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Fall 2025

Divergent Molecular Networks Drive Ancestry-Related Colorectal Cancer Disparities

By Salma Fareed

AUTHOR BIO

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ABSTRACT

Colorectal cancer (CRC) remains a leading cause of cancer-related morbidity and mortality, with African-ancestry populations experiencing higher incidence and poorer outcomes. Although socioeconomic factors contribute, growing evidence suggests biological differences also play a role. However, ancestry-associated molecular features of CRC remain insufficiently defined, largely due to the underrepresentation of non-European populations in genomic studies. In this study, transcriptomic profiles of African-Black and European-White CRC patients from The Cancer Genome Atlas (TCGA) were compared to identify ancestry-associated molecular programs. Differential expression analysis identified dysregulated genes, and pathway enrichment revealed distinct biological processes. White patients exhibited coordinated immune–metabolic pathways, whereas Black patients showed fragmented modules centered on CRYBB2 and MAP9. Immune profiling using single-sample gene set enrichment analysis (ssGSEA) further demonstrated higher enrichment of interferon alpha response, allograft rejection, and complement activation in White patients, complemented by increased expression of immune checkpoint genes. Bootstrap resampling confirmed the robustness of these findings despite sample imbalance. These results provide novel evidence of ancestry-linked transcriptomic differences in CRC and underscore the importance of including diverse populations in cancer genomics to develop equitable biomarkers and therapeutic strategies.

Keywords: *colorectal cancer, transcriptomics, ancestry, molecular signatures, immune microenvironment, health disparity, metabolic programming, network analysis.*

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INTRODUCTION

Colorectal cancer (CRC) remains a major global health challenge, ranking among the top three cancers in both incidence and mortality. In 2020, over 1.9 million new cases and nearly one million deaths were reported worldwide, with projections anticipating continued growth, particularly in younger populations (Morgan et al., 2023; Siegel et al., 2024). Within the United States, an estimated 152,000 new diagnoses are expected in 2024, highlighting a troubling rise in early-onset cases (American Cancer Society, 2024). These trends illustrate the urgency of improving understanding of CRC biology and developing strategies to reduce the burden across diverse patient populations.

Molecularly, CRC is heterogeneous and can be categorized into consensus molecular subtypes (CMS) that reflect variation in immune signaling, metabolic reprogramming, and stromal involvement, each linked to prognosis and therapeutic response (Guinney et al., 2015). Advances in sequencing technologies have deepened insights into these biological programs, while investigations into the gut microbiome have identified organisms such as Fusobacterium nucleatum as potential contributors to tumor progression and treatment resistance (Zepeda-Rivera et al., 2024). Parallel to these discoveries, clinical management increasingly incorporates biomarker testing, including microsatellite instability (MSI), RAS and BRAF mutations, HER2 amplification, and other actionable targets, to guide the use of immunotherapy and precision treatments (Cervantes et al., 2023). Novel agents, such as KRAS G12C inhibitors and HER2-directed antibody–drug conjugates, have further expanded therapeutic options (U.S. Food and Drug Administration, 2024a, 2024b). In addition, circulating tumor DNA (ctDNA) has emerged as a promising biomarker for minimal residual disease and dynamic treatment monitoring (Nakamura et al., 2024). Yet, most patients with microsatellite-stable (MSS) CRC derive limited benefit from current immunotherapies, underscoring the need for new molecular insights.

Population disparities in CRC remain striking. African-American and African-ancestry populations continue to face higher incidence and mortality compared to individuals of European ancestry, even after accounting for socioeconomic and healthcare access factors (Carson et al., 2023). Increasingly, molecular studies have demonstrated that ancestry contributes to these differences. Gene expression profiling has shown distinct patterns in African-American tumors compared with European-American cases, including consistent upregulation of CRYBB2 and PSPH (Jovov et al., 2012). Broader transcriptomic and pathway analyses have confirmed substantial ancestry-linked variation (Haskins et al., 2021), while immune-focused studies reported elevated pro-inflammatory cytokine expression and increased infiltration of exhausted immune subsets in tumors from African-American patients (Paredes et al., 2020). Large-scale genomic studies that integrate genetic ancestry estimates have strengthened these observations, revealing associations between greater African ancestry and higher rates of somatic APC, KRAS, and PIK3CA mutations, alongside lower BRAF mutation frequencies, with implications for CMS subtype distribution (Rhead et al., 2024). More recent analyses demonstrated that ancestry influences molecular profiles at specific disease stages, identifying a consistent five-gene signature that differentiates tumors from Black and White patients across multiple stages, as well as pathway-level differences such as downregulation of IL-17 signaling in localized disease among Black patients (El Moheb et al., 2025). Collectively, this evidence underscores that ancestry-associated molecular variation is biologically meaningful and potentially relevant to clinical outcomes.

Despite these advances, key limitations remain. Many studies are constrained by modest sample sizes, rely on self-reported race rather than genomic ancestry, and often focus narrowly on individual genes or pathways instead of broader systems-level patterns. To address these gaps, the present study applies transcriptomic analyses to CRC cohorts of African-Black and European-White genomic ancestry, integrating differential expression with pathway enrichment and network-level methods. By uncovering ancestry-specific molecular programs, this approach aims to improve mechanistic understanding of CRC disparities and provide a foundation for the development of equitable biomarkers and therapeutic strategies.

METHODS

Study Population and Inclusion Criteria

RNA sequencing data and matched clinical metadata for colorectal cancer (CRC) patients were obtained from The Cancer Genome Atlas (TCGA-CRC) cohort (Cancer Genome Atlas Network, 2012). Patients were included if they had primary tumor samples with available transcriptomic data and annotated ancestry information. Only patients whose genomic ancestry aligned as African-Black or European-White were retained for downstream analysis.

Data Acquisition and Preprocessing

RNA sequencing data and matched clinical metadata for CRC patients were retrieved from the TCGA-CRC cohort (Cancer Genome Atlas Network, 2012). Raw read counts were used as input for statistical modeling. To facilitate comparison across genes and samples, counts were normalized to transcripts per million (TPM). Metadata were harmonized to align patient identifiers across clinical and molecular datasets. Genes with low expression (counts per million < 1 in more than 80% of samples) were excluded to reduce noise. Normalized expression values were $\log_2$-transformed prior to downstream testing.

Differential Expression Analysis

Differentially expressed genes (DEGs) between African-Black and European-White CRC patients were identified using the DESeq2 package. Fold changes were computed using mean normalized expression values, and statistical significance was assessed with the Wald test. P-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) procedure. Genes with $|\log_2 \text{ fold change}| \geq 1$ and FDR < 0.05 were considered significant.

Pathway Enrichment Analysis (Over-Representation Analysis)

Over-representation analysis (ORA) was performed separately on ancestry-specific DEG sets using the Enrichr platform (Kuleshov et al., 2016). Fisher's exact test was used to determine whether pathways contained more DEGs than expected by chance. Database libraries included Gene Ontology (GO) Biological Processes 2021 (Ashburner et al., 2000; The Gene Ontology Consortium, 2021), KEGG 2021 (Kanehisa et al., 2021), and Reactome 2021 (Jassal et al., 2020). Enriched pathways were filtered at an FDR cutoff of < 0.25, an inclusive threshold suitable for exploratory, hypothesis-generating analysis.

Pathways were further categorized as immune-related, metabolic, or other biological processes based on library annotations.

Immune Activation Profiling

Single-sample gene set enrichment analysis (ssGSEA) was applied to transcriptomic data to quantify immune activity across patients. A panel of hallmark immune-related gene sets (e.g., interferon alpha response, allograft rejection, complement activation, UV response, estrogen response early) was retrieved from the Molecular Signatures Database (MSigDB). Normalized enrichment scores (NES) were computed for each patient, and between-group comparisons (White vs. Black) were performed using the Mann–Whitney U test.

Immune Checkpoint Gene Expression Analysis

Expression levels of key immune checkpoint genes, including PD-L1(CD274), CTLA4, LAG3, TIGIT, and HAVCR2, were extracted from the RNA-seq dataset. Between-group comparisons were performed using the Mann–Whitney U test. Results were visualized using boxplots with annotated p-values to assess ancestry-associated differences in checkpoint gene expression.

Sensitivity Analysis

To evaluate the robustness of ancestry-associated results given sample size imbalance, a bootstrap resampling framework was applied. Within each ancestry group (White and Black), samples were resampled with replacement 10,000 times while preserving sex stratification and the observed group ratio. For each replicate, ssGSEA enrichment statistics were recomputed. The mean statistic across replicates was plotted with error bars representing ±1 standard deviation. A dashed line at zero served as the null reference, indicating no enrichment. In parallel, sex-stratified t-tests were performed (comparing White vs. Black within each sex) to account for differences in group sizes. This dual framework ensured that both resampling variability and stratified comparisons were reflected in the analysis.

Network Analysis

Differentially expressed gene (DEG) sets for each ancestry group were submitted to the STRING database (Szklarczyk et al., 2023) to construct protein–protein interaction (PPI) networks. Networks were partitioned into functional modules using the Louvain community detection algorithm (Blondel et al., 2008). Biological processes and pathways enriched within each community were annotated, and network visualizations were generated to highlight ancestry-specific molecular subnetworks.

RESULTS

Patient Characteristics

A total of 592 colorectal cancer (CRC) patients from the TCGA-CRC cohort with available clinical and transcriptomic data were considered. Based on self-reported race, 284 patients were White (48.0%), 64 were Black or African American (10.8%), 12 were Asian (2.0%), one was American

Indian/Alaska Native (0.2%), and 231 were missing or unknown (39.0%). Genomic ancestry analysis further classified patients as predominantly European (EUR, n = 504, 85.1%), African (AFR, n = 47, 7.9%), African admixed (AFR_ADMIX, n = 18, 3.0%), East Asian (EAS, n = 13, 2.2%), or other/missing (n = 10, 1.7%). The cohort included 311 males (52.5%) and 279 females (47.1%), with a mean age at diagnosis of 66.2 ± 12.9 years. For downstream transcriptomic comparisons, only patients whose self-reported race aligned with genomic ancestry (EUR and AFR) were retained. Descriptive characteristics are summarized in **Table 1**.

Table 1
Descriptive statistics of the CRC cohort (N = 592).

Characteristic	*Category*	*N*	*%*
Self-reported race	White	284	48.0
	Black or African American	64	10.8
	Asian	12	2.0
	American Indian/Alaska Native	1	0.2
	Missing/Unknown	231	39.0
Genetic ancestry (genomic)	EUR	504	85.1
	AFR	47	7.9
	AFR_ADMIX	18	3.0
	EAS	13	2.2
	EUR_ADMIX	3	0.5
	Missing/Unknown	7	1.2
Sex	Male	311	52.5
	Female	279	47.1
	Missing/Unknown	2	0.3
Age at diagnosis	Mean ± SD (years)	–	66.2 ± 12.9
AJCC stage	Stage IIA	171	28.9
	Stage I	102	17.2
	Stage IIIB	80	13.5
	Stage IV	57	9.6
	Stage IIIC	54	9.1
	Stage II	35	5.9
	Stage IVA	26	4.4
	Stage III	22	3.7
	Stage IIIA	14	2.4

	Missing/Unclassified	14	2.4
	Stage IIB	12	2.0
	Stage IIC	2	0.3
	Stage IVB	2	0.3
	Stage IA	1	0.2

Differential Expression Analysis

Comparing White and Black CRC patients, differential expression analysis (DEA) identified 40 significant DEGs ($|\log_2$ fold-change$| > 1.0$; FDR $< .05$). Thirty-four genes were differentially expressed in White patients, the majority of which were downregulated relative to Black patients, while six genes were upregulated in Black patients. This pattern indicates that downregulation was predominantly observed in the White cohort, whereas genes significant in the Black cohort were consistently upregulated. Illustrative examples include ASB12, CXCL10, and ORM2 among the top genes downregulated in White patients, and CRYBB2, ACSM1, and FLJ26850 among the top genes upregulated in Black patients.

The complete distribution of effects is shown in **Figure 1** (volcano plot).

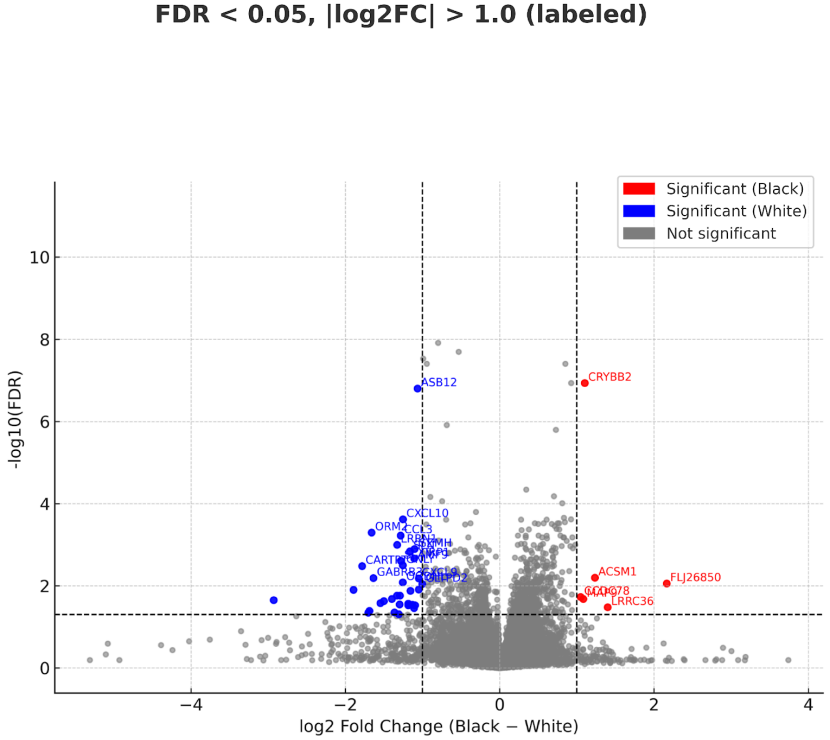

Figure 1
A volcano plot that shows the differentially expressed CRC genes in African American Black (Red) versus European White (Blue). The plot shows that ASB12, CXCL10, and ORM2 genes are among the top differentiated genes in White CRC patients, while genes CRYBB2, ACSM1, and FLJ26850 are among the top differentiated genes in CRC Black patients.

Pathway Enrichment Analysis

Over-representation analysis (ORA) of ancestry-specific DEG sets revealed distinct pathway profiles with no significantly shared pathways between groups (FDR < 0.25). Black-specific enrichments included metabolism, pancreatic signaling, and digestive tract left–right asymmetry. White-specific pathways were enriched for lipid and carbohydrate metabolism, including fatty acid oxidation, fucose metabolism, and short-chain fatty acid metabolism. Significant pathways and their statistics are displayed in **Figure 2**.

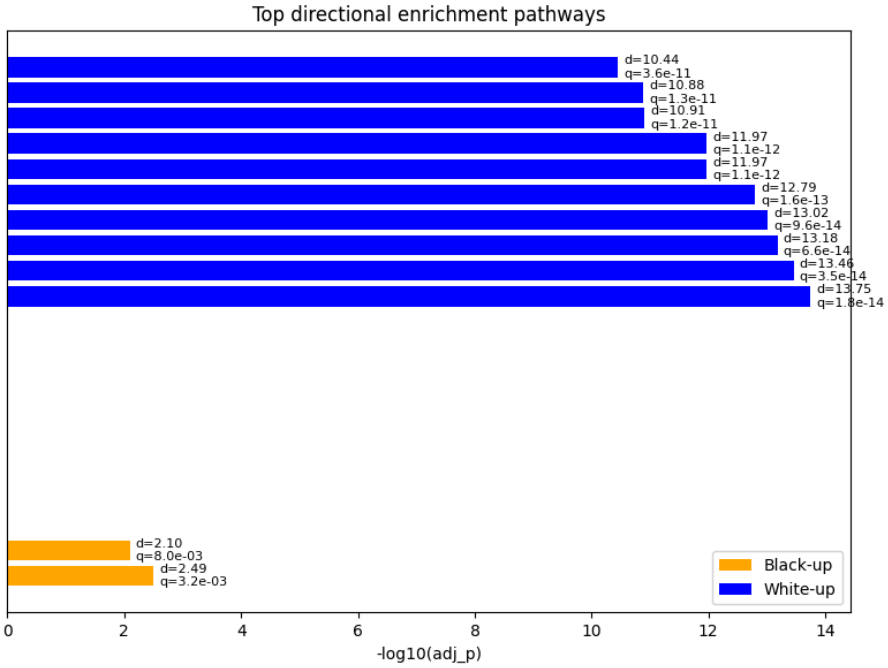

Figure 2
Pathway enrichment analysis of differentially expressed genes between African-Black and European-White colorectal cancer (CRC) patients. Over-representation analysis was performed using the Enrichr API. Bars represent significantly enriched pathways (**FDR** < 0.25). The bar length corresponds to the Enrichr combined score (***d***), while the adjusted ***q*** values (Benjamini–Hochberg false discovery rate) are shown next to each bar. Orange indicates pathways enriched in Black patients, and blue indicates pathways enriched in White patients.

Immune Signature Analysis

Single-sample GSEA of hallmark immune pathways showed higher enrichment in White patients for interferon alpha response, allograft rejection, and complement activation. Across-pathway distributions are shown in **Figure 3**, and the most pronounced divergence was observed for interferon alpha response (p = .0029), highlighted in **Figure 4.**

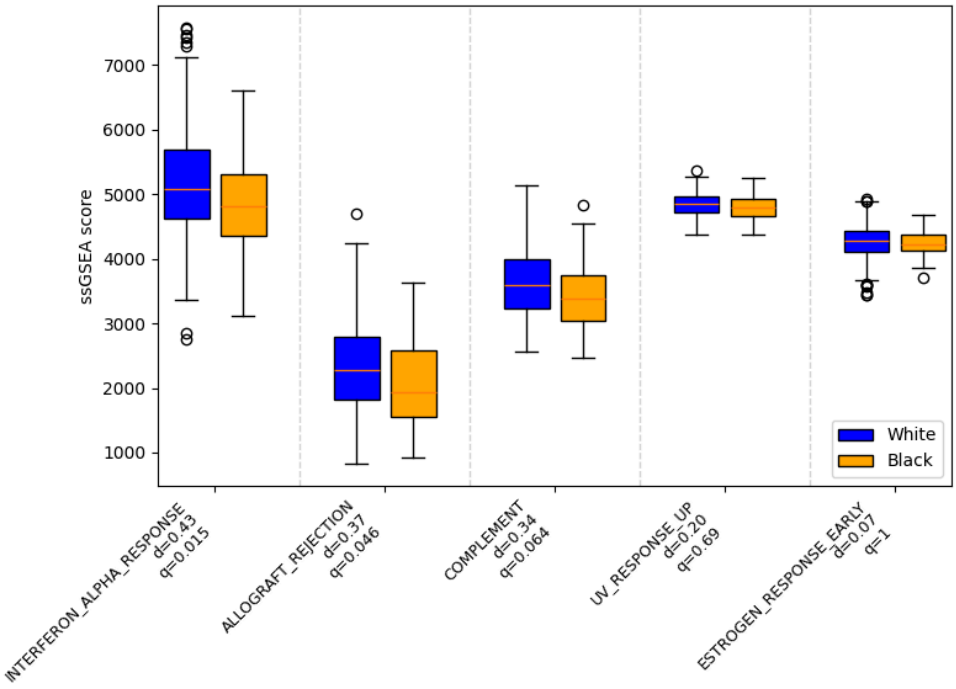

Figure 3
Boxplots of hallmark immune pathway ssGSEA enrichment scores by race. White patients showed higher scores across multiple pathways, including interferon alpha response, allograft rejection, and complement activation.

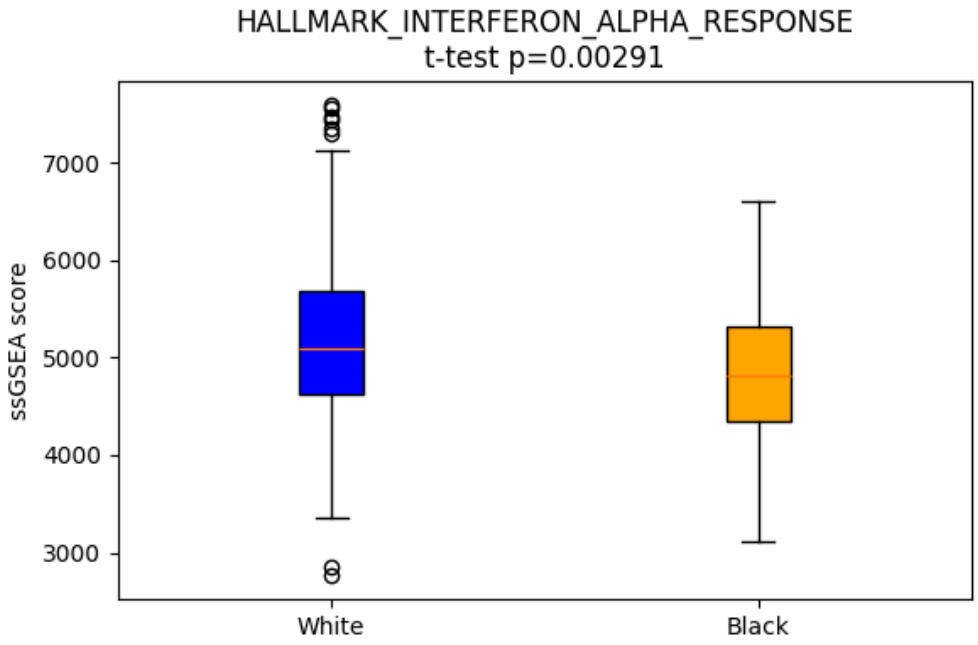

Figure 4
Boxplot of interferon alpha response pathway ssGSEA enrichment scores in White versus Black CRC patients. White patients exhibited significantly higher enrichment (t-test p = 0.0029).

Immune Checkpoint Gene Expression

Mean expression across canonical checkpoint genes (CD274/PD-L1, CTLA4, LAG3,TIGIT, HAVCR2) was significantly higher in White patients compared with Black patients (p = .015). Group means and variability are shown in **Figure 5**.

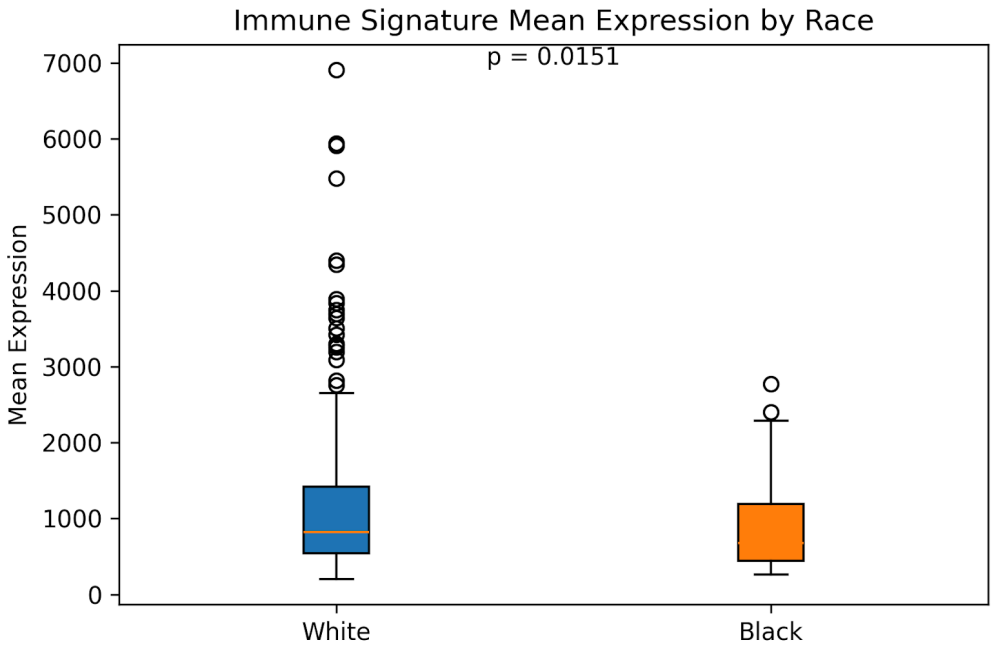

Figure 5
Mean immune checkpoint gene expression in White versus Black CRC patients. White patients demonstrated significantly higher expression (p = 0.015).

Sensitivity Analysis

Bootstrap resampling (10,000 iterations within ancestry, sex-preserving) confirmed the robustness of immune hallmark enrichments: INTERFERON ALPHA RESPONSE, ALLOGRAFT REJECTION, and COMPLEMENT remained strongly positive with error bars fully above zero; UV RESPONSE UP showed a weaker, positive effect; ESTROGEN RESPONSE EARLY was variable. Sex-stratified tests yielded consistent findings. Summary statistics with uncertainty are presented in **Figure 6**.

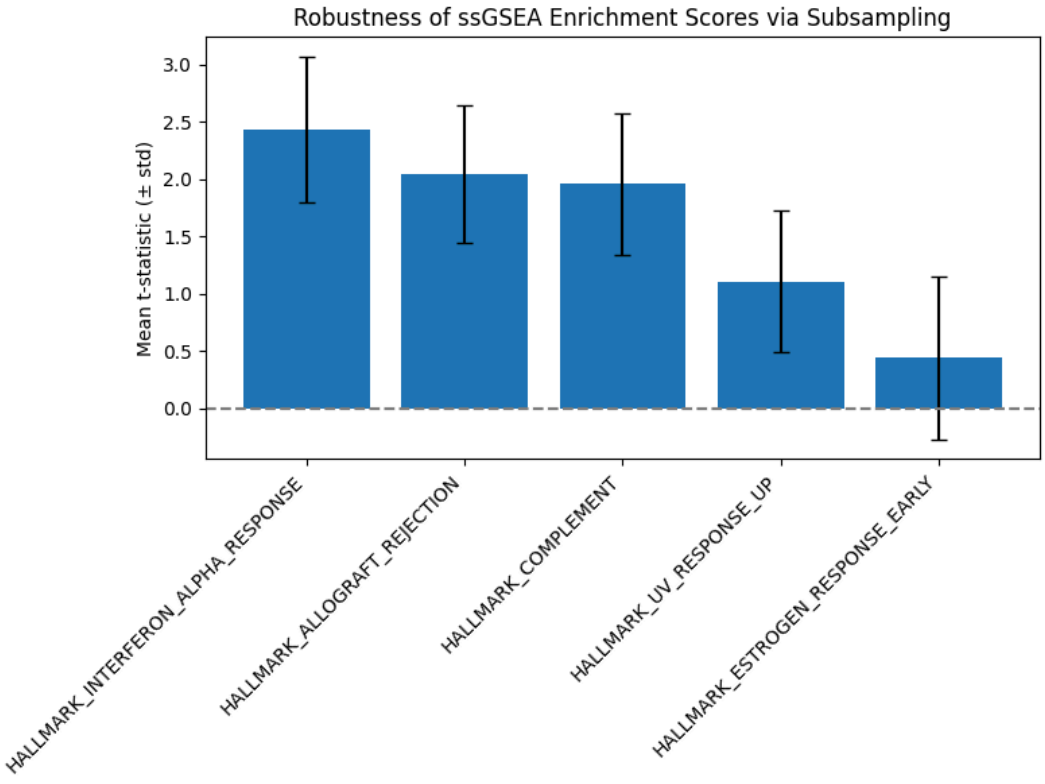

Figure 6
Bootstrap sensitivity analysis of immune hallmark enrichments. Blue bars show the mean ssGSEA enrichment statistic across 10,000 resamples, with error bars indicating ±1 standard deviation. The dashed line at zero represents the null expectation. Strong enrichments (INTERFERON_ALPHA_RESPONSE, ALLOGRAFT_REJECTION, COMPLEMENT) remained robust, while UV_RESPONSE_UP displayed a weaker but consistently positive signal.

Functional Clustering of DEGs via Protein–Protein Interaction (PPI) Networks

PPI networks constructed from ancestry-specific DEG sets revealed contrasting topologies, consistent with the DEG imbalance. White cohort. Using a high-stringency interaction threshold (STRING score > 0.9), downregulated DEGs formed a dense, highly connected network with multiple hubs and short paths between nodes, suggesting coordinated regulation across immune–metabolic axes. Prominent hubs included F11 (degree = 24; betweenness = 322.5), C19orf46 (degree = 19; betweenness = 261), CXCL10 (degree = 19; betweenness = 187.5), GNLY (degree = 16; betweenness = 120), and SERPINA6 (degree = 13; betweenness = 78), each downregulated (negative $\log_2$ fold-change). Hub metrics are listed in Table 2, and the corresponding subnetwork is visualized in **Figure 7a**.

Black cohort. Even under a more permissive threshold (STRING score > 0.4), the network remained relatively sparse and fragmented, dominated by smaller hubs. Under high-confidence filtering (STRING score > 0.8; **Figure 7b**), two hubs were evident: CRYBB2 (degree = 8; betweenness = 28;

log_2FC = +1.102) and MAP9(degree = 4; betweenness = 6; log_2FC = +1.084). These hubs mapped to stress/crystallin structural response (CRYBB2) and microtubule/cell-cycle regulation (MAP9), respectively. Hub metrics are summarized in **Table 3**.

Together, these findings indicate that White-ancestry DEGs assemble into an integrated immune–metabolic interactome, whereas Black-ancestry DEGs form smaller, less-interconnected clusters, consistent with lineage-restricted or module-limited activation rather than broad systems-level coordination.

Table 2
Hub genes in the White-ancestry CRC DEG PPI network (degree, betweenness, log_2 fold-change).

Node	Degree	Betweenness	Expression
F11	24	322.5	-1.050
C19orf46	19	261	-1.065
CXCL10	19	187.5	-1.254
GNLY	16	120	-1.330
SERPINA6	13	78	-1.256
CRABP1	12	66	-1.637
SLN	10	45	-1.097
UBQLN1	8	35	-1.364

Figure 7a
High-confidence (STRING score > 0.9) PPI subnetwork of White-ancestry DEGs. Larger nodes indicate higher degree; node color reflects expression values.

Table 3
Hub genes in the Black-ancestry CRC DEG PPI network (degree, betweenness, log_2fold-change).

Node	Degree	Betweenness	Expression
CRYBB2	8	28	1.102
MAP9	4	6	1.084

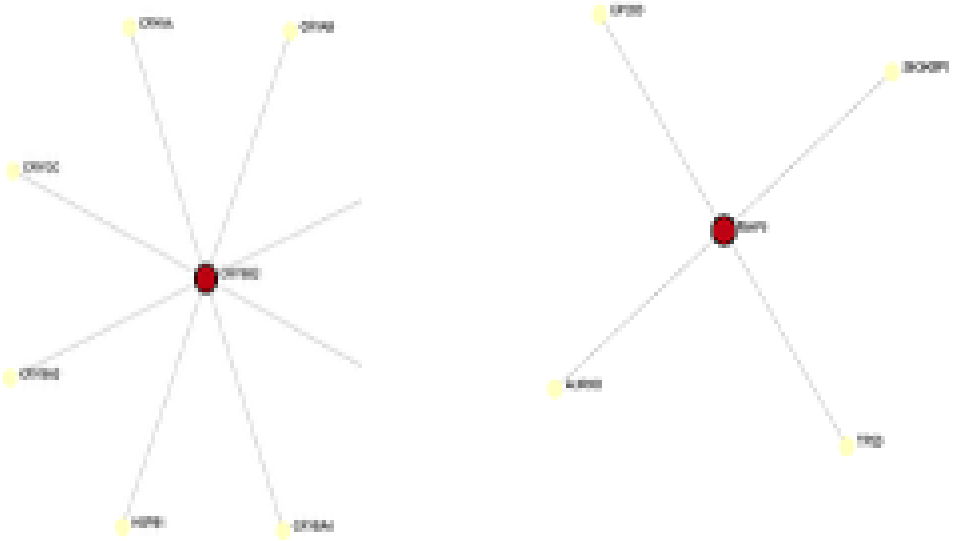

Figure 7b.
High-confidence (STRING score > 0.8) PPI subnetwork of Black-ancestry DEGs. Compared to White, the network is more fragmented, with CRYBB2 and MAP9 emerging as smaller hubs.

DISCUSSION

This study provides novel evidence that ancestry influences the transcriptomic landscape of colorectal cancer (CRC). By incorporating genomic ancestry rather than relying solely on self-reported race, a more accurate characterization of ancestry-associated biology was achieved. The analysis revealed that, despite overlapping clinical presentations, functional enrichment of differentially expressed genes uncovered distinct biological processes between African-Black and European-White patients. White patients demonstrated coordinated immune–metabolic signatures, whereas Black patients exhibited fragmented, lineage-specific modules dominated by CRYBB2 and MAP9. These findings extend prior reports of ancestry-related expression differences by identifying pathway- and network-level patterns that may underlie disparities in tumor biology and treatment response.

Several limitations must be acknowledged. First, the imbalance in sample sizes, with substantially fewer African-Black patients, was a constraint that reduced statistical power and raised the possibility of type II error. Bootstrap sensitivity analyses were performed to provide robustness checks, but larger cohorts will be required to confirm these results. Second, reliance on TCGA data introduced potential biases, as minority populations remain underrepresented. Unlike many prior studies that relied solely on self-reported race, genomic ancestry was incorporated to improve accuracy of group assignment. Although this strengthened confidence in the observed associations, inclusion of multi-omics layers (e.g., proteomics, epigenomics) would provide a more comprehensive view. Finally, while transcriptomic signatures suggested functional divergence, experimental validation will be necessary to establish causal mechanisms.

Despite these limitations, the findings highlight that ancestry-specific molecular programs may influence CRC progression and treatment responsiveness. Importantly, differences in immune-related pathways were observed that suggest ancestry could shape immunotherapy outcomes, warranting further investigation in clinical trials designed to include diverse populations.

CONCLUSION

An ancestry-stratified transcriptomic analysis of colorectal cancer patients was conducted, and distinct biological programs were observed between African-Black and European-White groups. White patients were found to display more coordinated immune–metabolic networks and heightened immune activity, whereas Black patients exhibited sparser, lineage-specific expression patterns. These findings underscore the importance of ensuring diverse representation in cancer genomics so that biomarkers and precision oncology approaches are applicable across ancestries. It is emphasized that in this study, genomic ancestry was incorporated to improve accuracy of classification, in contrast to prior studies that relied primarily on self-reported race. Future studies will be required in larger, more diverse cohorts, with validation across additional molecular layers, to confirm and extend these results and to explore their therapeutic implications.

ACKNOWLEDGEMENTS

I would like to thank Dr. Jordan Winter, MD and his lab for their lab mentorship. I would also like to thank my biology teachers and mentors from the Science Research & Engineering Program

(SREP) Fellowship for guidance, as well as the editorial board of the Scholarly Review Journal for their time and constructive feedback.

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