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INVITED REVIEW

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Improving genetic diagnosis of hereditary tumor syndromes: From expanded gene panels to functional genomics

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Abstract

Genetic tumor risk syndromes (genturis) contribute substantially to the overall cancer burden and provide opportunities for early detection, prevention, and individualized treatment. Yet, many affected individuals remain undiagnosed due to restrictive testing criteria and challenges in variant interpretation. This review summarizes recent advances in the diagnostic evaluation of genturis. We trace the evolution from single-gene testing to multigene panel testing, highlighting gains in diagnostic yield alongside the growing prevalence of uncertain and incidental findings. We then describe emerging functional approaches such as RNA sequencing and proteomics that generate molecular evidence to refine variant classification. Next, we outline how long-read sequencing overcomes technical limitations in complex genomic regions. Finally, we discuss practical aspects of clinical implementation, including reporting practices, workflow integration, and professional education, and propose strategies to improve diagnostic accuracy, efficiency, and equitable access to testing.

KEYWORDS

functional genomics, hereditary tumor syndromes, long-read sequencing, multigene panel testing, variant interpretation

Abbreviations: ACMG/AMP, American College of Medical Genetics and Genomics/Association for Molecular Pathology; AI, Artificial intelligence; APC (gene, protein), *Adenomatous polyposis coli*; ATM (gene, protein), *Ataxia telangiectasia mutated*; BRCA1 (gene, protein), *Breast cancer gene 1*; BRCA2 (gene, protein), *Breast cancer gene 2*; BS3, Benign Strong criterion 3 (ACMG/AMP); Cas9, CRSPR associated protein 9; cDNA, Complementary DNA; CHEK2 (gene, protein), *Checkpoint kinase 2*; CNV, Copy-number variant; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; DNA, Deoxyribonucleic acid; DRS, Direct RNA sequencing; ENIGMA, Evidence-based Network for the Interpretation of Germline Mutant Alleles; ERBB2/HER2 (gene, protein), *Erb-B2 receptor tyrosine kinase 2*; ERN GENTURIS, European Reference Network on Genetic Tumor Risk Syndromes; GENTURIS/genturis, Genetic tumor risk syndromes; GfH, German Society for Human Genetics; HBOC, Hereditary breast and ovarian cancer; HDI, Human Development Index; IHC, Immunohistochemistry; InDel, Insertion/deletion; InSiGHT, International Society for Gastrointestinal Hereditary Tumors (InSiGHT) Consortium; LRS, Long-read sequencing; METTL5 (gene, protein), *Methyltransferase-like 5*; MGPT, Multigene panel testing; *MutL homolog 1*, MLH1 (gene, protein); MMR, Mismatch repair; *MutS homolog 2*, MSH2 (gene, protein); *MutS homolog 6*, MSH6 (gene, protein); NASGE, Network of Accredited Genetics Services in Germany; NGS, Next-generation sequencing; ONT, Oxford Nanopore Technologies; PacBio, Pacific Biosciences; PALB2 (gene, protein), *Partner and localizer of BRCA2*; PCR, Polymerase chain reaction; PMS2 (gene, protein), *Postmeiotic segregation increased 2*; PMS2CL (gene, protein), PMS2 C-terminal-like; POLD1 (gene, protein), *DNA polymerase delta 1*; PRS, Polygenic risk score; PS3, Pathogenic Strong criterion 3 (ACMG/AMP); PTEN (gene, protein), *Phosphatase and tensin homolog*; *RAD51 paralog C*, RAD51C (gene, protein); RNA, Ribonucleic acid; RNA-seq, RNA sequencing; rRNA, Ribosomal RNA; SDHB (gene, protein), *Succinate dehydrogenase subunit B*; SNV, Single-nucleotide variant; SV, Structural variant; VCEP, Variant Curation Expert Panel; VUS, Variant of uncertain significance; WES, Whole-exome sequencing; WGS, Whole-genome sequencing.

Mayra Sauer and Morghan C. Lucas have contributed equally to this study.

1 | INTRODUCTION

1.1 | Clinical relevance of diagnosing patients with hereditary tumor syndromes

Genetic tumor risk syndromes (genturis) are defined by inherited pathogenic variants that markedly increase lifetime tumor risk. They are the most common category of inherited disorders[1] and account for nearly 10% of all solid cancers.[2] However, only a minority of affected individuals are diagnosed, limiting management and prognosis for patients and families. In Europe, the ERN GENTURIS network has emphasized that most genturis cases remain unrecognized in routine practice.[3] Accurate diagnosis enables surveillance, early tumor detection, and targeted treatment, which improves outcomes. A genetic finding also informs risk-reducing interventions and cascade testing in relatives, supporting prevention across families.

Despite this relevance, genturis remain underdiagnosed because testing is still guided mainly by syndrome-specific criteria rather than broader multigene panel testing. For hereditary breast and ovarian cancer (HBOC), testing is typically limited to those with a family or personal history of breast or ovarian cancer.[4,5] For Lynch syndrome, testing is generally restricted to individuals meeting Amsterdam or Bethesda criteria or with tumors showing mismatch repair deficiency or microsatellite instability.[6–9] In prostate cancer, germline testing is recommended for men with metastatic or high-risk disease, while in early-stage disease, it is usually reserved for those with a family history or ancestry-associated risk, such as Ashkenazi Jewish heritage.[10] These guideline-driven approaches aim to optimize resources but leave many patients undiagnosed.

1.2 | Diagnostic challenges in hereditary cancer testing

The diagnostic clarification rate for genturis remains modest at 15%–25%, depending on tumor type.[11–13] A major challenge is the high frequency of variants of uncertain significance (VUS), which complicates interpretation and clinical decision-making. The ACMG/AMP framework defines VUS as variants lacking sufficient evidence for classification as (likely) pathogenic or benign.[14] Nearly 40% of genturis-associated variants in ClinVar fall into this category (Figure 1). Even when clinical suspicion of hereditary cancer is strong, current testing often yields negative or VUS-only results, leaving patients and families without clear guidance. This issue is exacerbated by the underrepresentation of non-European populations in genetic databases, resulting in disproportionately high VUS rates among these groups.[15–17]

Beyond VUS, the diagnostic yield of current testing approaches is further constrained by inherent shortcomings of short-read next-generation sequencing (NGS). Structural variants, deep intronic or other non-coding changes, and mosaic variants are frequently missed. Homologous pseudogenes can interfere with variant calling in clinically important genes such as *PMS2*. Emerging technologies, including long-read sequencing, discussed later in this review, address some of these challenges but are not yet widely integrated into diagnostics.[18]

A further layer of complexity comes from polygenic contributions to cancer risk. Multiple common variants can act additively, as reflected in polygenic risk scores (PRS).[19] PRS are being evaluated for applications such as refining breast cancer screening, but clinical implementation remains limited. As this review focuses on monogenic genetics, PRS will not be discussed further.

This review explores strategies to improve the diagnosis of monogenic genturis. We begin with the shift from single-gene to multigene testing and its effect on diagnostic yield and variant interpretation. We then highlight functional approaches, including RNA sequencing and proteomics, that provide molecular evidence to support variant classification. We also examine the role of long-read sequencing in resolving complex loci. Finally, we address practical aspects of clinical adoption, including reporting practices, laboratory workflows, and clinician education, and outline future directions toward more comprehensive and equitable genetic testing in genturis.

2 | INCREASING DIAGNOSTIC YIELD WITH MULTIGENE PANELS IN HEREDITARY CANCERS

Hereditary cancer testing has historically focused on *BRCA1* and *BRCA2*, which were among the first high-penetrance cancer predisposition genes identified.[20,21] Their strong links to breast, ovarian,[22] and

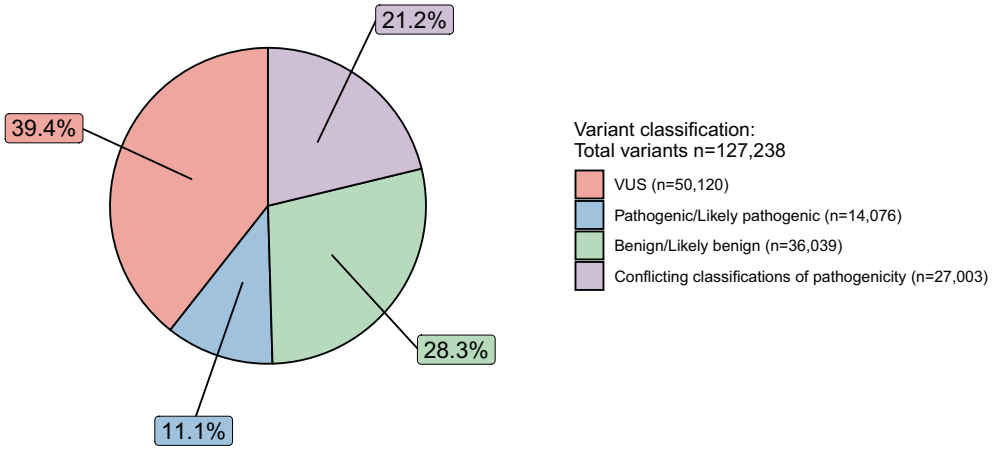

FIGURE 1 The distribution of clinically relevant genturis variants reported in the ClinVar database, filtered for gentrius association and applying quality filters for reliable variants (as of July 2025). [Color figure can be viewed at wileyonlinelibrary.com]

prostate cancer[23] made them the primary targets of genetic testing for many years. Breast cancer remains the most common cancer in women worldwide, with 2.3 million diagnoses and 670,000 deaths reported in 2022.[24] Lifetime risk is about one in 12 women in countries with a very high Human Development Index (HDI) compared with one in 27 in low-HDI countries.[24] Testing for *BRCA1* and *BRCA2* variants, therefore, provides a critical opportunity to identify individuals at elevated risk. However, these two genes account for only 30%–50% of hereditary breast cancer cases,[25–27] underscoring that narrow testing strategies leave many diagnoses incomplete or entirely missed.

The increasing capacity and affordability of NGS technologies have enabled the adoption of multigene panel testing (MGPT),[28] which interrogates multiple predisposition genes in parallel. Like whole-exome sequencing (WES), MGPT allows detection of variants beyond traditional core genes, thereby improving diagnostic yield.[29] Nevertheless, the genes recommended for genturis testing still differ between international guidelines, with only *BRCA1*, *BRCA2*, and *PALB2* being consistently included.[30]

Several studies highlight the benefits of broader testing. Henkel et al. analyzed more than 29,000 suspected HBOC cases tested at various German diagnostic laboratories within the NASGE network using both guideline-based panels and a comprehensive panel.[29] Detection of pathogenic variants ranged from 9.0% to 13.8% with small panels but rose to 14.9%–30.8% when including VUS. Most variants were in *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, and *ATM*, but the comprehensive panel also revealed actionable findings in genes such as *MSH6*, *MSH2*, *MLH1*, *PMS2*, and *APC*. Restricting testing to smaller panels was estimated to miss up to 1% of hereditary cancer cases.

Other cohorts report similar outcomes. Henn et al. found causative variants in 17% of unresolved cases using expanded panels, including actionable variants in *PMS2*, *PTEN*, and *POLD1*.[31] In an unselected cancer cohort, Ceyhan-Birsoy et al. reported a 16.7% diagnostic yield, with 8% of pathogenic variants in genes not typically associated with the presenting cancer type.[13] Patócs et al. demonstrated a 24% confirmation rate in endocrine tumor patients, along with shorter turnaround times and improved cost efficiency.[32] Together, these studies show that comprehensive gene panels consistently increase diagnostic yield and broaden the spectrum of identifiable syndromes.

Broader testing also increases the likelihood of detecting VUS, which complicates interpretation. Laboratories differ in their reporting practices: some include all VUS in relevant genes, while others restrict reporting to those plausibly linked to the patient's phenotype. To illustrate the distribution of variants across genturis genes, we analyzed ClinVar data,[33] a comprehensive repository of genetic variants and their clinical interpretations (Figure 1). After applying disease-specific and quality filters, we identified 127,238 unique variants across 155 genes (see Methods). According to ACMG/AMP criteria,[14] VUS constituted the largest group (39.4%) of variants, followed by benign/likely benign variants (28.3%) and pathogenic/likely pathogenic variants (11.1%). Conflicting classifications were present in 21.2% of variants.

Longitudinal studies show that many VUS are eventually reclassified as new evidence accumulates, with implications for patient management and ancestry-related difference.[34–36] To accelerate this process, ClinVar collaborates with ClinGen Variant Curation Expert Panels (VCEPs) to implement gene-specific adaptations of ACMG/AMP codes, providing more consistent and detailed frameworks. In *BRCA1 and BRCA2*, application of ENIGMA specifications reclassified the majority of VUS to benign or likely benign compared with only a minority under general ACMG/AMP + SVI guidance.[37] A parallel large-scale effort applying *APC*-specific ACMG/AMP criteria through the ClinGen–InSiGHT VCEP also showed a marked reduction in VUS rates.[38] Together with ongoing data sharing through ClinVar, these initiatives are expected to reduce ambiguity further and strengthen the clinical utility of expanded panel testing.

3 | FUNCTIONAL GENOMICS FOR VARIANT INTERPRETATION IN HEREDITARY CANCERS

As genetic testing for genturis expands from single-gene assays to larger panels and genome-wide approaches, the main challenge is shifting from variant detection to variant interpretation. This is particularly true for non-coding variants that lack functional or clinical annotation.[14,39,40] Functional genomics provides molecular evidence to clarify the significance of such variants. The ACMG/AMP guidelines recognize validated functional data as strong evidence for both pathogenic (PS3) and benign (BS3) classification.[14] Properly designed assays can therefore reclassify VUS into clinically actionable categories. Expert panels within ClinGen increasingly incorporate functional assays into gene- and disease-specific frameworks.[41,42] Early work has focused on high-priority genes such as those implicated in Lynch syndrome, but similar adaptations are now extending across a broader set of hereditary tumor predisposition genes.

In a recent review, we outlined strategies for reclassifying VUS, including functional assays, computational prediction tools, and enhanced detection methods such as long-read sequencing and RNA analysis.[43] These approaches encompass well-established methods, such as in vitro functional assays, deep mutational scanning, and transcriptomics, as well as newer technologies, including proteomics, epigenetic profiling, and optical genome mapping. In this section, we highlight functional omics strategies applicable at the individual–patient level, particularly RNA sequencing and proteomics.

3.1 | RNA sequencing in clinical practice

RNA sequencing (RNA-seq) provides direct evidence of transcript-level consequences and is increasingly used to resolve VUS in genturis by detecting splicing alterations, allele-specific expression, and expression outliers, effects not captured by DNA sequencing.[44–51] Splice-altering variants may occur in canonical splice sites, exonic splicing enhancers, branch points, or deep intronic regions that create

pseudoexons. These changes often lead to exon skipping, intron retention, or other aberrant isoforms that disrupt protein function.[52] Splicing alterations are more than twice as frequent as large deletions or duplications among pathogenic variants in genturis genes.[52] Allele-specific expression analysis identifies monoallelic expression caused by regulatory or structural changes, while outlier expression highlights abnormal transcript levels compared to reference datasets.[53,54]

Integrating RNA-seq with DNA sequencing increases diagnostic yield by 9%–30%, including a 9%–15% gain specifically in hereditary cancer syndromes.[51,54,55] RNA-seq is particularly powerful for recurrent VUS: once functionally resolved, the classification applies to all carriers, extending clinical benefit. In one study, three-quarters of RNA-based reclassifications involved recurrent variants, demonstrating a broad impact.[54] This is especially valuable in underrepresented populations, where limited reference data contributes to elevated VUS rates.[49,54] RNA-seq can also reveal causal variants in cases where DNA testing alone is uninformative.

Because transcriptome-wide RNA-seq is not feasible for all cases, a tiered strategy is recommended. Bioinformatic tools such as SpliceAI[56,57] can prioritize variants predicted to disrupt splicing, followed by targeted RNA-seq validation in selected high-probability cases. This approach strikes a balance between efficiency and the functional depth required for robust reclassification.

3.2 | Proteomic evidence for variant interpretation

Proteomics is emerging as a valuable complement to DNA- and RNA-based diagnostics for interpreting VUS, particularly missense variants that do not alter transcript levels or splicing. In clinical practice, proteomic data can support classification by assessing protein presence, abundance, and stability, as well as downstream functional effects.

The most established application is immunohistochemistry (IHC), routinely used to evaluate protein expression in tumor tissue. In Lynch syndrome, absence of MMR proteins (MLH1, MSH2, MSH6, PMS2) in IHC supports the pathogenicity of germline variants when combined with molecular and clinical findings.[42] Comparable applications exist in other syndromes, such as *SDHB* loss in hereditary paraganglioma[58] or *BRCA1 or BRCA2* loss in breast tumors.[59]

Beyond tissue-based assays, plasma proteomics platforms such as Olink and SomaLogic enable targeted quantification of hundreds to thousands of proteins from small samples. These methods are being studied in oncology for early detection, risk stratification, and therapy response,[60–66] and could be adapted to capture pathway-level effects of germline variants (e.g., altered signaling in DNA repair or immune regulation). Although not yet validated for variant-specific classification, such systemic protein signatures may ultimately complement genetic and transcriptomic evidence.[67]

Protein sequencing technologies are also advancing and may eventually allow direct confirmation of variant effects. Nanopore-based protein sequencing, for example, has the potential to detect altered amino acid sequences and post-translational modifications at single-molecule resolution.[68–70] While still in development and not commercially available, these approaches could verify variant-specific peptides or aberrant proteoforms in patient-derived samples, providing a direct molecular link between genotype and protein outcome.

4 | LONG-READ SEQUENCING FOR COMPLEX HEREDITARY CANCER LOCI

Long-read sequencing (LRS), enabled by platforms such as Pacific Biosciences (PacBio) and Oxford Nanopore Technologies (ONT), is increasingly used in genomics diagnostics because it overcomes many limitations of short-read sequencing. Short reads often fail in repetitive or homologous regions and in detecting structural variants (SVs). By generating contiguous reads spanning several kilobases, LRS provides advantages in variant detection, phasing (the ability to determine whether specific variants are located on the same chromosome copy, in cis, or on opposite copies, in trans), and coverage of difficult genomic regions.

One major benefit of LRS is direct detection of SVs such as large insertions, deletions, duplications, and inversions, which are often missed or misclassified by short-read methods. These variants are highly relevant in cancer predisposition syndromes, where genomic architecture is frequently disrupted. Examples include nested duplications and translocations around the *HER2* oncogene detected by PacBio LRS in breast cancer models,[71] and germline SVs in susceptibility genes resolved by ONT LRS that had escaped short-read analysis.[72] In hereditary breast cancer, adaptive sampling with ONT enabled accurate classification of a germline *BRCA1* duplication.[73] Similarly, ONT combined with optical genome mapping identified a 39 kb insertion in *MSH2* in a Lynch syndrome patient that had remained undetected by standard testing.[74] Beyond individual cases, LRS substantially increases overall SV detection yield. In breast cancer cohorts, hundreds of additional germline SVs per individual were identified, many in known predisposition genes and inaccessible to short-read sequencing.[75]

LRS also improves the phasing of variants, a key requirement when interpreting compound heterozygosity or multiple hits in tumor suppressor genes.[76–78] Direct phasing of SNVs, InDels, and SVs within cancer predisposition genes has been demonstrated in clinical cohorts.[75] Another strength is enhanced coverage of deep intronic, repetitive, and GC-rich regions, which are poorly captured by short-read workflows. For instance, targeted long-read DNA and cDNA ONT sequencing uncovered pseudoexon-creating variants in *BRCA1* and *ATM*, revealing ultra-rare splicing defects with clinical consequences.[79] A further advantage is the integration of epigenetic information. LRS can directly detect DNA methylation without chemical treatment,[80] which is particularly relevant in hereditary cancer syndromes where epimutations contribute to disease. Recent studies reported promoter methylation of *BRCA1* and *RAD51C* in cases of homologous recombination deficiency lacking sequence mutations.[81]

The *PMS2* gene, one of the four key MMR genes implicated in Lynch syndrome, exemplifies the clinical relevance of LRS. Accurate analysis of *PMS2* is hindered by its highly homologous pseudogene

PMS2CL, which shares up to 98% sequence identity across exons 9–15.[82,83] This causes misalignment and false variant calls in short-read sequencing and Sanger methods.[82] Gene conversion and recombination events further generate hybrid alleles, complicating interpretation without labor-intensive methods such as long-range PCR.[82] These issues have limited the diagnostic utility of *PMS2* and likely led to underestimation of its contribution to Lynch syndrome, even though it accounts for at least 5%–15% of cases.[84] Its reduced penetrance and risk of misclassification highlight the need for sequencing strategies that can unambiguously resolve *PMS2*. Targeted LRS provides that resolution and improves diagnostic accuracy for this gene and other technically challenging loci.

4.1 | Future directions for long-read sequencing in hereditary cancer testing

As LRS technologies evolve, their role in genturis diagnostics is set to expand. Applications will move beyond SNV and SV detection toward integrated multi-omic analyses, enabling simultaneous assessment of DNA sequence, epigenetic modifications, and full-length transcript isoforms from a single sample. Advances in chemistry, base modification detection, and workflow automation are driving improvements in accuracy, throughput, and cost, supporting broader clinical adoption.

A continuing priority is improving variant calling across all classes. While LRS already outperforms short reads for SVs, phasing, and complex loci, challenges remain for high-confidence detection of SNVs, InDels, and CNVs, particularly in repetitive or GC-rich regions. Historically higher per-read error rates have limited SNV and InDel sensitivity and specificity, and CNV detection remains difficult for small, exon-level events or multi-exonic rearrangements. Recent advances, including ONT's Remora and Dorado as well as PacBio's DeepConsensus, improved error correction,[85] and deep learning–based variant callers,[86–92] are narrowing this gap. Current base-calling accuracies reach ~95–99% for ONT[93] and ~99% for PacBio,[94] comparable to short-read whole genome sequencing (WGS) but still below the >99.99% accuracy of short-read platforms such as AVITI and Onso.[95,96] While long-read WGS performs well for germline variants, it may remain limited for mosaicism or low-frequency somatic variants.[96] For CNVs, emerging read-depth, split-read, and breakpoint-aware approaches are increasingly outperforming short-read methods in low-mappability regions.[97] Ongoing optimization of alignment, signal-level analysis, and filtering pipelines will be essential for clinical-grade performance.

Targeted enrichment strategies such as CRISPR/Cas9-based capture[98,99] and ONT's adaptive sampling[100] enhance efficiency by focusing sequencing on clinically relevant loci, increasing depth while reducing cost. Portable and benchtop sequencers, coupled with rapid, automated library preparation, may enable near real-time and point-of-care diagnostics, including intraoperative testing and personalized treatment decisions directly in clinical settings.

In parallel, direct RNA sequencing (DRS) is emerging as a complementary approach. Developed by ONT, DRS sequences native RNA molecules, capturing isoforms, splicing defects, allele-specific expression, RNA modifications, and poly(A) tail dynamics without reverse transcription or amplification bias. While most clinical and research long-read transcriptomics still use cDNA,[79,101,102] a recent preprint reported the first diagnostic application of true DRS: confirming loss of site-specific rRNA methylation in a patient with compound heterozygous *METTL5* variants, including a VUS, thereby establishing pathogenicity.[103] With improvements in accuracy, bioinformatics, and analysis pipelines, DRS may provide a direct, multi-dimensional view of transcriptomic and epitranscriptomic variation in genturis.

5 | PRACTICAL CONSIDERATIONS FOR CLINICAL IMPLEMENTATION

5.1 | National differences in VUS reporting

VUS reporting practices vary widely between laboratories and countries. A 2017 survey of 24 laboratories across Europe, Canada, and Australasia found that while some reported only VUS plausibly related to the clinical phenotype, most reported all VUS in genes relevant to the indication.[104] A U.S. survey of 21 laboratories showed that 19 reported any VUS considered potentially relevant.[105] In Germany, for example, reporting follows the German Society for Human Genetics (GfH)[106] recommendations, limiting VUS disclosure to variants plausibly linked to the presentation. Laboratories also differ in format, with some listing VUS separately and others including only those with partial pathogenicity evidence.[104] Restrictive reporting, however, can limit opportunities for re-evaluation as evidence evolves. For example, applying ClinGen ENIGMA specifications in *BRCA1 and BRCA2* reduced VUS rates from 83.5% to 20%, underscoring the value of gene-specific frameworks and regular reanalysis.[37] Without systematic reporting or tracking, laboratories and clinicians lose the ability to revisit classifications, reducing long-term clinical benefit.

5.2 | Building genomic literacy across the genetics community

Laboratories have also raised concerns that report recipients—clinicians, geneticists, and genetic counselors—may lack sufficient knowledge of NGS technologies and their limitations, especially if they are disease-focused specialists without formal genetics training. In a 2023 survey of 900 health professionals, only 20% felt adequately prepared to use genetic tests in practice; among cancer-focused specialists, confidence was higher (36%) but still insufficient for a rapidly expanding field.[107] Strengthening education and continuous training across the genetics workforce is critical to ensure high-quality, evidence-based care.

5.3 | Improving patient communication and support

Equally important is clear and supportive communication of genetic test results to patients. A diagnosis of hereditary tumor risk can be

emotionally and clinically burdensome, and uncertainty from VUS may amplify this. Best practice guidelines call for structured, standardized communication before and after testing to prepare patients for uncertain or incidental findings and to support comprehension.[108–110] This approach enables patients to make informed decisions, reduces anxiety, and ensures the appropriate use of genetic information.

Digital platforms are emerging to support healthcare providers, genetic counselors, and patients. In Germany, FindMe2Care (https://findme2care.de/) is a medical contact platform that connects patients with tailored disease information, current treatment options, suitable patient organizations, relevant registries, and opportunities to participate in clinical studies or research projects. PatientsLikeMe in the U.S. (https://www.patientslikeme.com)[111,112] provides peer communities where patients share experiences, track symptoms, and contribute data to research. In the U.K., HealthUnlocked (https://healthunlocked.com)[113] hosts over 700 condition-specific communities, linking patients, caregivers, and professionals. These platforms enhance self-care, provide peer support, and help bridge knowledge gaps, particularly in regions with limited genetics infrastructure, promoting more equitable access to services.

6 | OUTLOOK: TOWARD PRECISION RISK ASSESSMENT IN HEREDITARY CANCERS

Looking forward, genturis testing is moving toward precision risk assessment that integrates multigene panels with RNA- and protein-based analyses and LRS, aiming to maximize diagnostic yield while minimizing uncertainty. Such combined approaches capture not only DNA variants but also downstream effects on splicing, protein function, and other molecular mechanisms that contribute to cancer predisposition yet remain undetected with current methods. Mechanism-based diagnostics will further link variants to disrupted pathways, thereby strengthening evidence of pathogenicity and informing prevention and treatment strategies.

Achieving this vision requires robust infrastructure. Gene-specific frameworks, such as ACMG/AMP guidelines[14] and VCEPs,[41] will remain central for consistent variant interpretation. Systematic data sharing through ClinVar, combined with routine reclassification, is crucial for reducing uncertainty and improving the accuracy of genetic variant annotations. Artificial intelligence and machine learning tools may accelerate interpretation by integrating multi-omics data and prioritizing findings. Finally, closing ancestry representation gaps in genomic databases is crucial to ensure equitable benefits. Together, these advances will move genturis assessment toward broader, deeper, and more clinically actionable diagnostics.

AUTHOR CONTRIBUTIONS

Mayra Sauer: Conceptualization; methodology; investigation; supervision; writing – original draft; writing – review and editing. **Morghan C. Lucas:** Conceptualization; methodology; investigation; supervision; writing – original draft; writing – review and editing. **Vitus Prokosch:** Data curation; investigation; visualization; formal analysis; writing – original draft; writing – review and editing. **Thomas Keßler:** Formal analysis; writing – original draft; writing – review and editing. **Thomas Risch:** Software; formal analysis; writing – review and editing; visualization. **Andreas Laner:** Writing – review and editing; investigation. **Jan Henkel:** Investigation. **Anna Benet-Pagès:** Supervision; writing – review and editing. **Ariane Hallermayr:** Writing – review and editing; supervision. **Verena Steinke-Lange:** Investigation; writing – review and editing. **Elke Holinski-Feder:** Conceptualization; funding acquisition; supervision; writing – review and editing. **Barbara Klink:** Investigation; conceptualization; supervision; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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