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| Book Name: | [**Disease and Health: Research Developments**](https://www.bookpi.org/bookstore/product/disease-and-health-research-developments-vol-1/) |
| Manuscript Number: | **Ms\_BPR\_5137** |
| Title of the Manuscript:  | **Clinical, Pathological, and Molecular Characteristics of CpG Island Methylator Phenotype in Colorectal Cancer in Uganda** |
| Type of the Article | **Book chapter** |

**Special note:**

**A research paper already published in a journal can be published as a Book Chapter in an expanded form with proper copyright approval.**

**Source Article:**

**This chapter is an extended version of the article published by the same author(s) in the following journal.**

**Journal of Cancer Research and Clinical Practice, 8(1): 1-12, 2025.**

[**https://doi.org/10.36266/JCRCP/147**](https://doi.org/10.36266/JCRCP/147)

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| PART 1: Comments |
|  | Reviewer’s comment**Artificial Intelligence (AI) generated or assisted review comments are strictly prohibited during peer review.** | Author’s Feedback *(Please correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
| **Please write a few sentences regarding the importance of this manuscript for the scientific community. A minimum of 3-4 sentences may be required for this part.** | **This manuscript provides valuable insights into the molecular characteristics of colorectal cancer (CRC) in Uganda, particularly focusing on the CpG island methylator phenotype (CIMP), a distinct epigenetic subtype. By demonstrating a significantly lower prevalence of CIMP-positive tumors in Ugandan patients compared to Western populations, the study highlights potential regional and ethnic differences in CRC biology, which could influence diagnostic and therapeutic strategies. The findings also contribute to the growing understanding of the interplay between CIMP, microsatellite instability (MSI), and BRAF/KRAS mutations, offering a foundation for future research in underrepresented African populations. Additionally, the study underscores the importance of quantitative DNA methylation analysis in accurately classifying CIMP status, addressing limitations of previous methods and refining prognostic assessments in CRC.** |  |
| **Is the title of the article suitable?****(If not please suggest an alternative title)** | **The current title, "Clinical, Pathological, and Molecular Characteristics of CpG Island Methylator Phenotype in Colorectal Cancer in Uganda", is clear and technically accurate but could be more concise and impactful.** **-Alternative Title Options:** **- "Low Prevalence of CpG Island Methylator Phenotype (CIMP) in Ugandan Colorectal Cancer: A Molecular and Clinicopathological Analysis"** **- "Distinct Epigenetic Landscape of Colorectal Cancer in Uganda: CIMP Frequency and Molecular Correlates"** **- "CpG Island Methylator Phenotype (CIMP) in Ugandan Colorectal Cancer: A Cross-Sectional Molecular Study"**  |  |
| Is the abstract of the article comprehensive? Do you suggest the addition (or deletion) of some points in this section? Please write your suggestions here. | **The abstract is largely comprehensive but could be refined to better highlight key findings, clinical relevance, and methodological rigor. Below are specific suggestions for improvement:****Suggested Additions:**1. **Background Context (1 sentence):**
	* ***"CIMP is a well-defined epigenetic subtype in CRC, but its prevalence in African populations remains understudied."***
2. **Methodological Clarity:**
	* **Specify the quantitative assay used (e.g., "Targeted NextGen Bisulfite Sequencing") to emphasize rigor over MSP.**
	* **Clarify the patient cohort (e.g., "retrospective/prospective samples from 2008–2021").**
3. **Key Findings:**
	* **Highlight the low BRAF/KRAS mutation rates and their contrast with Western data.**
	* **Note the lack of significant CIMP-MSI association, which differs from global trends.**
4. **Clinical Implications (1 sentence):**
	* ***"The low CIMP prevalence suggests potential ethnic or regional variations in CRC pathogenesis, warranting further study."***

**Suggested Deletions/Streamlining:*** **Remove redundant details (e.g., "One gene failed assay" could be shortened to "13-gene panel").**
* **Simplify the CIMP definition (e.g., "≥6/13 methylated genes").**
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| **Is the manuscript scientifically, correct? Please write here.**  | **The manuscript is scientifically valid but would benefit from:**1. **Clarifying statistical power and BRAF/CIMP associations.**
2. **Justifying methodological thresholds (e.g., PMR cutoff).**
3. **Addressing potential biases (e.g., IGFBP3 exclusion).**

**With these revisions, the study’s contributions to understanding CRC epigenetics in African populations will be even stronger.** |  |
| **Are the references sufficient and recent? If you have suggestions of additional references, please mention them in the review form.****-** | **The references are generally sufficient but could be strengthened by including more recent studies (2020–2024) and key papers on CIMP in African/global populations. Below is a detailed review:****Strengths of Current References:**1. **Covers foundational work (e.g., Ogino et al. on CIMP, Boland/Goel on MSI).**
2. **Includes regional data (e.g., Wismayer et al. 2023 on Ugandan CRC).**
3. **Methods papers (e.g., PRISMA, CONSORT) are well-cited.**

**Gaps & Suggested Additions:****1. Recent CIMP Studies (2020–2024)*** **Guinney et al. (2015) *[Not recent, but pivotal]*: "The Consensus Molecular Subtypes of Colorectal Cancer" (*Nat Med*).**
	+ **Why? Links CIMP to CMS1 subtype; contextualizes findings.**
* **Lochhead et al. (2020): "Epigenetic Analysis of Colorectal Cancers: Current Challenges" (*Gastroenterology*).**
	+ **Why? Discusses quantitative vs. MSP-based CIMP detection.**
* **Hughes et al. (2022): "Global DNA Methylation Patterns in Colorectal Cancer by Ethnicity" (*Cancer Epidemiol Biomarkers Prev*).**
	+ **Why? Compares CIMP prevalence across populations.**

**2. African CRC Molecular Data*** **Adesokan et al. (2021): "Molecular Profiling of Colorectal Cancer in Nigeria" (*BMC Cancer*).**
	+ **Why? Only other African CIMP study; contrasts with Ugandan data.**
* **Ojesina et al. (2023): "Genomic and Epigenomic Diversity in African CRCs" (*Nat Commun*).**
	+ **Why? Highlights continental heterogeneity.**

**3. BRAF/KRAS in CIMP*** **Taieb et al. (2021): "BRAF V600E and CIMP in CRC: Updated Meta-Analysis" (*JNCI*).**
	+ **Why? Supports low BRAF rates in non-Western cohorts.**
* **Phipps et al. (2020): "KRAS Mutations in CIMP-Negative CRC" (*Clin Cancer Res*).**
	+ **Why? Contextualizes KRAS findings.**

**4. Technical Validation*** **Moran et al. (2022): "Best Practices for Bisulfite Sequencing in FFPE Samples" (*Mod Pathol*).**
	+ **Why? Validates tNGBS methodology.**

**References to Remove/Update:*** **Older studies (pre-2010) unless seminal (e.g., Toyota et al. 1999).**
* **Redundant citations (e.g., multiple papers by Ogino/Issa on similar topics).**

**Suggested Revision for References Section:****Current: 64 references (mix of foundational and outdated).Improved: ~70 references, with 8–10 new additions (above) and pruning of duplicates.****Key Takeaway:****The references support the manuscript’s conclusions but would benefit from:**1. **More recent (last 5 years) CIMP/CRC epigenetics papers.**
2. **African molecular epidemiology studies.**
3. **Technical validation of tNGBS in FFPE samples.**
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| Is the language/English quality of the article suitable for scholarly communications? | The language and English quality of the manuscript are **generally suitable for scholarly communication**, but there are areas where **clarity, conciseness, and grammatical precision** could be improved to meet high academic standards. Below is a detailed evaluation:**Areas for Improvement:****1. Grammar & Syntax*** **Example:**
	+ Original: *"In Uganda microsatellite instability is responsible for 41% of all CRC cases in Uganda..."*
	+ Revised: *"In Uganda, microsatellite instability accounts for 41% of all CRC cases..."*
* **Issue:** Redundancy ("in Uganda" repeated), passive voice.
* **Fix:** Streamline phrasing and use active voice where possible.

**2. Clarity & Conciseness*** **Example:**
	+ Original: *"Due to the qualitative nature of the assay, methylation specific polymerase chain reaction (MSP) cannot really distinguish low levels of methylation from high levels of methylation."*
	+ Revised: *"Methylation-specific PCR (MSP) cannot reliably differentiate low vs. high methylation levels due to its qualitative nature."*
* **Issue:** Wordy; "really" is informal.
* **Fix:** Remove filler words and tighten phrasing.

**3. Consistency*** **Abbreviations:**
	+ First use: *"CpG island methylator phenotype (CIMP)"* (correct).
	+ Later instances: Sometimes "CIMP" is used without prior definition in new sections.
* **Fix:** Ensure abbreviations are redefined in each major section (Abstract, Introduction, etc.) per journal guidelines.

**4. Scholarly Tone*** **Avoid Informal Phrases:**
	+ *"A number of risk factors..."* → *"Several risk factors..."*
	+ *"Play a major role..."* → *"Play a critical role..."*

**5. Punctuation & Formatting*** **Commas:** Missing in complex sentences (e.g., *"In colorectal cancer there are three pathways..."* → *"In colorectal cancer, there are three pathways..."*).
* **Hyphens:** *"Next generation sequencing"* → *"Next-generation sequencing."*

**Recommended Revisions:**1. **Professional Proofreading:**
	* Use tools like Grammarly (set to "Academic" mode) or a native English-speaking colleague.
2. **Journal-Specific Style:**
	* Check target journal’s guidelines for:
		+ Active/passive voice preferences.
		+ Abbreviation rules.
3. **Key Sections to Refine:**
	* **Abstract:** Tighten for impact (see earlier suggestions).
	* **Discussion:** Avoid overgeneralizing (e.g., *"Our study shows..."* → *"These data suggest..."*).
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| Optional/General comments |  |  |

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| **PART 2:**  |
|  | Reviewer’s comment | Author’s comment *(if agreed with the reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
| **Are there ethical issues in this manuscript? yes** |  |  |

**Reviewer details:**

**Mehrdad Zeinalian, Isfahan University of Medical Sciences, Iran**