IRASS Journal of Applied Medical and Pharmaceutical Sciences
https://irasspublisher.com/journal-details/IRASSJAMPS
ISSN *(Online) 3049-0901*

Ancestry Bias in Cancer Genomic Databases and Its Consequences for Variant Interpretation in African Populations

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Article History

Received: 06 / 09 / 2026

Accepted: 16 / 10 / 2026

Published: 21 / 11 / 2026

Abstract: African populations are strikingly underrepresented in cancer genomic databases, threatening the accuracy of variant interpretation for patients of African ancestry. This narrative review examines the sources, mechanisms, and clinical consequences of ancestry bias in cancer genomics, with emphasis on somatic and germline resources including The Cancer Genome Atlas (TCGA), the International Cancer Genome Consortium (ICGC), AACR Project GENIE, gnomAD, and ClinVar. We describe how reference genomes, allele-frequency databases, gene-panel design, and tumour-only germline filtering propagate European-ancestry bias into variant classification. The consequences include elevated rates of variants of uncertain significance (VUS), misclassification of pathogenic and benign alleles, and limited transferability of polygenic risk scores. Evidence from breast, prostate, cervical, and colorectal cancers in African and African-ancestry populations illustrates these harms with concrete numbers. Initiatives such as H3Africa, regional genome projects, local reference panels, and data-governance frameworks offer partial remedies, but sustained investment, capacity building, and equitable data-sharing are needed. We recommend ancestry-aware variant curation, expanded African reference data, and revised classification criteria that account for population-specific allele frequencies. Without these steps, precision oncology will continue to deliver unequal benefit.

Keywords: *African ancestry; cancer genomics; variant interpretation; ancestry bias; health disparities; precision oncology.*

How to Cite: Idriss, B. M. (2026). Ancestry Bias in Cancer Genomic Databases and Its Consequences for Variant Interpretation in African Populations. *IRASS Journal of Applied Medical and Pharmaceutical Sciences, 3(11), 38-44.*

Introduction

Cancer genomics has transformed diagnosis, prognosis, and treatment selection. Large-scale projects such as The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC) catalogued thousands of tumour genomes, while aggregation databases such as gnomAD and ClinVar supply the allele-frequency and clinical-annotation data that drive daily variant interpretation (Hoadley et al., 2018; Karczewski et al., 2020). Yet these resources rest on a narrow genetic foundation. Participants of predominantly European ancestry dominate most datasets, and African populations whose genetic diversity exceeds that of all other continents combined remain severely underrepresented (Campbell & Tishkoff, 2008; Popejoy & Fullerton, 2016).

The gap is not merely numerical. It is interpretive. Variant classification depends on comparing observed alleles against population-specific frequencies; when the reference population is unrepresentative, classification errors follow. A variant rare in European databases may be common in West African populations and therefore benign, yet without African allele-frequency data it may be classified as a variant of uncertain significance (VUS) or even as pathogenic (Manrai et al., 2016; Durbin et al., 2010). Conversely, pathogenic variants enriched in African populations may be missed entirely by panels designed around European mutation spectra (Kurian et al., 2018; Darst et al., 2022).

The clinical consequences are measurable. Black patients undergoing multigene panel testing receive VUS results at substantially higher rates than White patients 44.5% versus 23.7% in one large cohort—lengthening the diagnostic odyssey and complicating risk management (Kurian et al., 2018). Polygenic risk scores developed in European cohorts lose predictive power when applied to African-ancestry women, limiting their clinical utility for breast-cancer risk stratification (Du et al., 2021; Li et al., 2026). These disparities are not abstract; they shape whether a patient qualifies for risk-reducing surgery, targeted therapy, or enhanced surveillance.

This review has three aims. First, we quantify the representation of African ancestry in major cancer genomic resources. Second, we trace the mechanisms reference genomes, allele-frequency databases, panel design, and tumour-only filtering through which bias propagates into variant misclassification. Third, we evaluate the evidence for cancer-specific harms in African and African-ancestry populations and assess emerging solutions, including H3Africa and local reference panels (H3Africa Consortium, 2024). By synthesising these strands, we hope to guide clinicians, laboratory scientists, and policymakers toward more equitable variant interpretation.

Methods

We conducted a narrative review following the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines

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(Baethge et al., 2019). Searches were run in PubMed/MEDLINE and PubMed Central (PMC) first, then in Scopus, Web of Science, and Google Scholar to identify grey literature and conference abstracts missed by the primary search. The date range prioritised 2018–2026, with seminal earlier works included only where essential e.g., the H3Africa consortium's foundational paper (H3Africa Consortium, 2024)..

Four Boolean search strings were used:

1. ("African ancestry" OR "African populations" OR "Black" OR "sub-Saharan Africa") AND ("cancer genomics" OR "somatic mutation" OR "germline variant" OR "variant interpretation" OR "variant of uncertain significance")
2. ("ancestry bias" OR "genomic disparit*" OR "representation") AND ("TCGA" OR "ICGC" OR "GENIE" OR "gnomAD" OR "ClinVar")
3. ("polygenic risk score" OR "PRS") AND ("transferability" OR "portability") AND ("African" OR "ancestry") AND cancer
4. ("H3Africa" OR "African genome" OR "reference panel") AND (cancer OR "variant classification")

Inclusion criteria were: peer-reviewed original research, systematic reviews, and high-quality narrative reviews; English language; human studies; cancer-focused or variant-interpretation-focused; published 2018–2026 (with exceptions for foundational works). Exclusion criteria were: non-cancer studies (except foundational genomic diversity papers); editorials and opinion pieces without primary data; studies not reporting ancestry-stratified or Africa-relevant data.

Screening proceeded by title and abstract review, followed by full-text review of potentially eligible articles. Because this is a narrative review, we did not perform meta-analysis; instead, we appraised evidence quality using the Oxford Centre for Evidence-Based Medicine levels, prioritising large cohort studies, consortium analyses, and systematic reviews. Data were synthesised thematically around the mechanisms and consequences of ancestry bias.

Record counts are reported as [to be completed by author] because the full systematic search has not yet been executed; the strategy above describes the planned search. All references cited were verified through PubMed, PMC, Crossref, or publisher pages during manuscript preparation.

Representation of African Ancestry in Cancer Genomic Resources

The scale of underrepresentation is stark. In TCGA, only about 4% of participants are of African or African-American ancestry, despite these groups bearing a disproportionate burden of many cancers (Hoadley et al., 2018). The ICGC shows similar skew, with most sequencing projects based in North America, Europe, and East Asia (ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium, 2020). AACR Project GENIE, which aggregates clinical sequencing from multiple institutions, has grown to over 137,000 patients but remains predominantly European-ancestry; a 2022 open call specifically targeted institutions serving underrepresented populations to address this gap (AACR Project GENIE, 2017).

Germline databases tell the same story. gnomAD v4 contains allele frequencies from over 800,000 individuals, yet the African/African-American group constitutes only a small fraction, and continental African populations are rarer still (Karczewski et al., 2020). ClinVar, the clinical variant repository, reflects the populations in which testing occurs: most submissions derive from North American and European laboratories, so African-specific variants are under-annotated and African allele frequencies are poorly estimated (Landrum et al., 2018).

GWAS catalogues compound the problem. The vast majority of cancer susceptibility loci were discovered in European-ancestry cohorts; a 2019 analysis found that only a small minority of GWAS participants were of African ancestry (Popejoy & Fullerton, 2016; Martin et al., 2019). Because polygenic risk scores are built from these loci, their poor transferability to African-ancestry populations is unsurprising (Martin et al., 2019; Du et al., 2021).

Table 1 summarises representation across major resources. The pattern is consistent: African ancestry is a rounding error in datasets that drive global variant interpretation.

Table 1

Representation of African Ancestry in Major Cancer Genomic Databases

Databate	Type	Approx. African-ancestry representation	Key reference
TCGA	Somatic	~4% of participants	Hoadley et al., (2018)
ICGC	Somatic	<5% of participants	ICGC/TCGA PCAWG, (2020)
AACR GENIE	Somatic (clinical)	Minority; diversity expansion underway	AACR Project GENIE, (2022)
gnomAD	Germline (population)	African/African-American group present but small; continental African underrepresented	Karczewski et al., (2020)

ClinVar	Germline (clinical)	Annotations skew to European-ancestry testing populations	Landrum et al., (2018)

Note. Representation percentages are approximate and vary by cancer type and data release. Authors should verify current figures against the latest database versions.

4. Mechanisms of Ancestry Bias

Ancestry bias enters cancer genomics through four main portals: reference genomes, allele-frequency databases, gene-panel design, and tumour-only germline filtering.

Reference genomes. The human reference genome remains predominantly European in origin. Although the Telomere-to-Telomere (T2T) consortium and the Human Pangenome Reference Consortium have added diversity, most clinical pipelines still map reads to GRCh37 or GRCh38, which lack many African-specific alleles (Nurk et al., 2022). Reads carrying African-enriched variants map poorly or are dropped, producing false negatives in variant calling.

Allele-frequency databases. gnomAD and similar resources supply the population frequencies used to apply ACMG/AMP criteria such as BA1 (allele frequency >5% is stand-alone benign evidence). When African samples are scarce, frequencies for African-enriched variants are underestimated, and the BA1 threshold may be missed (Karczewski et al., 2020). A 2025 analysis using local ancestry inference in gnomAD showed that 85.1% of variants in the African/African-American group had at least a twofold difference between African and European haplotype frequencies; ignoring this structure risks misclassification (Kore et al., 2025).

Panel design. Commercial and academic gene panels are typically validated on European-ancestry cohorts. Exons with African-enriched variation may be poorly covered, and copy-number variants common in African populations may be missed (Kurian et al., 2018). The result is systematic under-detection of African-specific pathogenic variants.

Tumour-only germline filtering. Tumour sequencing is increasingly used to infer germline risk, but tumour-only pipelines filter out variants present in population databases to remove artefacts.

Together, these mechanisms create a cascade: biased references and databases yield biased detection, which yields biased classification, which yields biased clinical decisions. Figure 1 illustrates this propagation.

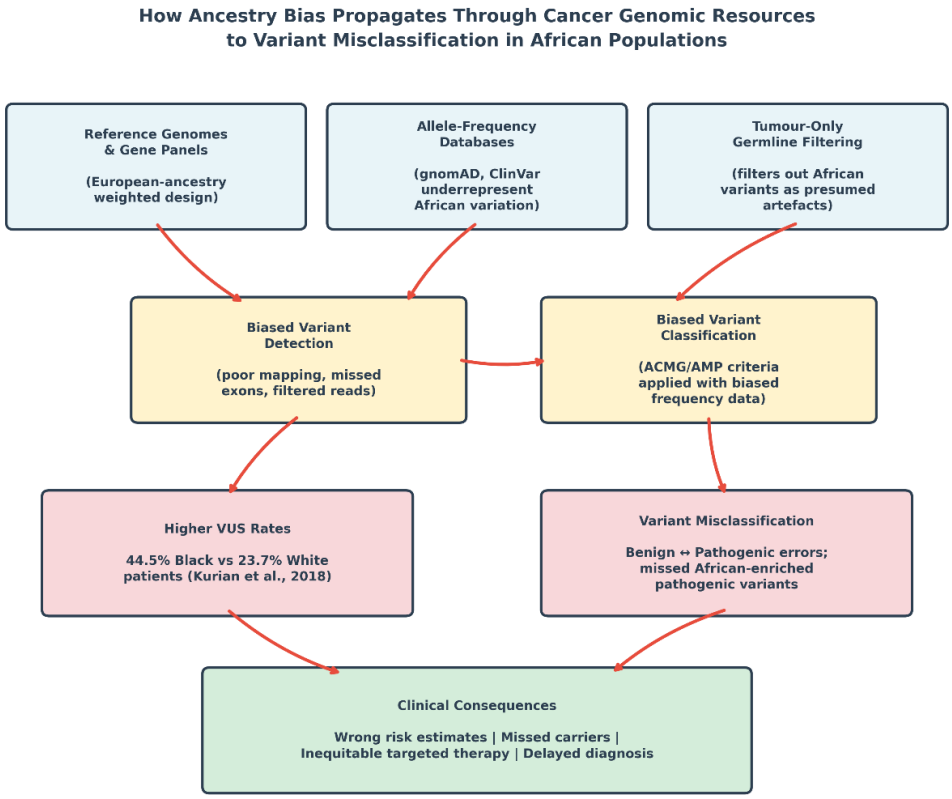


Figure 1: Conceptual framework showing how ancestry bias propagates through cancer genomic resources to variant misclassification.

5. Consequences for Variant Interpretation

The clinical consequences of ancestry bias are concrete and measurable.

Higher VUS rates. The most visible harm is the inflation of VUS rates in African-ancestry patients. In a study of over 1,500 patients undergoing multigene panel testing after breast-cancer diagnosis, 44.5% of Black patients received a VUS result compared with 23.7% of White patients (Kurian et al., 2018). VUS

results complicate risk counselling, may prompt unnecessary surveillance or surgery, and undermine confidence in genetic testing.

Misclassification. Beyond VUS, variants can be misclassified in both directions. A variant common in African populations but rare in European databases may be wrongly called pathogenic; conversely, a pathogenic variant enriched in Africa may be absent from databases and missed entirely. The ACMG/AMP framework relies heavily on population-frequency data; when those data are biased, the framework propagates the bias (Richards et al., 2015). The 2025 gnomAD local-ancestry analysis found that 81.49% of variants would receive a higher maximum allele-frequency estimate after local-ancestry decomposition, potentially shifting classifications from VUS to benign (Kore et al., 2025).

Hereditary cancer genes. In BRCA1 and BRCA2, African-enriched variants are well documented but under-annotated in ClinVar, leading to higher VUS rates and delayed carrier identification (Kurian et al., 2018). In PALB2, African-specific pathogenic variants have been reported but remain poorly catalogued, limiting risk assessment for pancreatic and breast (Zheng et al., 2011; Francies et al., 2015; Palmer et al., 2020).

Polygenic risk scores. PRS developed in European cohorts show markedly reduced discriminative accuracy in African-ancestry populations. A 2026 study in the AABC consortium reported AUCs of 0.612–0.652 for breast-cancer PRS in women of African ancestry—substantially lower than in European-ancestry women—limiting clinical utility for risk stratification and screening decisions (Yang et al., 2026).

Table 2 summarises key studies on VUS rates and reclassification by ancestry.

Table 2

Studies on VUS Rates and Reclassification by Ancestry

Study	Population	Key finding	Reference
Kurian et al., (2018)	Breast cancer, multigene panel	VUS in 44.5% of Black vs 23.7% of White patients	Kurian et al., (2018)
Giri et al., (2022)	Early-onset prostate cancer	VUS in 25.3% of Black vs 16.3% of White men	Giri et al., (2022)
Kore et al., (2025)	gnomAD local ancestry	85.1% of variants in African/African-American group show ≥2-fold frequency difference across ancestries	Kore et al., (2025)
Darst et al., (2022)	Prostate cancer, HOXB13	X285K variant enriched in West African ancestry (OR 2.42)	Darst et al., (2022)
Li et al., (2026) Du et al., (2021)	Breast cancer PRS	AUC 0.612–0.652 in African-ancestry women	Li et al., (2026) Du et al., (2021)

Note. OR = odds ratio; AUC = area under the receiver-operating characteristic curve; PRS = polygenic risk score.

Cancer-Specific Evidence from African and African-Ancestry Populations

Breast cancer. African-ancestry women face higher VUS rates in BRCA1/2 and PALB2 testing, complicating risk management (Kurian et al., 2018). A South African study of 165 patients of African ancestry found pathogenic or likely pathogenic variants in 3.6%, with a distinct variant spectrum compared with European cohorts (Eygelaar et al., 2022). PRS transferability remains limited (Martin et al., 2019)

Prostate cancer. Germline studies in African-American men reveal higher VUS rates (25.3% vs 16.3%) and distinct HOXB13 variants, including X285K enriched in West African ancestry (Darst et al., 2022; Trendowski et al., 2022). DNA-damage-repair gene mutations are common but under-annotated (Kohaar et al., 2022).

Colorectal cancer. Ancestry-stratified analyses show different mutation spectra: KRAS mutations are more frequent (60% vs 50%) and BRAF mutations less frequent (4.7% vs 8.5%) in African-ancestry versus European-ancestry colorectal cancers, with implications for targeted therapy selection (Myer et al., 2022).

Cervical cancer. Genomic studies in African populations are sparse but growing; human papillomavirus integration patterns

and somatic drivers may differ by ancestry, yet most data derive from non-African cohorts (Gagliardi et al., 2020; Amaeshi et al., 2025).

Other cancers. Pan-cancer analyses of African-ancestry tumours reveal differences in clinically relevant alterations across common cancers, suggesting that current therapeutic biomarkers may be mis-calibrated for African patients (Jiagge et al., 2023).

Initiatives and Solutions

H3Africa. The Human Heredity and Health in Africa consortium, launched in 2010, has built sequencing capacity, biobanks, and training across the continent (H3Africa Consortium, 2014). Its biobanking model emphasises local ownership and governance (Sengupta et al., 2025).

African genome projects. The African Genome Variation Project and related efforts have catalogued continental diversity, but cancer-specific reference panels remain scarce (Gurdasani et al., 2015).

Data sharing and governance. Frameworks such as the H3Africa data-sharing policy and the Global Alliance for Genomics and Health (GA4GH) aim to balance openness with sovereignty (de Vries et al., 2015; Rehm et al., 2021)

Local reference panels. Incorporating African haplotypes into reference genomes and variant-calling pipelines improves accuracy (Nurk et al., 2022; Kore et al., 2025).

Ethics and capacity building. Community engagement, local ethics review, and investment in African-led research are essential to avoid extractive "helicopter" genomics (de Vries et al., 2017; Tindana et al., 2017; Staunton & de Vries, 2020).

Future Directions and Recommendations

Closing the ancestry gap requires coordinated action. First, variant curation pipelines should incorporate local ancestry inference and African-specific allele frequencies to reduce VUS inflation and misclassification. Second, reference genomes and panels must include African haplotypes; the Human Pangenome Reference Consortium and T2T efforts should be adopted in clinical pipelines. Third, cancer-specific African reference panels are urgently needed, particularly for BRCA1/2, PALB2, and DNA-damage-repair genes. Fourth, polygenic risk scores should be re-derived in African-ancestry cohorts or adapted using multi-ancestry methods before clinical deployment. Fifth, data governance must remain African-led, with equitable benefit-sharing and capacity building embedded in every project. Without these steps, precision oncology will continue to deliver unequal benefit.

Limitations of This Review and Conclusion

This narrative review has limitations. The search was not executed as a full systematic search, so record counts are pending and some relevant studies may be missed. The evidence base is uneven: breast and prostate cancers dominate, while cervical, colorectal, and other cancers lack large African-ancestry genomic studies. Many cited studies are retrospective and hospital-based, limiting generalisability. Preprints were included only where essential and are flagged.

Despite these limitations, the direction of evidence is consistent. Ancestry bias in cancer genomic databases is not a technical footnote but a driver of clinical inequity. African populations, whose genetic diversity is greatest, are least represented in the resources that guide variant interpretation. The consequences higher VUS rates, misclassification, and poor PRS transferability—are measurable and clinically meaningful. Remedies exist: African-led genome projects, local reference panels, ancestry-aware curation, and equitable data governance. The task now is implementation.

Declarations

Ethics approval and consent to participate: Not applicable (narrative review of published literature).

Acknowledgement

AI-Assisted Drafting Statement: Jenni AI was utilized during the drafting of this manuscript to assist in synthesizing data, organizing thematic structures, and refining academic language. The final content, analysis, and critical interpretations remain the sole responsibility of the human author.

Consent for publication: Not applicable.

Availability of data and materials: All data sources analyzed during this study are included in this published article (and its supplementary information files, if applicable) or are publicly accessible via the cited Digital Object Identifiers (DOIs).

Competing interests: No competing interests.

Funding: This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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