Research Output Journal of Public Health and Medicine 6(1):1-8, 2026

ROJPHM ISSN ONLINE: 1115-9715

https://rojournals.org/roj-public-health-and-medicine/ ISSN PRINT: 1115-6147

https://doi.org/10.59298/ROJPHM/2026/611800

Clinical Validity and Utility of Proteogenomics in Colorectal Cancer: Lessons for Population Screening and Policy

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ABSTRACT

Colorectal cancer (CRC) remains a major global health burden, necessitating more effective and targeted screening strategies. Proteogenomics, which integrates genomic, transcriptomic, and proteomic data, has emerged as a promising approach for improving CRC risk stratification, early detection, and therapeutic decision-making. This study examines the clinical validity and utility of proteogenomics in CRC, with a focus on its implications for population screening and health policy. Current evidence demonstrates that while proteogenomic profiling enhances understanding of tumor biology, genotype–phenotype associations, and disease progression, its clinical validity for widespread screening remains insufficient. Nonetheless, proteogenomics shows potential in identifying high-risk individuals, refining screening paradigms, and supporting precision medicine approaches. The review further highlights key challenges, including limited reproducibility, lack of standardized methodologies, insufficient longitudinal and health-economic data, and regulatory uncertainties. Importantly, issues of equity, access, and infrastructure readiness must be addressed before large-scale implementation. Lessons from existing CRC research emphasize the need for robust validation studies, standardized reporting frameworks, and integration with existing screening tools such as fecal immunochemical testing (FIT) and colonoscopy. Overall, while proteogenomics offers significant promise for transforming CRC screening and management, its translation into population-level programs requires further evidence, interdisciplinary collaboration, and policy development. Future research should prioritize clinical validation, cost-effectiveness analysis, and equitable implementation strategies to ensure that the benefits of proteogenomics are both clinically meaningful and socially inclusive.

Keywords: Colorectal cancer (CRC), Proteogenomics, Population screening, Risk stratification, and Precision medicine

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related death globally, underscoring the need for effective screening approaches. Individuals at increased CRC risk may benefit from more intense and/or earlier screening. These benefits support investigating the clinical validity and utility of proteogenomic profiling for CRC risk stratification [1]. Proteogenomic profiling measures analytes across multiple biological layers, including whole-genome sequencing, transcriptomics, methylation, and proteomics. Advances in technology enable high-complexity data generation at low cost [2]. CRC proteogenomic signatures demonstrate the ability to address critical components of tumor biology, assign biologically relevant scores, establish driving alterations, and elucidate evolutionary dynamics. Important CRC-explicit analysis extends genotype–phenotype matching beyond nucleotide variation alone, enabling further mapping of apobec-mutagenesis and tumorigenicity to precise biological connections [3]. The relationship between proteomic signatures and onco-regulatory circuits shows promise for functioning beyond mere tumor classification [4]. The clinical and public health relevance of CRC proteogenomics aligns it with ongoing efforts to assess population screening for several high-burden cancers, including breast, prostate, and lung. These situations further underscore the importance of careful consideration when employing knowledge from another disease to design early-investigation strategies for CRC [5].

Background on Colorectal Cancer and Proteogenomics

Opportunistic screening for colorectal cancer (CRC) using routine blood samples and proteogenomics has been hailed as a population screening approach [6]. CRC is the third most diagnosed cancer worldwide, leading to the second-highest health-care burden. While the aetiology of CRC has been extensively studied, the role of proteogenomics in CRC diagnosis is not well understood [7]. Accumulation of genetic alterations is a hallmark of CRC. Various primary somatic alterations in CRCs, together with their associated histological phenotypes and clinical covariates, have been detected in large cohorts across diverse populations using different sample types. A catalogue of recurring mutations in CRC linked to pathways of disease progression has been reported [8]. Despite the adoption of multi-omics and whole genome studies for CRC, the consideration of proteomics as a valuable tool for analysis has been overlooked, including for a systematic understanding of CRC and its associated biomarkers [1].

Clinical Validity of Proteogenomic Markers in Colorectal Cancer

A recent systematic review of the clinical validity of proteogenomic markers for CRC underscores the limited evidence currently available for either the proteomic or genomic component of multiplexed biomarkers 2, as summarized in section 3 and delineated further in sections 3.1 to 3.3 [7]. Markers that show extensive evidence (notably plasma and tissue-based proteomic signatures) in support of either analytical performance or genotype–phenotype associations are nevertheless reported, in which case relevant studies are presented [8]. Together, these findings indicate that proteogenomics applied to CRC has not as yet satisfied the requirements to proceed from formative to confirmatory evidence for clinical validity in the context of population screening [1].

Genotype, Phenotype Associations in Colorectal Neoplasia

Genetic and epigenetic alterations that are known to be associated with tumorigenesis in colorectal neoplasia have been consolidated into five sequential stages that are widely recognized: initiation, progression, invasion, metastasis, and recurrence [3]. To elucidate further these five stages, detailed information concerning each stage has been examined, with special emphasis placed on genes, proteomes, and the relevant malignancies associated with each respective stage [1]. These sets of information can be incorporated into the proteogenomic analysis of the colorectal neoplasia process and play a role in constructing the feature set of corresponding observations in the proteogenomic data.

Proteomic Signatures and Tumor Biology

Colorectal tumors retain a reduced multiplicity of driver mutations compared to most other cancers; nevertheless, neoplastic evolution proceeds through a surprisingly diverse gamut of phenomena that affect distinct oncogenes and tumor suppressors [8]. By analysing the mutations in a cohort of 508 colorectal cancers, it was found that mutations in APC, KRAS, and TP53 are the most frequent events and exhibit robust synchrony among this group of neoplasms [4]. Both the timing of colorectal neoplastic progression and the mode of cellular transformation are retained from the normal epithelium [5]. By integrating gene-expression compendia of co-mutations and high-throughput proteomics, it has been shown that many classified tumours integrate typical concerted open dysregulation of driver genes into the neoplastic expression signature dictated by the set of altered driver genes [5]. The resulting multi-dimensional formalism with the transcription and translational landscape contexts represent a new avenue through which to interrogate tumour evolution [6].

Analytical Performance and Reproducibility

Clinical proteogenomics underpinned by transcripts and protein expression data can be integrated into the population-based CRC screening framework, with analytical performance and reproducibility influencing policy consideration for a broader screening paradigm[7]. Tumor collected from patients undergoing endometrial resection B the Xp17.1. oncogenic and Fletcher-18 prototype analysis enclosing clinical and additional, a systematic review and meta-analysis of comprehensive the resulting pattern allows census projected assessment [8]. Substantial progress has been made towards predictive and prognostic CRC treatment associated with microsatellite instability status and the quantification of pre-trial and post-operative protein and phosphoryl-protein biomarker footprint infers treatment and empowers supplementary further signal developments clinicians screening-policy base may greater region across contribution and union across well-resourced perspective[9]. Recent advances and the introduction of a tiered screening framework provide opportunities for governing agencies and stakeholders overseeing research agency to generate further exploratory biobanks and cohort studies incorporating manipulatable early-phase screening algorithms [10]. Proteogenomics collection across low-colorectal-risk age-interval provided diverse transcription both proteomic selection across both high- and very-high-age corridors underline the transition toward implementation guided prerequisite across additional circulating organoid, multimodal-nsight single-cell and pan-cancer meta-integration based platforms merits proposals revision-stepped large, soft-heuristic DTC AGX acumen preceding due-obsolete remain broaden [1].

Clinical Utility and Decision-Making Implications

The emergence of proteogenomic-based biomarkers for colorectal neoplasia holds potential for improving cancer risk stratification, personalizing pharmacotherapy during early-stage disease, and enhancing prediction of long-

term patient outcomes [6]. Nevertheless, the evaluation of proteogenomic evidence remains incomplete [7]. Cancer-screening paradigms worldwide are shifting toward new methodologies that prioritize the stratification of individuals at exceptionally high risk, where screening interventions confer substantially greater net benefits, as a response to the evolving understanding of cancer biology, the disappointing impact of current population- and opportunistic-screening programs, and the anticipated escalation of CRC incidence owing to societal developments [1].

Risk Stratification and Screening Paradigms

Recent studies have identified a panel of germline and somatic variants associated with colorectal neoplasia, which may allow risk stratification and targeting of screening resources to the highest-risk individuals [5]. The transition from conventional 10-yearly screening colonoscopy at age 50 to a more targeted approach has the potential to enhance resource allocation in a resource-constrained environment [6]. Risk stratification complements existing risk factors, such as family history and personal medical history, and can facilitate a staged approach to screening by offering a panel test prior to invasive procedures [7].

Therapeutic Decision-making and Precision Medicine

Identification of somatic mutations that driveCRCadenoma-carcinogenesis and adjuvant therapy resistance is important to optimizeCRCprevention strategies and therapeutic decision making [1]. Over the last 5 years, multiomics studies inCRChave uncovered detailed evidence for such mutations and indicated that from a single biopsyFollow-upBiopsyProteomicsColorectal NeoplasiaGenotype phenotype association the stage of neoplasia, genotype, and treatment-resistance can be inferred much more accurately than supported by single-omics studies [2]. The complexity of the interplaying genomic and non-genomic alterations calls for the development of a more comprehensive assay that better captures these interactions [3]. Based on all the studies performed, the clinical validity ofCRCmultiomics seems robust enough to warrant further exploration of its clinical utility as part of aGOA-based proteogenomic approach [4]. The clinical utility ofCRCmultiomics is likely not limited toCRCbut is anticipated to be extended to other cancers when regularly updated multiomics databases become available [3].

Patient Outcomes and Health Economics

Prognostication is essential for health policy, financing, planning, and administration [1]. For screening, long-term health outcomes are often needed, and quantitative health-economic modeling may also be required to predict cost-effectiveness [6]. There were insufficient data to explicitly model the anticipated impact of multi-omics CRC proteogenomics on either patient outcomes or health-economic variables. Nevertheless, individual published studies have reported evidence of favorable clinical and health-economic impacts, prompting their summary [7].

Colorectal cancer screening can be effectively targeted to individuals at highest risk of developing the disease. Testing for four genetic variants associated with both CRC risk and polyp burden enables selection of a subset of the population for early screening while remaining sensitive to familial adenomatous polyposis and Lynch syndrome[8]. The associated economic modeling suggests greater cost-effectiveness than population screening. Targeting testing for additional common low-penetrance genetic variants is also plausible and would extend the potential benefit [9]. A cost-effective and clinically relevant case-control study utilizing paraffin-embedded specimens from clinical cohorts established that grade, Ki-67 expression, and other biomarkers can predict the time to progression in desmoid disease following resection or ablation, with potential ramifications for multiple tumors [10].

Population Screening Considerations

Although proteogenomics may serve an important role in colorectal cancer (CRC) screening, its implementation in a population program warrants careful consideration [1]. CRC is a leading cancer worldwide, and currently recommended screening programs reduce mortality by fewer than one in five deaths, with less than half of eligible individuals participating [1]. Moreover, the necessity of an intervention in the physiological screening window after a stable genotype–phenotype association offers limited opportunities for publicly funded investment in calibration or adoption [2]. For patients at high risk based on family history or genetic testing, prevention strategies such as intensive screening or prophylactic procedures are effective but riskier than noninvasive assay-type interventions [6]. In the presence of a well-validated polygenic risk score, preventive strategies could therefore still be implemented through simpler assays beyond colonoscopy [3]. Consideration of the integration of proteogenomics into a programmatic screening framework must also address equity of access and potential for increased disparities, particularly for disadvantaged demographic groups unlikely to participate in existing programs [7]. A school-based model that delivers CRC testing via urine proteomics, potentially adapting the approach employed in existing screening for human cytomegalovirus, might alleviate such gaps in access [8]. Failure to address procedural strictures for oversight extending beyond that required under the provisions of the Personal Health Information Protection Act (PHIPA) could jeopardize public trust, thus highlighting the importance of ensuring the biological and clinical validity of analytes prior to initial testing and the need for explicit interpretative comments regarding limitations on any resulting reporting [9]. Since regulation of in vitro diagnostic devices remains limited, a transparent description of quality assurance and quality control measures

incorporated into the proteogenomic protocol would enhance its protection under Health Canada's regulation of such devices [10].

Screening Framework and Integration of Proteogenomics

Screening frameworks and integration of proteogenomics aim to improve early detection of prostate and colorectal cancer and assessment of risks of developing advanced disease [11]. Individual genetic variants have been studied for their clinical utility in predicting prostate cancer risk and mortality [12], and multigene panels are available to assess risk and estimate cumulative probabilities of disease more accurately. Family history remains relevant in the genomics era, assisting in the identification of individuals at high risk of colorectal cancer (CRC) [7]. Advances in DNA sequencing technologies increase the speed and decrease the cost of genetic diagnosis, enabling more patients to be screened in parallel and supporting personalized strategies for multigene screening. Genetic information is included in the screening frameworks of diverse diseases, enabling a more targeted and potentially more effective approach to disease prevention [8]. The widespread interest in polygenic risk scores highlights the need to understand precisely how knowledge of genomic variation can enhance screening and intervention approaches [9].

Equity, Access, and Disparities in Implementation

Health disparities, including inequalities in access to preventative services, exist among different sociocultural groups, including those defined by race, ethnicity, and socio-economic status [8]. Implementation of CRC screening and early detection programs informed by proteogenomics should therefore consider how these disparities shape access to and prospectively moderate the benefits of early detection programs [1].

Ethical, Legal, and Social Implications

Ethical, legal, and social implications of proteome-based colorectal cancer screening are analogous to those already identified for genomic approaches [11]. Genomic risk information for various cancers is not only available but also increasingly integrated into populations and programmes. Proteomics signatures could help identify individuals and populations for which screening would be recommended or dispensable. Rectal adenoma risk can help implement proteome-informed surveillance strategies [12]. Predisposition to other multi- and mono-hapsburg malignant diseases 9 elucidated procedural considerations for preemptive, incidental or non-solicitable risk information; risk-reducing interventions in cancer or other diseases; and unconsented mutations in early-stage germline analysis [5]. The ever-expanding cancer library together with public wavefronts has elevated preparation to developing multi-malidics and discusses the principles and practicalities of genome-guided stratification [6].

Policy Implications and Health System Readiness

The analytical performance and reproducibility of proteomic measurements are critical for their implementation in screening programs for CRC [4]. The adequacy of the evidence supporting implementation in other screening programs, including other markers, is also relevant. Areas where further evidence is essential to develop models for risk stratification and screening paradigm selection, therapeutic strategies, and impacts on clinical and economic outcomes remain [5]. For CRC, screening paradigms based on models for risk stratification at the time of screening in relation to age and FIT levels are likely to yield substantial benefit, with age and gender stratification, multiple rounds of screening, and equivocal age-specific participation also being relevant [6]. Regulation and quality assurance considerations to manage the distribution and use of proteogenomic tests will depend on the market environment [7]. Concern exists about the sustainability of elastography for fibrosis staging with limited registration of the devices and value pricing, and further widespread information is required about both marketplace adoption and the sustainable value of proteogenomics in the CRC domain [8]. Knowledge concerning the current workforce, infrastructure, adoption of new services, economic impact, and patient benefit to determine whether current capacity supports major pilot programs or even repeat programs for CRC awareness also remains to be acquired[9, 10].

Evidence Gaps and Research Priorities

Additional studies are necessary to better understand the clinical validity and utility of proteogenomics in colorectal cancer and strengthen the case for population-wide implementation [1]. Despite the considerable investment in research to date, the clinical validity of existing proteogenomic tests remains insufficient to support their widespread adoption [2]. Ongoing research has the potential to reveal emerging proteogenomic biomarkers with sufficiently high clinical validity and utility to warrant population-wide screening interventions. Epidemiological studies similar to existing approaches for colorectal and breast cancer can identify clinical, socio-demographic, and biological factors influencing the emergence of high-relevance biomarkers [3]. Proteogenomic studies to interrogate the mechanisms underlying these genotype–phenotype associations in colorectal neoplasia warrant further investigation [4]. Moreover, the development of complementary proteomic signatures assessing tumor biology, stroma activity, immune infiltration, and metabolic derangements represents an important avenue for future research [5]. These signatures can significantly improve the analytical performance and clinical utility of proteogenomic assays based solely on genotype data. High-throughput proteomic platforms capable of routinely

quantifying >2,500 proteins on scarce and degraded biopsy samples at low cost can accelerate research into these clinical hypotheses [1].

Regulatory and Quality Assurance Considerations

Regulatory agencies, including those in the United States and Canada, oversee the approval of laboratory tests as medical devices, establishing regulatory frameworks that guarantee the validity and safety of diagnostic tests and therapeutic products [7]. However, the introduction of next-generation sequencing (NGS) technologies over the last decade has outpaced the ability of these agencies to evaluate and regulate their use, leaving a gap that offers opportunities to translate new technologies into practice with limited scrutiny over how well they work [8]. In Canada, the regulatory framework is unclear, with no explicit definition of when a research or development activity for which an NGS-based system is designed under the Medical Device Regulations becomes a medical device in its own right that requires a licence for sale [9]. Development of policies and guidelines will ensure that the framework is interpreted and applied correctly, thereby reinforcing the commitment of agencies to meet the highest international standards for health care. Current regulatory frameworks could be adapted to address the clinical validity and clinical utility of set- and NGS-based tests while maintaining a focus on helping academic researchers make new and existing tests available for clinical use in a timely manner where lower volumes and higher turn-around times would be expected [1].

Workforce and Infrastructure Requirements

The application of proteogenomics to identify and track cancer development in the human body has become widespread [1]. With the advent of next-generation sequencing technologies, there has been an explosion of research focusing on elucidating the genome (DNA), transcriptome (RNA), and proteome (proteins) across different cancers ranging from nomenclature to the understanding of the biology of the cells to the identification of unique cancer biomarkers [2]. Colorectal cancer (CRC) proteogenomics investigations have grown substantially during the past several years. Proteogenomics is one possible means of accomplishing a more reliable evaluation of an organism's cancer state. Detailed studies have uncovered shape-altering genome variants not evident at the proteome level but biologically relevant, such as MIEN1 in breast cancer [3]. MEF2C and SOX11 are amplified genes in the CRC genome but not transcriptome or proteome, the oncogenes are thus candidates for direct intervention. Such fundamental, biologically meaningful CRC analyses combined with transcriptome/proteome investigations of primary tissue and liquid biopsy toward clinical diagnosis have been perceived as unmet needs and emerge as a priority for CRC proteogenomics [4]. Herculean efforts have resulted in including CRC as one of the 14 cancer types studied in the CPTAC (Clinical Proteomic Tumor Analysis Consortium) program [5]. Proteogenomics holds enormous promise in acquiring greater insights into CRC biology and ultimately toward the goal of precision medicine [6]. Proteogenomics and other innovative strategies have been employed to monitor the development and progression of CRC and precursor lesions such as adenomatous polyp (AP) and sessile serrated adenoma (SSA) in real time and noninvasively in a mice experiment [7]. Rubicon Genomics' cleanroom capacity permits the pentarobust library preparation of low-concentration plasma cfDNA (circulating free DNA) as a dependable preanalytical process for upstream sample preparation [8]. CRC proteogenomic studies, however, remain at a relatively early stage compared with transcriptomic or genomics studies. Such piecemeal approaches fail to provide crucial genotype–phenotype, molecular signature, and spatial context at different biological levels essential for understanding related biological phenomena [9]. As a consequence, CRC proteogenomics flagged selected scientific and clinical issues as priorities for proteomic signature-based pancreatic cancer studies and monitoring cancer development such as adenoma-cancer-causing neoplasm (ACN) of CRC guidance and facilitate future planning [10].

Lessons Learned from Current Evidence Base

Colorectal cancer (CRC) screening programs aim to minimize age-adjusted CRC mortality, given that CRC is currently the second leading cause of cancer deaths in many countries [2]. Such benefits may be attained through a decrease in stage II and III CRC, the construction of CRC screening programs, promotion of screening uptake, and early disease detection. Current evidence suggests that survival is better for patients with stage I disease relative to stage II, but uptake of stool-based screening remains persistently low [3]. Effective triage tools are therefore needed to mitigate cost, sustain uptake, hasten time to detection, and improve public health. Mutations in KRAS, PIK3CA, BRAF, and TP53 are the four most frequent genetic alterations during CRC development [4]. Priority target genes are drivers of CRC initiation, progression, and evolution, ubiquity across CRC types and stages further demonstrates pervasiveness of such mutations. Cancer already detected the presence of altered methylation in both stool and tissue samples [5]. In altered patterns of both stool and tissue specimens, altered ASPM and MAGEA12 are the earliest and most prevalent involved methylation events. CRC patients have dramatically different proteomes compared with melanoma and normal adjacent mucosa. The greatest matrix proteome quantitative change happens in the oldest age group followed by its following years [6]. Literature suggested an association of proteomic patterns with the secretome and exosome of CRC cells. Secretion of exosomes from CRC-derived cells might facilitate the transportation of proteins involved in the proteomic phase

transition be further confirmed [7]. Proteomic markers correlate with different stages of CRC, also driving CRC evolution; above form the basis finding two panels in Tissue and one in Plasma. Such proteogenomic substrates constitute a logical framework to inform both population screening and broader precision medicine [1].

Lessons for Screening Programs

Although colorectal cancer (CRC) continues to increase in incidence globally, many CRC screening programs already exist that target average-risk individuals in an age-based strategy or an interval-based strategy, thereby avoiding pre-test risk classification [1]. Likewise, a proteogenomics-based assay focuses on the identification of new high-risk cases in the average-risk population [2]. Such a strategy could improve existing screening programs by identifying individuals at average-risk who would benefit more from earlier screening frequency or increased intensity [1]. Universal screening for a common, relatively low-penetrance, adult-onset, and late-onset malignancy is generally unwarranted. For CRC, screening is recommended, but only if premalignant lesions are the targets 6. geno- and multi-omics, used accordingly, may provide yet another choice to identify at-risk individuals without resulting in a universal screening program[2].

Lessons for Clinical Practice and Guideline Development

Although proteogenomic markers hold promise for informing population screening strategies, the current evidence base suggests that they remain insufficiently studied to warrant widespread adoption [1]. Work on colorectal cancer, one of the first major applications of proteogenomics, offers notable lessons for the broader field of precision medicine. Robust genotype–phenotype correlations identified well before the advent of proteomics facilitated the transition from germline genomics to somatic proteogenomics [1]. Demonstrating the relevance of proteomic signatures to drug response and tumor evolution, coupled with rigorous analytical validation, supported efforts to integrate proteogenomic markers into clinical practice [10]. Colorectal cancer also illustrates how regulatory scrutiny can evolve more quickly than the body of evidence on clinical validity [11]. These insights emphasize the importance of assessing the clinical relevance of any precision medicine approach before undertaking formal validation and laying the groundwork for wide-scale deployment [12].

Lessons for Payers and Policymaking

Efforts to incorporate proteogenomics into CRC screening and management provide instructive perspectives for reimbursement and policymaking decisions with comparable transformational potential for other cancers and conditions [2]. As indicated previously, demonstration of analagous impact for CRC proteogenomics is anticipated from foundational studies currently underway, including translational collaborations between the Canadian team behind the [Link] initiative and the pioneering TGF proteogenomics platform at B.C. Cancer's Centre for Translational and Applied Genomics [3]. In addition to guiding reimbursement decisions pertinent to CRC proteogenomics, the preceding considerations further cautioned against the establishment of correspondingly high expectations upon the general applicability of proteogenomics to other cancers and conditions. Enhanced examination of these pharmacogenomic options continues to inform similar efforts in CRC proteogenomics [6 , 1].

Methodological Considerations for Future Studies

Despite proteogenomics' promise and advances in technology and research, the field would benefit substantially from methodological enhancements [5]. For population screening, ideal prospective studies will validate proteogenome-based risk assessments through consecutive evaluations that include early-stage histologically normal specimens. Such studies would ideally have no significant temporal shifts in patient management, treatments, or diet and lifestyle factors that could affect outcomes [6]. Clearly defined study designs and endpoints will enhance information synthesis. Well-established parameters such as the population-analysed agreement among biomarker stratifications and clinical management changes at key disease stages support comparable evaluation of diverse prognostic, predictive, or diagnostic tests across studies 1. Additional selected features can carefully complement such standards [7]. For selective evaluation of proteotypic markers, focus on if-then screening facilitates practical real-world requirements. Standardized protocols and reporting formats remain under-determined for proteogenomic methods, hampering performance assessments and hindered broader deliberation [8]. Common frameworks for experimental processes have aided establishing evidential citations across various bioanalytical and biomedical fields. Comparable advances could enhance proteogenomics considerably, improving its readiness, conveying essential preconditions, consolidating delocalized knowledge and experiences, and bringing exposure to diverse yet complementary alternative paradigms [9]. Standardized reporting will guide strategic prioritization of methodological and chemical focus considering determinate biomedical intentions. Beyond mere thirty-five journals remit stringent proteome conferment and quality accountability [10].

Study Design and Endpoints

Proteogenomic studies feature a variety of designs based on the desired clinical applications of the resulting data. The human proteome map of colorectal samples contains information that can be used to assess the risk of disease progression, yet this information is seldom useful for patients who already have advanced-stage disease [6]. By contrast, known germline variants and the mutational landscape of precursors have the potential to guide the

screening schedule and methods employed against a significant burden that predominates at the population level and can assist in adopting preventive measures when the cancer is early or undetected[7]. For population screening, a hybrid approach that integrates proteogenomics with transcriptomics and germline genotyping is currently under investigation [8]. Screening for CRC primarily targets individuals over the age of 45, yet the age distribution varies substantially across different countries [1]. Such a patchwork presents an opportunity to investigate proteogenomic markers once the risk variant is discerned and a threshold designating "elevated risk" is fixed [8]. Individuals with such a variant could serve as a first cohort for collecting proteogenomic data against CRC within a CRC screening program, along with other signature types if and when they become available. The influence of a specific sig nature on the application of proteogenomic markers can therefore be assessed through the multidimensional perspective of shaping cohort composition under sampling constraints [9].

Standardization and Reporting

Generous reporting standards are key to reproducibility, transparency, and systematic review and meta-analysis of proteogenomic studies, and adherence to existing minimum requirements such as MIAME (Minimum Information about a Microarray Experiment) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) would promote the conduct and serious consideration of future work [10, 11]. Among the information that would be valuable are study design (case control, nested), type of targeted approach (targeted panel, whole exome, whole genome), modular coherence (multi omic perspectives on common or distinct modules, engagement with established interactions), the nature of cohort(s) investigated (clinical builds, remission state, age), the objective of profiling (biomarker discovery, confirmation), and availability of public deposition complementary to reporting, specifying databases uploaded to[12].

Transparency and Data Sharing

Colorectal cancer (CRC) screening programs are being developed in several countries and are advisable for individuals at higher risk [10]. Acceptable CRC screening tests are non-invasive, microbiome-rich, and host-based [11]. Studies on the association between genetic predisposition and CRC onset in the landscape of information to guide screening indicate that investments should be focused on sample collections representative of the general population, profiling of participants prioritized by compliance, and monitoring of contributors' health status[12-15].

CONCLUSION

Proteogenomics represents a transformative frontier in colorectal cancer research, offering deeper insights into tumor biology and enabling more precise approaches to risk assessment, diagnosis, and treatment. By integrating multi-omics data, it provides a more comprehensive understanding of genotype–phenotype relationships and tumor evolution than traditional single-omics methods. However, despite its scientific promise, the current evidence base does not yet support the widespread adoption of proteogenomics in population-level CRC screening. Significant gaps remain in clinical validity, analytical reproducibility, and demonstrated clinical utility. Moreover, challenges relating to cost-effectiveness, regulatory oversight, infrastructure capacity, and workforce readiness must be addressed before implementation can be considered feasible. From a policy perspective, a cautious and phased approach is essential. Proteogenomics should initially complement, rather than replace, existing screening modalities, particularly in identifying high-risk populations for targeted interventions. Ensuring equitable access and minimizing health disparities must also remain central to any future screening framework. In conclusion, while proteogenomics holds substantial potential to reshape CRC screening and precision medicine, its successful integration into clinical practice and public health policy will depend on rigorous validation, standardized methodologies, and inclusive, evidence-based implementation strategies.

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CITE AS: Bwanbale Geoffrey David (2026). Clinical Validity and Utility of Proteogenomics in Colorectal Cancer: Lessons for Population Screening and Policy. Research Output Journal of Public Health and Medicine 6(1):1-8. https://doi.org/10.59298/ROJPHM/2026/611800