RESEARCH PAPER

Molecular Pathogenesis and Surgical Intervention in Colon Cancer: Integrating Multi-Omics Insights with Precision Surgical Oncology — A Systematic Review

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Abstract

Colorectal cancer (CRC) arises through a multistep process involving the accumulation of genetic and epigenetic alterations that transform benign adenomatous polyps into invasive malignancies. Key molecular drivers include dysregulation of the Wnt/β-catenin pathway and activation of the RAS/RAF/MEK/ERK signaling cascade, alongside mutations in critical genes such as *APC*, *KRAS*, *TP53*, and *BRAF*. In addition to the classical adenoma–carcinoma sequence, the serrated pathway represents a distinct route characterized by CpG island methylator phenotype and microsatellite instability, contributing to tumor heterogeneity and diverse clinical outcomes. Epigenetic mechanisms, including DNA methylation, histone modification, and non-coding RNA regulation, play a central role in tumor progression, metastasis, and therapeutic resistance. Emerging biomarkers such as circulating tumor DNA (ctDNA), microRNAs, and methylation signatures have significantly improved early detection, prognostic assessment, and real-time monitoring of disease progression. Advances in liquid biopsy technologies and multi-omics approaches enable minimally invasive and highly sensitive diagnostic strategies that complement conventional screening methods. The integration of artificial intelligence (AI) into CRC management has further transformed diagnostic and surgical practices. AI-assisted digital pathology and intraoperative imaging enhance tumor characterization, improve resection accuracy, and support personalized treatment planning. Modern surgical approaches increasingly incorporate molecular profiling and real-time analytics to optimize therapeutic outcomes. Despite these advancements, challenges remain in clinical translation, including the need for standardized protocols and large-scale validation. Future strategies emphasize precision oncology, integrating molecular diagnostics, AI-driven decision-making, and minimally invasive surgery to improve survival and reduce recurrence in colorectal cancer patients.

Keywords: Colorectal cancer; Molecular pathogenesis; Epigenetic regulation; Circulating tumor DNA (ctDNA); Artificial intelligence in surgery

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Introduction

In the early stages of colorectal cancer, genetic and epigenetic changes transform benign adenomatous polyps into malignant neoplasms capable of metastasis. The Wnt/β-catenin axis and the *KRAS* proto-oncogene are two critical signaling pathways frequently disrupted during the initiation of tumorigenesis. Gharib and Robichaud (2024) state that the Vogelstein model is supported by evidence that inactivation of tumor suppressor genes such as *TP53* accelerates the progression from localized dysplasia to advanced carcinoma. Histone modification and DNA methylation further exacerbate this biological process by influencing cellular proliferation and survival [1].

Surgical approaches must be adapted to target the molecular alterations accompanying histological progression in order to reduce tumor aggressiveness [2]. The use of biomarkers, including microsatellite instability (MSI) status and *BRAF* mutation patterns, improves risk assessment and enhances surgical precision [3]. The extent of lymphadenectomy and adjuvant therapy protocols may vary depending on the inactivation of apoptosis-regulating pathways and the presence of aneuploidy. A comprehensive understanding of this molecular heterogeneity is therefore essential for accurate prognostication and optimization of surgical-oncological management in advanced colorectal cancer [4].

Nguyen describe that the serrated pathway as a distinct clinical entity separate from the conventional adenoma–carcinoma sequence, characterized by *BRAF* mutations and the CpG island methylator phenotype [5]. It also demonstrated that hyperplastic polyps and sessile serrated adenomas exhibit complex morphologies, complicating early detection [6]. Due to their rapid progression and association with microsatellite instability, these lesions require careful endoscopic surveillance and timely resection to prevent malignant transformation [7]. In MSI-high variants, *RNF43* mutations frequently activate the Wnt pathway independently of *APC* loss [8].

Changes in Colon Cancer Genetics

Somatic mutations in driver genes, particularly those associated with the Wnt/β-catenin signaling pathway, play a central role in the progression from normal colonic epithelium to invasive carcinoma. Inactivation of the APC complex is critical for β-catenin stabilization and its nuclear translocation through aberrant signaling pathways. Subsequent somatic alterations, including

*Author for Correspondence: devendrakhwairakpam@gmail.com mutations in KRAS and TP53, contribute to genomic instability and facilitate the malignant transformation of benign tubular adenomas [9].

Mutations in BRAF or KRAS, often in conjunction with microsatellite instability or a high CpG island methylator phenotype, initiate serrated neoplasia [10,11]. These lesions exhibit a characteristic saw-tooth crypt architecture resulting from excessive epithelial infolding [12]. Additionally, mutation or epigenetic silencing of RNF43 is frequently observed in this pathway, disrupting ubiquitination processes and leading to the accumulation of Wnt-activating frizzled receptors. As dysplastic lesions acquire secondary mutations, enhanced interactions between the Wnt and MAPK pathways further accelerate tumorigenesis [13].

Beyond genetic alterations, targeted therapies against epidermal growth factor receptor (EGFR), including monoclonal antibodies such as cetuximab, have been developed. The effectiveness of these therapies depends on the mutation status of the MAPK signaling cascade [14]. Activating mutations in KRAS or BRAF result in constitutive MAPK pathway activation, thereby conferring resistance to anti-EGFR therapies [15].

Furthermore, deregulation of mitotic regulators, including Aurora kinases and Polo-like kinases, contributes to chromosomal instability and increased genomic heterogeneity in advanced-stage tumors [16]. These genetic alterations necessitate surgical strategies tailored to the molecular classification of the tumor, as microsatellite instability significantly influences biological aggressiveness and therapeutic response [17].

Signaling Pathways During Colon Cancer Growth

Disruption of the Wnt/β-catenin pathway is a hallmark of conventional colorectal cancer, whereas the serrated pathway is characterized by early activation of the MAPK signaling cascade driven by BRAF or KRAS mutations [18,19]. Epigenetic alterations, particularly CpG island methylation, are commonly observed and lead to the silencing of tumor suppressor genes such as p16, IGF2, and MGMT [20].

Inactivation of the negative regulators RNF43 and ZNRF3 plays a significant role in aberrant Wnt signaling in colorectal tumors harbouring the BRAF V600E mutation, representing an alternative mechanism of pathway dysregulation that distinguishes serrated lesions from conventional adenomas [21,22].

For treatment-resistant malignancies, genetic profiling is increasingly essential in preoperative planning due to underlying molecular heterogeneity [23]. Emerging technologies such as liquid biopsies and patient-derived organoids enable real-time molecular monitoring and facilitate the development of personalized therapeutic strategies to overcome drug resistance [24,25].

The phosphoinositide 3-kinase (PI3K)/AKT pathway has also emerged as a critical therapeutic target, as it interacts with the RAS/RAF/MEK/ERK signaling cascade to promote colorectal tumor growth [19,26]. This signaling synergy is further enhanced in the absence of SMAD4, which disrupts TGF-β-mediated growth inhibition and promotes epithelial–mesenchymal transition, facilitating metastatic progression [27].

Tumors characterized by mismatch repair deficiency and CpG island methylator phenotype often display distinct metastatic patterns and differential sensitivity to cytotoxic therapies. Consequently, surgical planning must account for this biological complexity. Advanced classification systems that identify these molecular subgroups enable clinicians to tailor surgical and therapeutic strategies, thereby improving clinical outcomes [28].

The clinical integration of molecular profiling is essential, as BRAF mutations are associated with poor prognosis and reduced responsiveness to conventional anti-EGFR therapies [29]. Recent studies suggest that incorporating RNF43 mutation status into diagnostic frameworks may further refine therapeutic decision-making by addressing the complex interplay between the Wnt and MAPK pathways [30].

Conventional molecular classification systems categorize colorectal cancer into four major subtypes based on genomic instability, immune infiltration, and metabolic reprogramming patterns. These frameworks are increasingly enhanced by the use of circulating tumor DNA for real-time monitoring and improved patient stratification in targeted therapies [31].

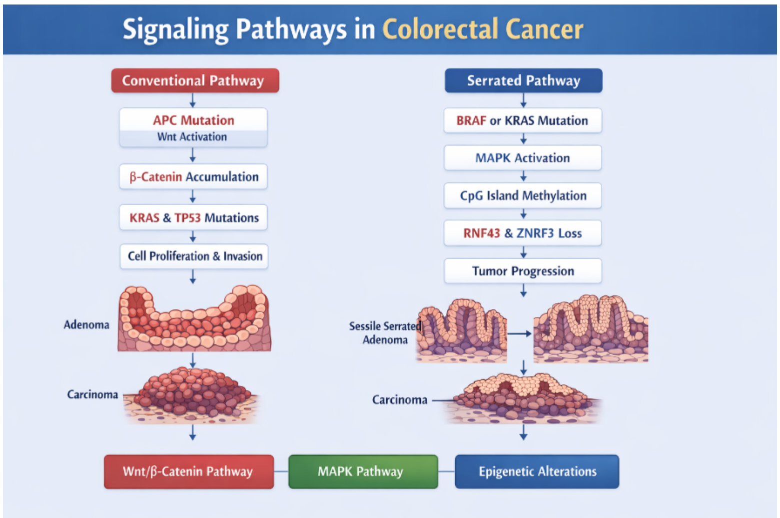

Figure 1 Signalling cascade and pathways in colorectal cancer.

The colorectal cancer signaling network is primarily driven by aberrant activation of the Wnt/β-catenin pathway, often initiated by APC inactivation, leading to uncontrolled cellular proliferation (figure 1). Concurrently, mutations in KRAS and BRAF activate the MAPK (RAS/RAF/MEK/ERK) cascade, promoting tumor growth, survival, and resistance to targeted therapies such as anti-EGFR agents. Additional interactions with the PI3K

Table 1. Molecular pathways, biomarkers, and clinical implications in colorectal cancer

Category	**Key Components**	**Molecular Mechanism**	**Clinical Significance**
Wnt/β-catenin Pathway	APC, β-catenin	Inactivation of APC leads to β-catenin accumulation and nuclear transcriptional activation	Initiates colorectal tumorigenesis; potential target for early therapeutic intervention
MAPK Pathway	KRAS, BRAF	Constitutive activation of RAS/RAF/MEK/ERK signaling cascade	Promotes tumor proliferation and survival; associated with resistance to anti-EGFR therapy
PI3K/AKT Pathway	PI3K, AKT	Enhances cellular survival, metabolism, and growth signaling	Contributes to tumor progression and therapeutic resistance
Tumor Suppressor Genes	TP53, APC	Loss of cell cycle regulation and apoptosis control	Facilitates progression from adenoma to carcinoma
Epigenetic Modifications	DNA methylation, histone modification	Silencing of tumor suppressor genes via chromatin remodeling	Useful biomarkers for early detection and prognosis
Microsatellite Instability (MSI)	Mismatch repair genes	Defective DNA repair leading to mutation accumulation	Predicts prognosis and response to immunotherapy
CpG Island Methylator Phenotype (CIMP)	Methylated gene promoters	Epigenetic silencing of multiple genes	Associated with serrated pathway and BRAF mutations
Serrated Pathway	BRAF, RNF43	Alternative Wnt pathway activation and epigenetic dysregulation	Rapid disease progression; requires enhanced surveillance
Non-coding RNAs	miR-200, miR-135b	Regulation of gene expression and	Emerging diagnostic and therapeutic targets

		epithelial–mesenchymal transition	
Liquid Biopsy	ctDNA, circulating miRNA	Real-time detection of tumor-derived genetic material	Enables early detection and monitoring of recurrence
AI & Digital Pathology	Deep learning models	Automated image analysis and tumor classification	Improves diagnostic accuracy and surgical planning
Surgical Innovation	Robotics, augmented reality	Precision-guided tumor resection and intraoperative navigation	Enhances surgical outcomes and reduces complications

Epigenetic Changes and Colorectal Cancer

Besides DNA methylation, non-coding RNAs such as hsa-miR-200 and hsa-miR-135b-3p regulate gene expression and promote colorectal cancer metastasis [32]. These molecules play a crucial role in maintaining cellular plasticity. Promoter hypermethylation of the miR-200 family accelerates epithelial–mesenchymal transition in mesenchymal-like subtypes [33]. Histone acetylation and methylation act synergistically to produce large-scale chromatin modifications that sustain oncogenic transcriptional programs [34].

These aberrant epigenetic profiles often exhibit persistent, tumor-specific methylation patterns that serve as reliable biomarkers for early diagnosis and prognosis [35]. Circulating tumor DNA and advanced gene panel sequencing enable more sensitive detection of these dynamic molecular changes compared to conventional carcinoembryonic antigen testing, thereby improving surgical and adjuvant decision-making [36].

Dysregulation of histone methyltransferases and demethylases is essential for maintaining the malignant phenotype, making their characterization critical for therapeutic intervention [37]. Such epigenetic adaptations promote rapid clonal proliferation, complicating surgical management and highlighting the importance of chromatin-modifying agents to restore transcriptional regulation prior to extensive oncological resection [34].

Integration of epigenomic data with clinical subtyping frameworks is necessary to address intratumoral heterogeneity, which often reduces the effectiveness of standardized surgical and systemic therapies [38,39]. The transition from molecular diagnostics to clinical application is exemplified by non-invasive approaches, including cell-free miRNAs and other non-coding RNAs, which provide high sensitivity for detecting early-stage colorectal lesions [40].

These biomarkers also facilitate monitoring of metastatic progression, as epigenetic alterations influence key migratory and adhesion pathways, promoting cellular invasiveness. The reversibility of epigenetic modifications, including DNA methylation and histone alterations, enables targeted pharmacological interventions that enhance tumor sensitivity to surgical treatment [41,42].

Recent advances in liquid biopsy technologies, including genome-scale DNA methylation analysis and ultra-low-input sequencing, provide a strong foundation for translating molecular biomarkers into clinically applicable diagnostics [43]. Emerging screening strategies utilizing blood, exhaled air, and tumor tissue analyses offer comprehensive profiling of minimal residual disease, thereby improving diagnostic frameworks [44].

Epigenetic-modifying agents and biofilm-targeting strategies may further improve surgical outcomes by reducing cytotoxic resistance and microbiome-associated tumor progression [45]. Modulation of quorum sensing pathways within the gut microbiome has been shown to reduce biofilm-associated inflammation and enhance postoperative recovery [45].

Circulating tumor DNA (ctDNA) is increasingly recognized as a critical clinical endpoint, with the potential to complement or replace radiological imaging for monitoring remission and recurrence [46]. Concurrently, advancements in surgical techniques, including robotic systems and natural orifice specimen extraction, aim to reduce physiological stress associated with conventional procedures [47,48]. Minimally invasive surgery combined with extended ctDNA monitoring may improve detection of minimal residual disease and guide adjuvant therapy decisions, thereby reducing recurrence risk.

Assessment and Initial Identification

The identification of novel genetic and epigenomic biomarkers remains a key objective for improving early-stage screening and prognostic accuracy [49,50]. Aberrant DNA methylation patterns and altered non-coding RNA expression can reveal malignant transformation before detectable structural changes appear on imaging [32,51].

Molecular characterization of pre-neoplastic lesions can be achieved through analysis of promoter hypermethylation in tumor suppressor genes and circulating miRNA profiles [52]. Advanced techniques such as bisulfite sequencing and chromatin immunoprecipitation arrays are enhancing understanding of tumor biology and guiding therapeutic decisions [53].

These high-throughput methods require rigorous standardization in sample processing and analytical procedures to minimize variability in DNA extraction and quantification [54]. The integration of liquid biopsy with continuous monitoring enables real-time assessment of disease progression and therapeutic resistance without invasive procedures. This approach supports the concept of "molecular residual disease," representing a distinct phase requiring proactive clinical intervention [55,56].

Recent studies highlight that chromatin spatial capture technologies can identify aberrant enhancer–promoter interactions driving ectopic oncogene activation [57]. Integration of spatial genomics with multi-omics approaches facilitates the identification of epigenetic regulators within complex cellular networks, forming the basis of precision oncology. Validation of these biomarkers in large, well-characterized cohorts remains essential for clinical translation [58,59].

Screening for Colon Cancer

Genome-wide methylation profiling and multigene stool-based assays are enhancing detection of precursor lesions beyond conventional colonoscopy [60,61]. Multiomic analyses, including extracellular vesicles, metabolites, and immune cell profiling, reflect tumor heterogeneity and improve early diagnosis [62].

Artificial intelligence has significantly improved real-time endoscopic screening by identifying subtle mucosal abnormalities that may otherwise be missed [63]. Microbial signatures, including dysbiotic patterns and *P. gingivalis*, further characterize the pro-inflammatory tumor microenvironment [64].

Multimodal diagnostic systems, supported by big data analytics and digital twin modeling, are becoming essential for personalized risk assessment and monitoring [65]. AI-enhanced surgical platforms enable real-time decision-making using high-dimensional datasets, improving navigation within complex tumor environments [66,67].

Quick-Detection Biomarkers

Liquid biopsy approaches that measure circulating tumor DNA (ctDNA) and proteomic signatures are increasingly being integrated into clinical workflows for the early detection of asymptomatic colorectal lesions [68]. These minimally invasive techniques offer a dynamic and real-time assessment of tumor burden, enabling clinicians to monitor disease progression and therapeutic response more effectively than traditional methods.

Microfluidic technologies further enhance the sensitivity and precision of these assays by allowing high-throughput, real-time analysis of biological samples, including blood and fecal matter [69]. This advancement facilitates continuous disease monitoring and supports early intervention strategies.

In parallel, the application of machine learning algorithms to these high-dimensional datasets has significantly improved patient risk stratification. These computational models can identify complex patterns within genomic and proteomic data, thereby addressing limitations in sensitivity and specificity associated with conventional screening modalities [70].

Additionally, polygenic microbiome-based risk scores represent an emerging frontier in colorectal cancer diagnostics. By integrating host genetic susceptibility with gut microbial composition, these models provide a more comprehensive understanding of adenoma development and progression, potentially enabling personalized screening strategies [71].

Pathological Classification of Colonic Neoplasms

Histological evaluation of colorectal neoplasms has evolved from traditional subjective morphological assessment to advanced, high-dimensional spatial analysis driven by deep learning technologies. Digital pathology platforms now enable the extraction of complex features from whole-slide images, facilitating the identification of novel biomarkers and the objective classification of prognostic histological subgroups [72].

Artificial intelligence-driven image segmentation and real-time augmentation tools have further enhanced intraoperative visualization. These systems allow surgeons to delineate tumor boundaries with greater accuracy, thereby improving surgical precision and oncological outcomes [73].

Despite these advancements, the clinical translation of AI-based diagnostic systems requires rigorous multi-center validation to ensure robustness, reproducibility, and generalizability across diverse patient populations. Addressing these challenges is essential for widespread adoption and integration into routine clinical practice [74,75].

Surgery for Colorectal Cancer

Modern colorectal cancer surgery increasingly incorporates high-resolution histopathological data and intraoperative analytics to support real-time, data-driven decision-making. AI-assisted imaging technologies enable rapid tissue characterization, facilitating precise tumor localization and prognostic stratification during surgical procedures [76].

Advanced intraoperative systems integrate preoperative imaging, patient-specific clinical data, and real-time surgical inputs to optimize operative planning. This comprehensive approach reduces intraoperative complications, enhances surgical accuracy, and improves postoperative recovery outcomes [77,78].

To fully realize the potential of these technologies, standardized evaluation frameworks and clinical validation protocols are essential. These frameworks will ensure consistent implementation, improve clinician confidence, and promote the safe integration of AI-driven tools into surgical oncology practice [79].

Discussions

The present systematic review underscores the multifactorial nature of colorectal cancer pathogenesis, highlighting the intricate interplay between genetic mutations, epigenetic alterations, and tumor microenvironment dynamics. Central to disease progression is the disruption of canonical signaling pathways such as Wnt/β-catenin, MAPK, and PI3K/AKT, which collectively regulate cellular proliferation, differentiation, and apoptosis. Mutations in key driver genes, including *APC*, *KRAS*, and *TP53*, initiate a cascade of molecular events that facilitate the transition from benign adenomatous lesions to invasive carcinoma. Concurrently, epigenetic mechanisms, including DNA methylation, histone modification, and non-coding RNA-mediated regulation, contribute to transcriptional reprogramming and tumor heterogeneity. These molecular events operate within a highly adaptive network, enabling tumor cells to evade immune surveillance and develop resistance to therapeutic interventions, thereby complicating clinical management and adversely affecting patient outcomes [80,81].

Recent advances in multi-omics technologies have revolutionized the understanding of colorectal cancer by providing comprehensive insights into tumor biology at multiple molecular levels. The integration of genomics, transcriptomics, proteomics, metabolomics, and epigenomics has facilitated the identification of distinct molecular subtypes, each characterized by unique biological signatures and therapeutic vulnerabilities. These stratification frameworks have significant clinical implications, particularly in guiding personalized treatment strategies and optimizing surgical planning. For instance, tumors exhibiting microsatellite instability or CpG island methylator phenotype demonstrate differential responses to chemotherapy and immunotherapy, necessitating tailored perioperative approaches. Furthermore, liquid biopsy platforms, including circulating tumor DNA (ctDNA), circulating tumor cells, and extracellular vesicles, have emerged as powerful tools for non-invasive disease monitoring. These technologies enable early detection of recurrence, assessment of minimal residual disease, and real-time evaluation of treatment response, thereby enhancing clinical decision-making and improving long-term prognosis [82,83].

From a surgical oncology perspective, the integration of molecular profiling into clinical workflows represents a transformative shift toward precision medicine. Traditional surgical approaches, which primarily relied on anatomical and histopathological criteria, are increasingly being supplemented by molecular diagnostics to achieve more individualized treatment strategies. The incorporation of biomarkers into preoperative assessment allows for more accurate risk stratification, enabling surgeons to determine the optimal extent of resection and the necessity for neoadjuvant or adjuvant therapies. Technological innovations, including robotic-assisted surgery, fluorescence-guided imaging, and intraoperative molecular analysis, have significantly enhanced surgical precision and reduced operative morbidity. In parallel, the application of artificial intelligence and machine learning algorithms to large-scale clinical and molecular datasets has improved intraoperative decision-making, facilitating accurate tumor localization, margin assessment, and prediction of postoperative outcomes. These advancements collectively contribute to improved surgical efficacy and patient survival while minimizing unnecessary interventions [84,85].

Despite the promising advancements in multi-omics integration and precision surgical oncology, several challenges remain in translating these innovations into routine clinical practice. One of the primary limitations is the lack of standardized methodologies for data generation, integration, and interpretation, which can lead to variability in clinical outcomes. Additionally, the high cost and technical complexity associated with multi-omics platforms may limit their accessibility, particularly in low- and middle-income settings. There is also a critical need for large-scale, multicentre validation studies to establish the clinical utility and reproducibility of identified biomarkers. Ethical considerations related to data privacy, as well as the integration of complex bioinformatics pipelines into clinical workflows, further complicate implementation. Future research should focus on developing cost-effective, scalable diagnostic tools and establishing standardized guidelines for multi-omics data utilization. The convergence of molecular biology, computational analytics, and advanced surgical techniques holds immense potential to redefine colorectal cancer management, ultimately enabling more precise, personalized, and effective therapeutic strategies that improve patient outcomes and quality of life [86,87].

Conclusion

The convergence of genomic diagnostics, robotic precision, and artificial intelligence is reshaping colorectal cancer surgery toward a more patient-centered and evolutionarily informed paradigm. These technological advancements are expected to enhance the quality of oncological resections, including complete mesocolic excision, while minimizing postoperative complications and improving long-term outcomes.

Emerging innovations such as deep learning-based hyperspectral imaging systems offer the potential to distinguish anatomical layers with high accuracy, thereby supporting complex surgical tasks and improving intraoperative decision-making. The ability of AI systems to autonomously identify critical surgical phases and provide real-time guidance represents a significant step toward fully integrated, digitally assisted cancer surgery.

However, the successful implementation of these advanced technologies depends on continuous refinement through large-scale, multi-center clinical research. Ensuring their reliability across diverse healthcare settings remains a key priority. Equally important is the establishment of robust ethical frameworks that align technological innovation with patient-centered care, transparency, and accountability.

Future progress will rely on sustained interdisciplinary collaboration, increased investment in clinical research, and the development of adaptive regulatory frameworks that can accommodate rapidly evolving technologies. Enhancing human–machine interfaces, including the integration of haptic feedback systems, may further improve surgical precision and decision-making in complex oncological procedures.

Addressing current limitations, such as the lack of standardized annotated surgical video datasets and variability in intraoperative workflows, will be critical for advancing real-time AI-assisted surgical systems. Ultimately, maintaining a balance between human expertise and machine intelligence will be essential to ensure trust, safety, and optimal patient outcomes in the evolving landscape of precision surgical oncology.

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Ethics approval: Not Applicable. The research work and the report were made in an ethical and responsible manner.

Consent to participate: Not Applicable.

Consent for publication: Not Applicable.

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