traditional fecal occult blood tests. Fecal DNA testing is especially useful in colorectal cancer in people at high risk due to a family history of the disease [54-56]. However, this method is not without its obstacles, such as simply low rates of adoption as a result of discomfort within the patient as it pertains to stool sample collection [34].

Methylation-Specific PCR (MSP)

There are many methylation methods including those applied in Colon cancer and Methylation-specific PCR (MSP), a lot of methylated DNA is found in CRC patients. This method is very sensitive; it is possible to use blood or stool samples to find methylated DNA which is present in CRC. The successful use of MSP to detect colon cancer early, particularly in familial high-risk patients has been proven [28, 57, 58]. Because it is non-invasive, MSP is an appealing alternative in the screening strategies for families with a history of colorectal cancer [33].

Genetic Testing for High-Risk Families

Genetic testing is crucial for identifying people with hereditary mutations that increase the risk of colon cancer. Lynch Syndrome or FAP families use genetic tests for *MLH1, MSH2 & APC* gene testing to identify mutations[59, 60]. Identification of the mutations allows including preventive measures like surgery, chemotherapy, or even a combination of both. Therefore, in Medina the identification of genetic predisposition can be implemented by population-based hospital interventions at risk individuals are detected and management is directed to individuals [18].

Classification of Colorectal Cancer Based on Molecular Pathology

While this research has focused heavily on the genetic markers associated with familial CRC, it is essential to recognize the broader molecular pathology of CRC, particularly its classification into different types. According to molecular pathology, CRC can be categorized into three primary types: hereditary, familial, and sporadic. This classification is crucial for understanding the mechanisms behind CRC development and its implications for early detection.

• Hereditary Colorectal Cancer (5%)

Hereditary colorectal cancer constitutes only about 5% of all CRC cases and is primarily driven by inherited genetic mutations, such as those found in familial adenomatous polyposis (FAP) and Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer, or HNPCC) [9]. Lynch syndrome, in particular, is linked to mutations in DNA mismatch repair (MMR) genes such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*, which lead to a significantly increased risk of developing CRC [12]. FAP, on the other hand, is caused by mutations in the *APC* gene and is associated with the development of hundreds to thousands of polyps in the colon, which almost invariably progress to CRC if untreated [4].

The hereditary form of CRC, despite being the focus of considerable attention because of its identifiable genetic markers and the possibility of early detection via genetic testing, accounts for only a small percentage of all cases. This article concentrates on this hereditary subset, particularly investigating APC and MMR gene mutations. However, it is critical to recognize that hereditary CRC is uncommon.

• Familial Colorectal Cancer (20-25%):

Familial CRC represents about 20-25% of cases and is marked by a heightened risk of CRC among relatives, lacking the specific genetic mutations that characterize hereditary syndromes[16]. In such instances, the cancer can arise from a mix of shared genetic factors, environmental influences, and lifestyle decisions. Familial CRC usually appears in families with a history of CRC crossing several generations, but the genetic basis is often unclear or encompasses multiple factors.

This category is different from hereditary CRC as it does not have perceptible genetic markers like those found in Lynch syndrome or FAP. Consequently, although genetic screening can be beneficial in certain familial cases, molecular diagnostics must consider a wider array of factors, such as gene-environment interactions. Due to their increased risk, studies indicate that people in familial CRC groups may benefit from more frequent screenings beginning at a younger age[3].

• Sporadic Colorectal Cancer (70-75%):

Sporadic CRC constitutes the largest category, making up around 70-75% of all CRC cases. Sporadic cases of CRC arise in individuals who do not have a significant family history of the disease, unlike hereditary or familial CRC. These cases are mainly caused by somatic mutations that happen in colon cells over the course of an individual's life rather than inherited mutations [33]. The most common mutations in sporadic CRC are found in genes such as *KRAS*, *TP53*, and *BRAF*, and these mutations are often associated with environmental factors, lifestyle choices, and aging.

Recent studies have clearly shown the rising occurrence of sporadic CRC in people younger than 50, which has sparked worries and demands for broader screening measures[4]. Due to genetic predisposition, hereditary CRC is usually diagnosed in younger individuals. Sporadic cases in the young individuals are especially alarming, however, as they often present at more advanced stages because of delayed screening[3, 4].

Significance of the Molecular Pathology Classification

Classifying CRC into hereditary, familial, and sporadic types has significant implications for clinical practice, especially regarding screening and early detection strategies. Although genetic testing can often identify hereditary CRC earlier on, sporadic cases which make up the majority of CRC instances are more difficult to detect prior to the onset of symptoms. This highlights the necessity of molecular diagnostics capable of detecting sporadic mutations and epigenetic changes, like methylation- specific PCR and ctDNA analysis, in routine screenings for those under 50 [18].

This study focuses on genetic mutations, particularly those linked to hereditary CRC. While this focus is significant, it neglects the reality that hereditary mutations constitute only 5% of all CRC cases. The vast majority of CRC cases particularly sporadic cases develop due to scattered mutations that occur later in life, often as a result of environmental and lifestyle factors [33]. These sporadic cases, which are becoming more common in younger individuals, present a significant public health challenge, and molecular diagnostics for detecting them at an early stage must be prioritized in future research.

Familial CRC Risk Factors

Familial colorectal cancer seems to account for about 20-25% of all CRC cases, being largely contributed to by such acquired syndromes as Lynch syndrome or FAP [3]. This is crucial in coming up with good strategies for early cancer detection especially in high prevalence areas such as those in Medina.

• Hereditary Syndromes

1. The most common cause of Hereditary CRC syndrome is Lynch syndrome which is caused by a mutation in the MMR (Mismatch Repair system) genes [12]. Affected individuals with Lynch syndrome can have a lifetime risk of developing colorectal cancer of up to 85%. Such a high risk of developing CRC within the latter ages of these individuals facilitates the need for intensive screening. On the other hand, familial adenomatous polyposis (FAP) is the condition when up to hundreds or thousands of adenomas appear in the colon and if untreated, expect that cancer sooner or later evolves [9]. The use of genetic testing in families with these syndromes is an effective means of determining family members at risk and thus making it possible to plan for initial management properly.

2. Genetic Mutations and Family History; A family history of colorectal cancer is an important risk factor in the development of the disease. Such individuals are two to three times more likely to develop CRC disease themselves if they have one or more first- degree relatives with a diagnosis of CRC [16]. In families with a greater incidence of colorectal cancer, there are many genetic mutations, especially those relating to the *APC, MLH1, and MSH2* genes, indicating the correlation between CRC and genetic epidemiology in populations at risk. In Medina, a family-wide analysis of CRC patients indicates that genetic factors may be effectively utilized, demonstrating a marked need for government-funded health screening programs in the region [3].

3. Environmental and Lifestyle Factors; Inevitably disposition factors are not the only factors that trigger colorectal cancer in familial cases in addition to the genetic disposition there are also environmental and lifestyle that have been triggered as well. High consumption of red and processed meat, physical inactivity as well as use of tobacco have all been linked to an increased risk of being diagnosed with CRC [18]. It is however also plausible that these behaviors may serve to enhance the risk of cancer development along with the underlying mutation and is the reason why it is important to have lifestyle modification as part of preventive measures for high-risk families. On the other hand, how these factors work together with genetic factors in Medina is not very well understood; more studies are needed in this regard.

Gaps in the CRC Literature

Despite great improvements achieved in molecular screening methods and identification of genetic markers, still there are some gaps in the literature with regards to inducing these findings in the cases of familial CRC in Medina. Here in the article we will be discussing part of these areas to bridge such gaps.

Lack of Region-Specific Studies

Western populations have the highest report of incidence cases and most of the molecular studies on early detection of CRC have emphasized these populations failing to study the specific gene and environmental determinants in regions such as Medina [3]. Cancer-predisposing genes for colon cancer in the Medina population might be different from those of other regions due to different genetic and environmental profiles. There is a need for further studies to localize genetic mutations and molecular markers in people with a family history of the disease in Medina.

Limited Implementation of Molecular Screening in Clinical Practice

Although promising, the application of molecular techniques such as liquid biopsy and ctDNA tests for early diagnosis of oncological disorders is still unsatisfactory and restricted to basic examinations in Medina and other developing areas [16]. The expensive nature of the Technologies as well as the unavailability of the platform for the genetic test to be conducted are major challenges. Complimentary studies are necessary to come up with cheap screening methods that can be used at local health facilities.

Lack of Evidence on Family Aggregation Activities Including Cancer in Medina

In Medina, there is no sufficient data on cancers that run in families such as CRC. There is an important need to appreciate the genetics and family history risks that are unique to the members of this population so that appropriate screening interventions can be designed. Research on specific ethnic populations such as those of Medina who are affected by CRC and studying the carcinogenic mutations that exist in their families would provide important information that surely will help in bridging these gaps [18].

Familial Risk Factors

- **Lynch Syndrome**

Lynch syndrome, caused by mutations in MMR genes (*MLH1* , *MSH2* , *MSH6* , and *PMS2*), accounts for approximately 3-5% of all colorectal cancer cases but is more prevalent in familial cases. The syndrome predisposes individuals to a lifetime risk of up to 85% for developing CRC [12]. Early detection through genetic screening is crucial, as individuals with Lynch syndrome often develop cancer at a younger age compared to those with sporadic CRC [4]. Numerous studies emphasize the importance of regular surveillance, including colonoscopy and molecular screening, for individuals with Lynch syndrome to catch malignancies at a treatable stage.

• **Familial Adenomatous Polyposis (FAP)**

FAP is a hereditary condition caused by mutations in the *APC gene*, leading to the development of numerous adenomatous polyps in the colon. Nearly all individuals with FAP develop colorectal cancer if prophylactic surgery is not performed. Genetic testing for *APC* mutations allows for early diagnosis of FAP in high-risk families, enabling timely intervention [9].

• **Environmental and Lifestyle Factors in Familial CRC**

Although familial CRC is primarily driven by genetic factors, studies have identified environmental and lifestyle contributors that may interact with genetic predispositions to increase cancer risk. High- fat diets, sedentary lifestyles, smoking, and alcohol consumption have been shown to exacerbate the likelihood of developing CRC in individuals with a family history of the disease [18].

• **Comparative Analysis**

Studies that were reviewed in this article explored both the similarities and extremes in the performance of molecular markers and screening technologies concerning early diagnosis of CRC. For instance, at times when most of the studies seemed to agree over the diagnostic role of ctDNA in early detection, a few however had stigma regarding its addressable area in detecting small or localized tumors. Dekker et al. (2019) asserted that although ctDNA has its place in the assessment of larger tumors and the post-treatment surveillance of their patients, other techniques such as methylation- specific polymerase chain reaction – MSP, were better placed than ctDNA at detecting the early stages of CRC[33].

Likewise, the analysis of the miRNA biomarkers such as that of Akimoto et al. (2021) showed that there are miRNA tests that can be useful in the diagnosis of CRC even at home, particularly for people with a genetic predisposition to the disease[3]. Nonetheless, Zygulska and Pierzchalski (2022)[16] observe that miRNA testing is of prognostic and predictive value in CRC but challenges remain in terms of application in practice as further validation is needed for population- based accuracy. The discrepancy shows that applying miRNA tests as the sole means for screening s a limitation that shows the need for more localized studies, especially in regions such as Medina.

All of the findings presented in this review show how important the role of molecular techniques is in terms of the early diagnosis of familial cases of CRC. The majority of cases of hereditary colorectal cancer (CRC) involve genetic alterations of specific genes including, APC, which is common in familial adenomatous polyposis (FAP) and *MLH1, and MSH2*, which are involved in lynch syndrome [9, 12]. Widespread use of these cancer markers determination techniques leading to genetic testing would prompt early management options including clinical monitoring and preventive surgeries. During screening for CRC, molecular methods such as circulating tumor DNA (ctDNA) and methylation- specific PCR (MSP), which have shown high efficacy in CRC detection have made it possible to efficient and non- invasively screen high- risk asymptomatic populations [17].

In particular, some miRNAs such as *miR-21 and miR-31* are potential biomarkers for CRC in a non- invasive fashion which enhances diagnostic accuracy in patients with a positive family history of cancer [3]. Overall, it can be said that currently available molecular methods will be able to detect CRC at an early stage, especially in patients with a positive family history of CRC [61].

Relevance to Medina

The salience of these findings to the hospitals in Medina is particularly important because the cases of colon cancer in the Saudi Arabian population is on the increase. The presence of familial aggregation of colorectal cancer implies that there exists some heritable component in this region, which shows there is a need for specific screening programs. The application of molecular diagnostic procedures such as ctDNA mutation and *APC and MLH1* gene mutation analysis could be very useful in enhancing early diagnosis in the local hospitals in Medina where diagnostic technology is still emerging but developing [4]. Halting the advancement of these programs in high-risk families who are at risk of developing CRC could be helpful to ease the strain on the healthcare system in terms of the costs of handling CRC.

Limitations

This is because the studies reviewed in this section are still providing substantial contributions, but there are some weaknesses. First of all, the majority of the studies have been carried out in Western countries, and this might affect how the population of Medina applies the findings to its genetic environmental context. In addition, while techniques like ctDNA and MST are very good, the price however is very steep and will include advanced laboratory infrastructure which is hard to come by in a resource-strained location [17]. Other limitations are that a lot of the literature is observational and there is little clinical trial data that incorporate these techniques within the standard clinical evaluation for familial colorectal cancers.

Future Research

Further studies on Medina should also include comparative regional studies to identify the genetic determinants prevalent among the local population and how they may contribute to CRC diagnosis. It has become evident that clinical studies undertaken in the hospitals of Medina are required to assess the possibilities and cost- effectiveness of the introduction of molecular techniques into colonoscopy [18]. Furthermore, further research into the new genetic markers and their use in the clinical setting, together with the existing ones in routine family screening in Medina, could improve the management of high-risk families.

Conclusion

This article has highlighted the importance of molecular diagnostics in the early identification of colorectal cancer (CRC) in familial cases. Essential genetic indicators, including *APC, MLH1*, and *MSH2*, those are associated with hereditary disorders such as familial adenomatous polyposis (FAP) and Lynch syndrome. The implication of genetic testing in families with high risk. The various molecular screening approaches like circulating tumor DNA (ctDNA) analysis, methylation-specific PCR (MSP), and miRNA assays provide promising non-invasive approaches for early detection of CRC, especially in asymptomatic individuals with a family history. When these methods are used in conjunction with an emphasis on familial risk factors, the incidence and mortality rates of CRC can be significantly reduced.

Practical Implications

By integrating molecular diagnostics like ctDNA analysis and genetic testing for *APC, MLH1,* and *MSH2* mutations, in Medina hospitals can improve early detection of familial CRC. This would facilitate the identification of individuals at high risk who need careful observation and prompt intervention. Moreover, incorporating non-invasive molecular methods like liquid biopsies and MSP might reduce the necessity for invasive procedures. Moreover, this could result in improved patient compliance and facilitate early- stage detection [18]. Creating a regional database of familial CRC cases in Medina will enhance screening protocols adopted to the genetic profile of the local population.

Recommendations

It is important for healthcare authorities and researchers to conduct foundational epidemiological studies to establish the genetic profile of CRC in Medina. Thus, to pave the way for hospitals in Medina to implement genetic testing programs for families at high risk, with special focus on identifying mutations such as those well documented in the Western data in

for example; *APC, MLH1,* and *MSH2*. Similarly; this might pave the way for employing the ctDNA analysis and MSP in routine screening for familial cases to enable earlier intervention and enhance patient outcomes. Certainly, to save ministry's budgets from managing late cancer patients' cases to the preventative policy.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Omar A Alfaroqi, Zakaria Eltahir Mohammad H. Fakieh, and Mohamed Morsi M. Ahmed, Conceptualization, methodology, software, formal analysis, investigation, data curation, writing original draft preparation, writing review and editing. All authors have read and approved to the published version of the manuscript.

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Declaration on the Use of Artificial Intelligence (AI)

The authors used an artificial intelligence (AI)- assisted language tool solely to improve the grammar, language, readability, and overall clarity of the manuscript. The AI tool was not used to generate, analyze, interpret, or modify the study data, results, or scientific conclusions. All scientific content, study design, data collection, statistical analyses, interpretation of findings, and final manuscript preparation were performed by the authors. The authors have carefully reviewed, verified, and approved the final version of the manuscript and accept full responsibility for the accuracy, integrity, and originality of all content presented.

Tables

Genetic Marker	Role in Familial CRC	Screening Technique	Study References
APC	Mutation linked to FAP causes adenomatous polyps	Genetic testing, ctDNA analysis	[9, 12]
MLH1, MSH2	Lynch syndrome, defective DNA repair	Genetic testing, MSP	[4, 17 & 62]
MGMT	Hypermethylation, inactivation of tumor suppressor gene	Methylation-specific PCR	[17, 63]
KRAS, TP53	Mutation driving colorectal tumor growth	Liquid biopsy, ctDNA analysis	[16, 18 & 64]
miR-21, miR-31	Overexpressed in colorectal tumors	miRNA assays	[3]

Table 1: Key genetic and epigenetic biomarkers in familial colorectal cancer (CRC) and corresponding screening modalities. The table outlines major genetic mutations, DNA methylation alterations, and microRNA expressions driving the pathogenesis of familial CRC syndromes, including Familial Adenomatous Polyposis (FAP) and Lynch syndrome. The functional role of each marker is mapped to its primary clinical detection technique and relevant foundational literature. Abbreviations: CRC, Colorectal cancer; ctDNA, circulating tumor DNA; FAP, familial adenomatous polyposis; miRNA, microRNA; MSP, methylation-specific polymerase chain reaction.

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