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EDITORIAL

Expanding the genetic landscape of colorectal polyposis: Progress and challenges

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Abstract

The study by Dos Santos *et al* marks a significant advancement in understanding the genetics of colorectal polyposis, particularly within the underrepresented Brazilian population. Utilizing whole-exome sequencing in 27 patients with unexplained polyposis, the researchers identified 16 candidate genes in 44.4% of cases-an impressive outcome given strict exclusion criteria. Many identified variants were linked to the Wnt/β-catenin signaling pathway, reinforcing their biological relevance. However, the study underscores key challenges in genomic medicine, especially the gap between gene discovery and clinical application. A substantial proportion of variants (60.1%) were classified as of uncertain significance, and the absence of functional validation or segregation analysis limits clinical interpretation. Notably, the potential for oligogenic inheritance complicates traditional monogenic models of hereditary cancer risk. The study's focus on a genetically diverse Brazilian cohort emphasizes the need for population-specific genomic resources and interpretation guidelines. Moving forward, functional studies, including organoid models, loss-of-heterozygosity analyses, and genotype-phenotype correlations, are essential to validate findings. Clinically, discovering novel candidate genes may inform future screening and testing pro-

tocols, though careful consideration is needed to manage uncertain results. Overall, the study represents a critical step in polyposis genetics, highlighting both progress made and the work still required for clinical translation.

Key Words: Colorectal tumor; Whole exome sequencing; Genetic heterogeneity; Wnt/beta-catenin pathway; Genetic variant

Core Tip: This study applies whole-exome sequencing to a Brazilian cohort with unexplained colorectal polyposis, identifying candidate germline variants in 44.4% of patients. The findings highlight the involvement of genes in the Wnt/β-catenin signaling pathway, suggesting biological relevance to colorectal cancer development. Notably, the study addresses the potential for oligogenic inheritance, challenging the traditional monogenic framework for hereditary cancer syndromes. The work emphasizes the need for functional validation, population-specific variant databases, and careful clinical interpretation to translate genetic discoveries into meaningful patient care.

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INTRODUCTION

The colorectal polyposis landscape has undergone significant transformation over the past two decades, evolving from a relatively simple genetic paradigm dominated by *APC* and *MUTYH* mutations to a complex heterogeneous spectrum involving multiple genes and pathways. The manuscript by Dos Santos *et al*[1] exemplifies both the promise and challenges inherent in contemporary genetic research for polyposis syndromes, offering valuable insights into the expanding genetic architecture while highlighting persistent diagnostic gaps.

PROGRESS IN GENETIC DISCOVERY

The traditional understanding of polyposis genetics has been fundamentally challenged by advances in whole-exome sequencing (WES) and multi-gene panel testing. While *APC* mutations account for the majority of classic familial adenomatous polyposis (FAP) cases, with detection rates of 70%-80% in patients with ≥ 1000 adenoma, and biallelic *MUTYH* mutations represent the second most common cause at approximately 7% of adenomatous polyposis cases, a substantial proportion of patients remain genetically unexplained[2,3].

Recent studies have expanded the genetic spectrum to include genes such as *POLE*, *POLD1*, *NTHL1*, *MBD4*, *MSH3*, and *MLH3*[4]. The manuscript by Dos Santos *et al*[1] extends this paradigm further, identifying pathogenic or likely pathogenic variants in 16 novel candidate genes, including *ST7L*, *A1CF*, *DKK4*, *NTHL1*, *PNKP*, *PMS2*, and *FRK*, in 44.4% of their *APC*- and *MUTYH*-negative polyposis cohort. This represents a significant diagnostic yield that challenges the conventional notion of "unexplained" polyposis.

The identification of variants in Wnt/β-catenin signaling pathway genes such as *DKK4* and *A1CF* is particularly noteworthy, as dysregulation of this pathway is central to colorectal cancer development[5]. The authors' pathway enrichment analysis, revealing alterations in "negative regulation of protein adenosine diphosphate-ribosylation", provides mechanistic insight, as this process is involved in Wnt signaling pathway activation. These findings align with recent comprehensive genomic studies that have identified over 250 putative colorectal cancer driver genes, many previously unassociated with polyposis syndromes[6].

The current study's methodological approach represents current best practices in polyposis genetics research. The use of WES covering 203058 target regions across 19682 genes with a mean coverage of 150 × ensures comprehensive variant detection. The filtering strategy, requiring ≥ 30 reads, ≥ 25% variant allele fraction, and < 1% population frequency, helps distinguish genuine pathogenic variants from technical artifacts and common polymorphisms. However, there were a few limitations that warrant consideration. The lack of functional validation for most identified variants represents a significant constraint. While the authors applied American College of Medical Genetics and Genomics criteria for variant classification, many variants remain classified as variants of uncertain significance (VUS), comprising 60.1% of all identified variants. This high VUS rate reflects broader challenges in variant interpretation that plague the field of clinical genetics[7]. The absence of tumor analysis represents another limitation. Loss of heterozygosity analysis could have provided crucial evidence supporting the pathogenic role of identified germline variants. Additionally, the study's relatively small sample size (n = 27) limits statistical power for detecting rare variants and establishing genotype-phenotype correlations.

CLINICAL IMPLICATIONS AND DIAGNOSTIC YIELD

The diagnostic yield reported in this study (44.4% carrying at least one pathogenic/Likely pathogenic variant) is remarkably high compared to other recent studies. For context, a large United Kingdom (UK) study of 259 patients with 10-99 adenomas reported a 25.5% diagnostic yield for pathogenic variants, while studies focusing on patients with ≥ 10 adenomas typically report yields of 10%-30%[8]. This disparity may reflect differences in patient selection, with the Brazilian cohort potentially representing a more enriched population given the context of the specialized referral center. The finding that participants with pathogenic/Likely pathogenic variants tended to be younger at diagnosis (mean age 47 *vs* 55 years) aligns with established patterns in hereditary cancer syndromes. However, the difference did not reach statistical significance in this small cohort.

Notably, the lack of correlation between genetic findings and family history is intriguing and potentially concerning. This observation challenges traditional risk assessment models that heavily weight family history in determining genetic testing eligibility. Current National Comprehensive Cancer Network (NCCN) guidelines recommend genetic testing for patients with ≥ 10-20 cumulative adenomas, but the optimal threshold remains debated[9]. Table 1 compares diagnostic yields and pathway findings across ethnic cohorts of colorectal polyposis.

CONTEMPORARY CHALLENGES IN POLYPOSIS GENETICS

Despite technological advances, significant challenges persist in polyposis genetics. First, the "missing heritability" problem remains substantial, with approximately 20%-35% of patients meeting clinical criteria for polyposis syndromes lacking identifiable genetic causes[10,11]. While studies like Dos Santos *et al*[1] make important contributions to addressing this gap, the clinical actionability of many newly identified genes remains uncertain. Second, the interpretation of variants in emerging polyposis genes presents ongoing challenges. For genes like *NTHL1*, conflicting evidence exists regarding the cancer risk associated with monoallelic variants[4]. Third, the high rate of VUS (60.1%) reported by Dos Santos *et al*[1] is a cause for concern, as these findings are non-actionable in clinical practice and create significant anxiety and uncertainty for patients and clinicians[12]. The absence of functional validation data, such as from organoid disease models, clustered regularly interspaced short palindromic repeats-based screens, or loss-of-heterozygosity analyses in matched tumors severely limits the interpretability of these candidate variants. Fourth, the cost-effectiveness of expanded genetic testing remains a concern. While multi-gene panel testing has become more affordable, with costs decreasing from United States dollar (USD) 4000 in 2014 to approximately USD 200-500 currently, the clinical utility of identifying variants in genes with uncertain penetrance or actionability raises important health economic questions[13].

CURRENT TESTING STRATEGIES AND GUIDELINES

Professional guidelines have evolved to recommend multi-gene panel testing for polyposis evaluation, typically including *APC*, *MUTYH*, *POLE*, *POLD1*, and *NTHL1*[3]. The European Society for Medical Oncology guidelines specifically recommend panel testing, including these five genes, for patients with > 10 adenomas, while the NCCN guidelines suggest testing for patients with ≥ 20 cumulative adenomas[9,14].

However, significant variation exists in testing thresholds globally. UK guidelines recommend an individualized approach for patients with multiple colorectal adenomas (≥ 10 metachronous adenomas), considering factors such as age at diagnosis, family history, and total polyp burden[15]. Japanese guidelines take a more conservative approach, suggesting that genetic testing is not routinely necessary for typical FAP but may be considered for differential diagnosis[16].

Recent studies suggest that optimization of testing strategies could improve cost-effectiveness. A probability calculator incorporating polyp count and age has shown promise for identifying patients most likely to benefit from genetic testing [17]. Such tools could help address the challenge of low diagnostic yields in certain patient populations, particularly older patients with fewer adenomas.

EMERGING TECHNOLOGIES AND FUTURE DIRECTIONS

The integration of artificial intelligence (AI) and machine learning approaches represents a promising frontier in polyposis genetics. AI algorithms are already showing remarkable success in polyp detection during colonoscopy, with sensitivities approaching 95%-99%[18]. Extension of these technologies to genetic variant interpretation and patient risk stratification could significantly enhance diagnostic accuracy and clinical decision-making. Emerging high-throughput technologies, such as deep mutational scanning (typically used for functional evaluation of single amino acid mutations in a protein of interest), can help solve the VUS challenge *via* simultaneous and unbiased evaluation of large protein variant libraries, thus generating comprehensive genotype-phenotype functional maps. This opens up the possibility of classifying VUSs that have been observed thus far[19].

Whole-genome sequencing is increasingly replacing WES for comprehensive genetic analysis, offering the advantage of detecting non-coding variants, structural rearrangements, and copy number variations that may be missed by exome-based approaches[18]. The identification of *APC* promoter mutations and complex structural variants in a recent study by Yang *et al*[20] demonstrates the importance of comprehensive genomic analysis.

Table 1 Comparative diagnostic yields and pathway findings across ethnic cohorts in colorectal polyposis

Ref.	Country	Sample size (*n*)	Diagnostic yield (% with P/LP variants)	Major mutations identified	Key pathway findings
Dos Santos *et al*[1]	Brazil	27	44.4	*ST7L*, *A1CF*, *DKK4*, *NTHL1*, *PNKP*, *PMS2*, *FRK*	Wnt/β-catenin dysregulation; oligogenicity
Yang *et al*[20]	China	120	74.2	*APC*, *MUTYH*, *POLE*, *POLD1*, *PTEN*, *MLH3*, *SMAD4*	Structural variants, *APC* promoter mutations
Mak *et al*[8]	United Kingdom	259	25.5	*APC*, biallelic *MUTYH*, *POLD1*, *GREM1*, *MLH1*, *MSH2*	DNA repair, base excision repair

P/LP: Pathogenic/Likely pathogenic.

The emerging understanding of the gut microbiome's role in polyposis represents another exciting avenue. Recent evidence suggests that colibactin-producing *Escherichia coli* may account for a significant proportion of unexplained adenomatous polyposes, with approximately 30% of such cases harboring *APC* mutations associated with bacterial genotoxin exposure[4]. Figure 1 describes a multi-omics validation and clinical actionability pipeline for novel candidate genes to bridge the gap between genomic discovery and clinical implementation.

IMPLICATIONS FOR PERSONALIZED MEDICINE

The expansion of the genetic landscape of polyposis has implications for personalized medicine approaches. Genetic testing results increasingly inform surgical timing, surveillance strategies, and family counseling. However, identifying variants in genes with uncertain clinical significance poses challenges for genetic counseling and clinical management.

The study's identification of variants in genes like *FRK*, which encodes a tumor suppressor involved in *PTEN* regulation, illustrates the potential for discovering clinically relevant pathways. However, the clinical actionability of such findings remains unclear without clear evidence of penetrance, cancer risks, and appropriate management strategies. To address this, Food and Drug Administration-recognized frameworks, like the ClinGen Clinical Actionability curation process, can systematically evaluate and categorize new genes (*e.g.*, *FRK*) based on the strength of evidence supporting their association with polyposis and defined cancer risks. This would provide clinicians with much-needed information regarding surveillance intervals and management strategies for patients with variants in emerging genes[21].

The integration of multi-omic approaches, as demonstrated in recent studies of FAP, may provide a more comprehensive understanding of disease mechanisms and inform personalized treatment strategies. Such approaches could help distinguish passengers from drivers among the numerous variants identified in comprehensive genetic testing[22].

COST-EFFECTIVENESS CONSIDERATIONS

Economic evaluation of expanded genetic testing remains complex. While the cost of sequencing has decreased dramatically, the downstream costs of genetic counseling, increased surveillance, and potential over-treatment of patients with VUS must be considered. Cost-effectiveness analyses of Lynch syndrome screening suggest that targeted approaches with appropriate risk thresholds can achieve favorable cost-effectiveness ratios of USD 8000-26000 *per* quality-adjusted life year[23].

For polyposis syndromes, the cost-effectiveness equation is complicated by the variable penetrance of newly identified genes and uncertainty regarding appropriate surveillance strategies. Studies suggest that genetic testing yields of > 10% support current guidance for constitutional testing, but this threshold may need refinement as our understanding of genetic architecture evolves[8].

FUTURE RESEARCH PRIORITIES

Several critical research priorities emerge from this analysis. First, large-scale population-based studies are needed to establish the true prevalence and penetrance of variants in newly identified polyposis genes. Such studies should include diverse populations to ensure the broad applicability of findings.

Second, functional validation studies are essential for establishing the pathogenic role of candidate variants. The high rate of VUS in current studies underscores the need for robust functional assays and mechanistic studies to support variant classification.

Third, the development of clinical decision support tools incorporating genetic, clinical, and potentially microbiome data could optimize patient management and improve cost-effectiveness. AI-powered risk prediction models could help stratify patients for appropriate testing and surveillance strategies.

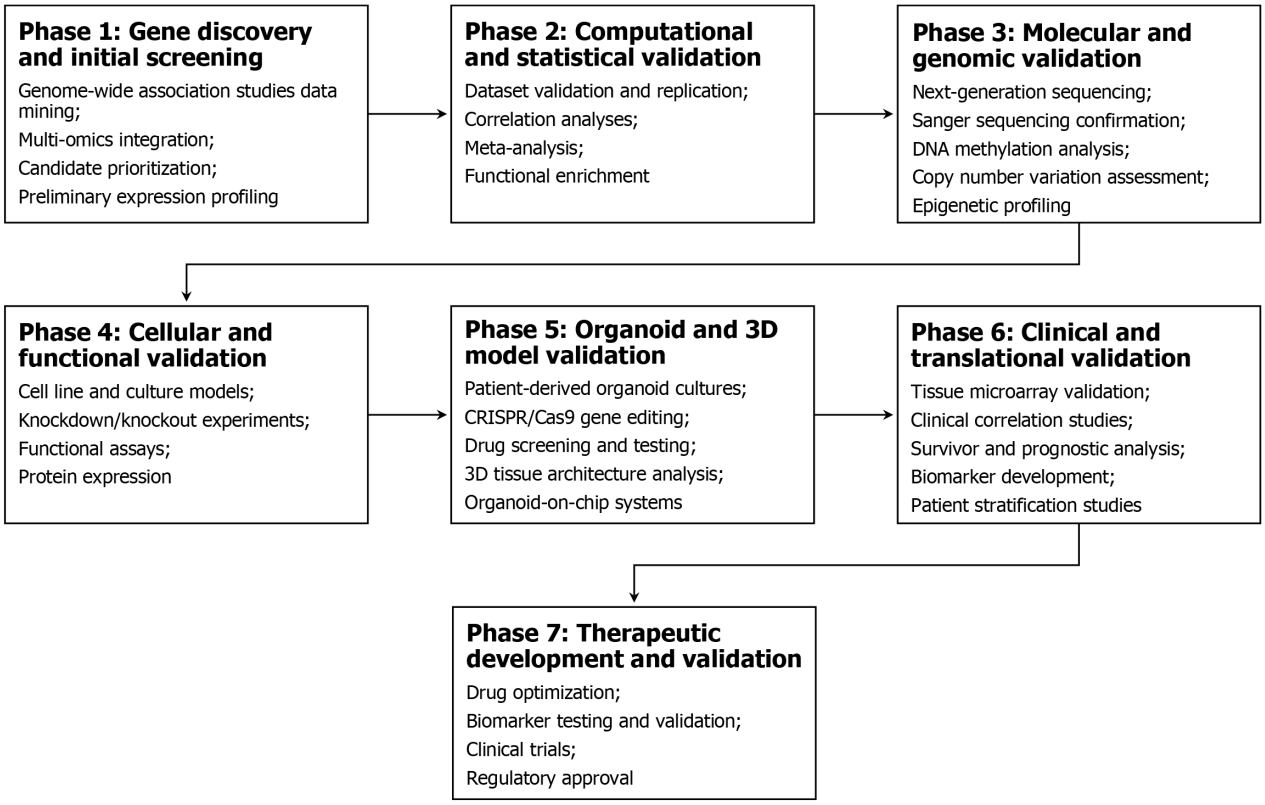

Figure 1 Seven-phase validation pipeline for novel candidate genes. 3D: Three dimensional; CRISPR/Cas9: Clustered regularly interspaced short palindromic repeats/associated protein 9.

Finally, the integration of multi-omic approaches, including transcriptomics, proteomics, and metabolomics, may provide a more comprehensive understanding of disease mechanisms and identify novel therapeutic targets.

CONCLUSION

The study by Dos Santos *et al*[1] highlights the growing ability of comprehensive genetic analysis to uncover pathogenic variants in unexplained colorectal polyposis cases, marking significant progress in the field. However, challenges remain in translating these findings into clinical practice due to uncertain variant significance. As technological advancements outpace clinical interpretation, future efforts must prioritize functional validation, clinical correlation, and evidence-based strategies. True success lies not in gene discovery alone, but in improved patient outcomes through precision medicine. Continued multidisciplinary collaboration will be essential to transform genetic insights into effective, personalized prevention and treatment strategies for hereditary colorectal cancer syndromes.

FOOTNOTES

Author contributions: Dhali A conceptualized the article and wrote the primary manuscript; Maity R conducted literature review and wrote the primary manuscript; Biswas J wrote the primary manuscript; Dhali A and Maity R have contributed equally to the article and are co-first authors; All authors agreed with the final version of the manuscript.

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