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Active Reclassification of Genetic Variants in Hereditary Cancer Panels: Clinical Impacts and Experience from a Brazilian Reference Laboratory

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Tables 1 to 12 are available in the Supplementary Files section.

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Abstract

Introduction: Multigene panels for hereditary cancer predisposition have substantially improved diagnostic accuracy and informed risk management strategies. Germline variant interpretation is typically performed according to guidelines from the ACMG-AMP, which classify variants into five categories: benign, likely benign, variant of uncertain significance, likely pathogenic, and pathogenic. The continuous accumulation of scientific evidence may lead to variant reclassification, potentially altering clinical interpretation and patient management. However, structured active reclassification programs remain limited in many settings. **Methods**: This retrospective study evaluated the reclassification rate of germline variants in individuals who underwent multigene panel testing for hereditary cancer predisposition at the Fleury Group between January 2020 and February 2025. Variant monitoring was conducted through an internally developed bioinformatics pipeline that systematically tracks updates in major public variant databases. When new evidence was identified, variants were reassessed by the laboratory's technical and medical team according to ACMG–AMP guidelines. Variants eligible for reclassification prompted the issuance of an updated clinical report, with notification to both the ordering physician and the patient in accordance with recommended best practices for variant reinterpretation. **Results**:A total of 39 variants across 15 genes were reclassified. Of these, 32 (82%) were upgraded, including 23 (72%) in clinically actionable genes and 9 (28%) in non-actionable genes, while 7 variants (18%) were downgraded, only one of which occurred in an actionable gene. Among 53,574 hereditary cancer panels analyzed during the study period, these reclassification events resulted in 110 updated clinical reports (0.21%), directly impacting clinical management or genetic counseling. **Conclusions**: Active variant reclassification is a feasible

strategy with meaningful clinical impact and should be considered an essential component of genetic follow-up programs. These findings also highlight the importance of continuous collaboration among laboratories, clinicians, and patients in the long-term monitoring of genomic data to maximize the clinical utility of genomic medicine.

Keywords: Hereditary cancer, Next-generation sequencing, Variant reclassification, ACMG-AMP

Introduction

Advances in DNA sequencing technologies, particularly through next-generation sequencing (NGS) platforms, have revolutionized our understanding of genomic alterations in humans and their clinical implications (Suwinski *et al.*, 2019). NGS enables the detection of a wide spectrum of genetic variants, including single-nucleotide variants (SNVs), small insertions and deletions (indels), structural variants, and copy number variations (CNVs), across both coding and noncoding regions of the genome (Abel e Duncavage, 2013). The characterization of these variants has direct clinical applications in molecular diagnosis of monogenic disorders, risk stratification for complex diseases (*i.e*, cancer, cardiovascular diseases, and neurodegenerative disorders) (Hampel *et al.*, 2015; Hershberger *et al.*, 2018; Xiao *et al.*, 2021; Geroldi *et al.*, 2024) and in guiding targeted therapies within precision oncology contexts (Morganti *et al.*, 2019; Nccn, 2025). Consequently, the study of such alterations using genetic panels in precision oncology has enhanced clinical variant interpretation accuracy and reinforced the implementation of personalized and predictive medicine approaches (Yoshida, 2021).

Genetic testing plays a fundamental role in the clinical management of hereditary cancer, contributing not only to diagnosis and therapeutic decision-making but also to screening, surveillance, and prevention strategies. These tests benefit both the individuals tested and their family members by enabling the adoption of prophylactic and risk-reducing measures based on identified genetic predispositions (Narod e Salmena, 2011; Daly *et al.*, 2021).

Within this framework, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) have established clinical interpretation guidelines for genetic variants detected in hereditary cancer panels. These guidelines define classification categories (benign [B], likely benign [LB], variant of uncertain significance [VUS], likely pathogenic [LP] and pathogenic [P]) and prescribe systematic criteria for classification, including variant population frequency, disease association studies, functional evidence, *in silico* predictions, familial segregation data, and phenotypic correlation with clinical presentation (Richards *et al.*, 2015). Since the publication of the ACMG-AMP guidelines in 2015 for the interpretation of germline variants, several professional societies have contributed to refining the analysis and classification of these findings, thereby enhancing the accuracy of the

interpretative process. In this regard, the recommendations of the ACGS (Association for Clinical Genomic Science) and ClinGen (Clinical Genome Resource) are particularly valuable (Clingen; Richards *et al.*, 2015; Miranda Durkie, 2024).

Pathogenic (P) and likely pathogenic (LP) variants are deemed clinically actionable in the hereditary cancer setting, directly informing genetic counseling, risk stratification, and defining preventive and therapeutic practices for patients and indicating cascade genetic testing to relatives at risk (Hampel *et al.*, 2015; Richards *et al.*, 2015; Daly *et al.*, 2023; Nccn, 2025). In contrast, VUS as well as benign and likely benign variants are considered non-actionable and should not guide clinical decisions until their significance is clarified (Richards *et al.*, 2015; Hoffman-Andrews, 2017; Adam *et al.*, 2023). It is important to emphasize that variant classification is dynamic: as new population, functional, and clinical evidence emerges, variants may be reclassified upward (upgrade) or downward (downgrade), substantially altering patient management. In studies involving hereditary cancer panels, VUS reclassification rates reach up to 25% over time, underscoring the importance of continuous monitoring of genetic interpretations (Richards *et al.*, 2015; Mersch *et al.*, 2018; Rivera-Munoz *et al.*, 2018).

In hereditary cancer predisposition panels, the identification of VUS remains a significant clinical challenge. These variants should be interpreted with caution, not be used as predictive testing in at-risk relatives, and should not guide clinical decisions owing to the lack of sufficient evidence to be considered benign or pathogenic. Nevertheless, variant interpretation is a continuous process: ongoing genetic research produces new functional, epidemiologic, and bioinformatic data that gradually clarifies the significance of these variants. Thus, many VUS originally reported may later be reclassified to likely/pathogenic (upgrade) or benign (downgrade), with both directions of reclassification having direct consequences for patient and family management (Mersch *et al.*, 2018; Slavin *et al.*, 2019). Variant reclassification for patients who have already undergone genetic panels can be of high clinical relevance, especially in oncogenetics, where genes like *BRCA1*, *BRCA2*, and *TP53* are frequently evaluated.

Genomic analysis using multigene panels has become an essential tool in detecting variants linked to hereditary cancer predisposition. Yet interpreting these variants, particularly those initially reported as VUS, represents a persistent clinical challenge. With the expansion of scientific literature and new population and functional data, these variants can be re-evaluated in light of fresh evidence, leading to their reclassification into clinically actionable or non-actionable categories. In this regard, an active reclassification model in which the laboratory proactively conducts periodic reanalysis of previously identified variants has emerged (Slavin *et al.*, 2019). In Brazil, Fleury Group is at the forefront of offering a structured active reclassification service for hereditary cancer-associated variants. This study aims to evaluate the number of patients who

benefited from active reclassification between 2020 and 2025, highlighting the clinical impact of this practice, including its implications in the context of genetic counseling.

Materials and Methods

This retrospective study aimed to evaluate the reclassification rate of germline variants in patients who underwent multigene panel testing for hereditary cancer predisposition at Fleury Group between January 2020 and February 2025. Genetic data were generated using next-generation sequencing (NGS) on the Illumina platform (Illumina, Inc., San Diego, CA, USA). This study focused on the continuous monitoring of classification updates for all variants identified in the patient's VCF (Variant Call Format), including those not initially reported, in light of emerging scientific evidence.

As part of an active variant reclassification protocol, all germline variants identified during this period were systematically reviewed monthly. A custom-built internal algorithmic pipeline was employed to screen potentially reclassifiable variants by aggregating newly available evidence from key public databases, such as ClinVar. This process flagged candidate variants that merited re-evaluation based on the updated population frequency, clinical variant interpretation repositories, gene-disease association databases, *in silico* predictions tools, scientific literature and curated mutation databases.

This study systematically evaluated genetic variants to identify those that underwent reclassification from variants of uncertain significance (VUS) to pathogenic (P) or likely pathogenic (LP) categories, or from (P)/(LP) to VUS, according to ACMG-AMP guidelines (Richards *et al.*, 2015). In addition to the ACMG-AMP guidelines, the re-evaluation process for variants eligible for reclassification also incorporated the recommendations of the ACGS (Association for Clinical Genomic Science) and ClinGen (Clinical Genome Resource), aiming to enhance the accuracy and consistency of variant interpretation (Clingen; Miranda Durkie, 2024). To optimize and standardize this process, we developed an algorithm for monthly re-evaluation of variants, enabling continuous and automated monitoring of the scientific evidence supporting potential reclassifications. New clinical reports are issued only for reclassifications with direct clinical impact, specifically, cases in which variants initially classified as VUS are upgraded to pathogenic or likely pathogenic or downgraded from pathogenic/likely pathogenic to VUS. Reclassifications from VUS to benign or likely benign do not trigger new patient reports; instead, these updates are recorded internally to maintain database accuracy and ensure proper classification in future cases involving the same variants.

A multidisciplinary team comprising clinical geneticists and molecular analysts reviewed the variants identified by the algorithm. The variant classification process adhered strictly to the guidelines established by the American College of Medical Genetics and Genomics and the

Association for Molecular Pathology (ACMG-AMP) (Richards et al., 2015), which include 28 evidence-based criteria (16 supporting pathogenicity and 12 supporting benignity).

Evidence sources consulted during reanalysis included:

- Population frequency databases:
    - gnomAD – https://gnomad.broadinstitute.org/
    - AbraOM – http://abraom.ib.usp.br/
- Clinical variant interpretation repositories:
    - ClinVar – https://www.ncbi.nlm.nih.gov/clinvar/
    - ClinGen – https://clinicalgenome.org
- Gene-disease association databases:
    - OMIM – https://omim.org
- *In silico* prediction tools:
    - Used to assess the potential molecular impact of variants on gene structure and function (specific tools integrated into the internal pipeline)
- Scientific literature and curated mutation databases:
    - PubMed – https://pubmed.ncbi.nlm.nih.gov/
    - HGMD – https://www.hgmd.cf.ac.uk/ac/index.php

Each reclassification was verified by the clinical and technical teams, when applicable, issuance of an updated clinical report, with formal notification to the ordering physician and the patient, in accordance with international best practices for variant reinterpretation and recontact (Mersch *et al.*, 2018; Slavin *et al.*, 2019).

Results

Between January 2020 and May 2025, a total of 53,574 hereditary cancer predisposition panels were processed and systematically monitored for variant reclassification. During this period, variants were actively reviewed according to the ACMG-AMP guidelines (Richards *et al.*, 2015), focusing on those involving clinically actionable genes and those associated with autosomal dominant (AD) or autosomal recessive (AR) inheritance patterns, even when not considered actionable. Reclassifications were categorized according to their clinical impact: (i) upgrades (from VUS to LP/P); and (ii) downgrades (from LP/P to VUS or LB/B). A total of 39 variants in 15 genes were reclassified; 32 (82 %) were upgraded, with 23 (72 %) in actionable

genes and 9 (28 %) in non-actionable genes, while the remaining 7 (18 %) were downgraded, only one of which was in an actionable gene. Considering the total of 53,574 hereditary cancer panels processed during the study period, 110 new clinical reports (0.21%) were issued following reclassification events of these 39 variants, with a direct impact on clinical or genetic counseling, as described in the methodology section.

From 2020 to 2023, a total of 49 reclassified reports were issued. Among these, 27 (55.1%) involved clinically actionable genes, including *MSH2, BRCA2, POLE, ATM, BRCA1, CHEK2, NF1, SDHB,* and *FLCN*. All 27 cases represented upgrades from variants of uncertain significance (VUS) to likely pathogenic or pathogenic (LP/P), with the highest reclassification frequency observed in *BRCA1*, *BRCA2*, and *CHEK2* (Table 1). The remaining 22 reports (44.9%) corresponded to variants in non-actionable genes. Within this subset, 15 (68.2%) were upgrades (VUS → LP/P) and 7 (31.8%) were downgrades (LP/P → VUS). Although these variants were not classified within actionable genes, their reclassification had a direct impact on genetic counseling and patient risk assessment (Table 2). The *POLE* gene, as shown in Table 1, underwent two sequential reclassification events during the study period: initially upgraded from VUS to LP, followed by a subsequent downgrade from LP back to VUS. This exemplifies the dynamic nature of germline variant classification and emphasizes its potential to directly impact clinical management and decision-making.

In June 2023, two distinct reclassification events were identified involving the *NTHL1* and *PRF1* genes, encompassing a total of nine cases. Specifically, two new clinical reports were issued following the reclassification of a variant in *NTHL1*, while seven additional cases were associated with a reclassified variant in *PRF1* (Table 3). Both events corresponded to upgrades from VUS to LP, underscoring the importance of active variant surveillance, even for genes not traditionally considered clinically actionable.

In July 2023, a total of eight new clinical reports were issued involving clinically actionable genes. Among these, one report corresponded to a variant reclassified from VUS to LP in the *BRCA2* gene, while seven reports involved variants reclassified from VUS to LP in the *PALB2* gene (Table 4).

In August 2023, a variant in the *TP53* gene was reclassified from VUS to LP, resulting in the issuance of a new clinical report (Table 5). It is noteworthy that, during the preparation of this manuscript, the variant NM_000546(*TP53*):c.829T>C:p.(Cys277Arg) (ClinVar ID: 421804) underwent a reclassification by our laboratory in August 2026, resulting in a downgrade from likely pathogenic (LP) to variant of uncertain significance (VUS), in accordance with the gene-specific guidelines established by the ClinGen Variant Curation Expert Panel (VCEP) for *TP53*.

Notably, the other variants described in this study involving genes with available VCEPs have not undergone any recent changes in their classifications.

From November to December 2023, a total of nine new reports were issued: one involving a variant in *BRCA2* reclassified from VUS to P, and six reports related to a variant in *CHEK2* reclassified from VUS to LP, both genes considered clinically actionable (Table 6). Additionally, during this period, a downgrade event was observed in the *HNF1* gene, where a variant was reclassified from LP to benign, leading to the update of clinical reports for two patients (Table 7).

In January 2024, a downgrade from LP to VUS was documented for a variant in the *POLE* gene, prompting the issuance of a new clinical report (Table 8).

In June 2024, 17 new reports were issued following the reclassification of a variant in the *RAD51C* gene from VUS to LP, classified as clinically actionable (Table 9).

In August 2024, nine reports were updated due to the reclassification of a *CHEK2* variant from VUS to LP (Table 10).

Finally, in February 2025, seven new clinical reports were issued, including two related to *TP53* and five related to *CHEK2* variants reclassified from VUS to pathogenic; both genes are classified as clinically actionable (Table 11).

Out of the 110 new clinical reports issued over the entire study period, 77 (70%) corresponded to reclassifications involving clinically actionable genes (Table 12).

For certain time intervals, results are presented in aggregated periods; for example, Table 1 summarizes data from January 2020 to May 2023, reflecting the combined analysis used for this study. However, variant reclassification analyses and clinical report updates are performed monthly whenever cases meet eligibility criteria for reclassification. Likewise, some months may not appear in the results, for instance, there is a gap between August 2023 to November 2023, indicating that no variants were selected for reevaluation during that interval, and consequently, no new clinical reports were issued.

When considering the number of affected cases rather than unique variants, actionable genes most impacted by reclassification included *CHEK2* (29 cases) and *RAD51C* (17 cases), followed by *BRCA2* (5 cases), *PALB2* (7 cases), *FLCN* (5 cases), and *POLE* (4 cases). In some genes, the same reclassified variant was observed across multiple unrelated individuals, thereby amplifying the patient-level impact.

At the patient level, reclassifications predominantly involved splice-site and missense variants. Splice-site variants accounted for the highest number of affected cases, particularly in clinically actionable genes such as *CHEK2*, *FLCN*, *BRCA1*, *BRCA2* and *RAD51C*. Missense

variants represented the second most frequent category, often impacting multiple patients through recurrent reclassifications of the same variant. Frameshift and nonsense variants were less frequently reclassified and were primarily observed in genes associated with autosomal recessive conditions.

This structured and continuous reclassification workflow enabled systematic identification of clinically meaningful variant changes, particularly in high-impact genes such as *ATM, BRCA1, BRCA2, CHEK2, MSH2, NF1, PALB2* and *TP53* which play a critical role in hereditary cancer risk management.

Discussion

From January 2020 to February 2025, our service analyzed about 53,574 hereditary cancer panels, reflecting the rapid expansion and consolidation of sequencing technologies in clinical molecular diagnostics.

In germline variant analysis and interpretation, the clinical classification process distributed among the five categories proposed by the ACMG-AMP guidelines (benign, likely benign, variant of uncertain significance, likely pathogenic, and pathogenic) (Richards *et al.*, 2015) is inherently dynamic and subject to change as new scientific evidence emerges.

In recent years, the analytical process has become increasingly complex, with the introduction of additional recommendations and interpretative frameworks that complement the 2015 ACMG-AMP guidelines. This complexity extends beyond the establishment of new criteria and includes the challenge of continuously integrating new data and maintaining up-to-date expertise among clinical genomics professionals. In this regard, the contributions of the ACGS and ClinGen have been instrumental in reducing interpretative bias, improving variant classification accuracy, and providing gene-specific refinement through the ClinGen *Variant Curation Expert Panels* (VCEPs) (Clingen; Miranda Durkie, 2024). VCEPs have become increasingly important in the interpretation of genetic variants, as they provide gene- and phenotype-specific recommendations developed through expert curation. These guidelines are currently considered to represent the most robust application of the ACMG-AMP framework for variant interpretation. Accordingly, their use is increasingly encouraged in germline variant analysis whenever gene-specific VCEP recommendations are available.

The active reclassification model assumes that the laboratory responsible for sequencing maintains an ongoing, proactive review of previously reported variants, systematically searching for updated evidence that may warrant reclassification (Slavin *et al.*, 2019). Although the 110 reclassifications identified during the study period represent a small proportion of the total 53,574 panels analyzed, each case corresponds to an individual patient whose clinical management,

surveillance, and genetic counseling may have been directly impacted by updated genetic evidence.

Active reclassification represents a cornerstone of best practices in clinical genomics. The capacity to reclassify VUS over time contributes to a more accurate understanding of genetic findings and enables more precise and personalized clinical decision-making for patients and their families.

In our study, we observed that over a period of 5 years, 39 variants were reclassified, and the vast majority were upgrades (82%) from VUS to LP/P in actionable genes, directly impacting patients and their at-risk relatives. This study has several limitations that warrant careful consideration. First, we did not have access to data on the overall prevalence of VUS among the more than 50,000 genetic panels analyzed. Consequently, we were unable to calculate the reclassification rate of VUS within the evaluated panels, which limits our capacity to accurately assess the longitudinal clinical utility of systematic reanalysis.

Additionally, the analytical design of this study focused exclusively on report updates that resulted in the issuance of a revised clinical report to the patient, specifically cases in which variants underwent a classification upgrade or downgrade relative to the original interpretation. However, the majority of VUS reclassified during the study period were downgraded to benign or likely benign and did not prompt a formal report reissuance; in these instances, only the internal database was updated by the analyst. As a result, these cases were not captured in the present analysis.

It is therefore important to emphasize that the results reported here consistent with findings in the scientific literature, demonstrate a relatively low proportion of reclassifications with direct clinical impact on patients. In this cohort, such cases represented 0.2% of all analyzed cases during the study period. This percentage includes both upgrades and downgrades that led to modifications of the original clinical report. While this rate appears low, it reflects only those reclassifications with clinically significance to genetic counseling and consedering the study's inclusion criteria and does not encompass the broader spectrum of VUS reinterpretations occurring within the laboratory database.

A important study of more than a million people who underwent genetic testing for hereditary cancer found that 7.7 % of VUS were reclassified; of those, 91.2 % were downgraded to LB/B after an average of 1.17 years, while 8.7 % were upgraded to P/LP after an average of 1.86 years (Mersch *et al*., 2018).

In another similar study, 1,412 VUS were found in 49.9% of the patients tested, and 6.7% of those variants were reclassified over six years. The majority (94.1%) were downgraded to

B/LB, with a smaller proportion of 5.9% upgraded to P/LP. Variants in actionable genes were reclassified in 31% of patients. The mean time to reclassification was 1.62 years (Chiang *et al*.,2021)

Among the most notable findings were reclassifications involving clinically actionable genes. A particularly illustrative case was the double reclassification of a variant in the *POLE* gene (Table 1). Initially reported as a VUS, the variant was subsequently reclassified as likely pathogenic based on its predicted loss-of-function effect. However, subsequent publications have clarified that only missense variants and in-frame insertions or deletions within the exonuclease domain of *POLE* are associated with the autosomal dominant polymerase proofreading-associated polyposis (PPAP; MIM #615083), a condition characterized by multiple colorectal polyps and an increased risk of colorectal câncer (Mur *et al.*, 2023).

Conversely, loss-of-function variants in *POLE* have been linked to distinct rare syndromes such as FILS (MIM #615139) and IMAGE-1 (MIM #618336), with no established association with hereditary cancer predisposition. Therefore, in the context of hereditary cancer testing, reporting *POLE* variants outside the exonuclease domain should be approached with caution and appropriate clinical context.

These observations underscore the critical importance of continuous evidence review and the timely incorporation of updated gene-specific knowledge into variant interpretation. They also highlight the need for laboratories to transparently communicate these nuances in their clinical reports, ensuring that genomic interpretations remain aligned with the most current and robust scientific evidence available.

Reclassification can have a significant impact on the clinical guidance provided to patients and their families. In the context of hereditary cancer, when a variant is reclassified as pathogenic or likely pathogenic in an actionable gene, it carries direct and practical clinical implications. This is because, for many genes, established clinical strategies exist to reduce cancer risk or enable early detection. These strategies may include intensified screening, risk-reducing surgery, chemoprevention, as well as genetic counseling and cascade testing within the family to identify other relatives who may be at risk. (Slavin *et al.*, 2019; Chiang *et al.*, 2021).

Among the genes in which variants have been reclassified, several high-risk cancer genes are particularly noteworthy. These include *BRCA1*, *BRCA2*, and *PALB2*, which are associated with breast, ovarian, pancreatic, and prostate cancers (Miki *et al.*, 1994; Wooster *et al.*, 1995; Rahman *et al.*, 2007). The *MSH2* gene, associated with Lynch syndrome, confers a high susceptibility to colorectal cancer as well as extra-colonic tumors, including cancers of the endometrium, ovary, stomach, and urinary tract (Leach *et al.*, 1993). Additionally, the *TP53* gene, associated with Li-Fraumeni syndrome, confers a high risk of developing a broad spectrum of

tumors throughout life, particularly at a young age (Malkin et al., 1990). Furthermore, variants in genes with moderate penetrance for breast cancer, such as *ATM*, *CHEK2*, *RAD51C*, and *NF1* (associated with Neurofibromatosis type I), have also been reclassified (Wallace *et al.*, 1990; Swift *et al.*, 1991; Meijers-Heijboer *et al.*, 2002; Meindl *et al.*, 2010)

The *SDHB* gene, associated with hereditary Paraganglioma/Pheochromocytoma Syndrome; the *FLCN* gene, associated with Birt-Hogg-Dubé Syndrome, which confers an increased risk of kidney cancer; and the *POLE* gene, in which germline mutations in the exonuclease domain are associated with adenomatous polyposis and an increased risk of colorectal, endometrial, and other cancers, also warrant careful attention. (Nickerson *et al.*, 2002; Gimenez-Roqueplo *et al.*, 2003; Palles *et al.*, 2013).

All of these genes exhibit autosomal dominant inheritance for the hereditary cancer phenotype, confer a well-established cancer risk, and are associated with specific guidelines for screening and prevention, directly impacting the clinical management and monitoring of carriers and their families.

Monoallelic variants identified in autosomal recessive genes, such as *NTHL1*, *PRF1*, and *HNF1A*, have also been reclassified. These variants indicate a carrier status, which generally has no direct clinical implications for the individual tested but may have reproductive significance. Genetic counseling should address the inheritance pattern, discuss the potential need for testing of the individual's partner, and assess the associated reproductive risks. Additionally, counselors should provide guidance on family planning strategies and, when appropriate, recommend testing of other at-risk family members.

Ultimately, implementing an active reclassification process represents a critical component of good clinical genomics practice, ensuring that variant interpretations remain dynamic, evidence-based, and directly beneficial to patient care. The Fleury Group has been a pioneer in establishing this initiative within the Brazilian context, reinforcing the importance of systematic variant review in national clinical genomics practice.

This proactive model enables the continuous delivery of clinically relevant genomic updates, supporting evidence-based clinical decisions not only for the index patient but also for at-risk relatives, particularly in the context of hereditary cancer syndromes. This approach ensures timely communication of clinically relevant results and underscores the importance of proactive, ongoing variant monitoring for risk assessment, individual and familial management, and the development of evidence-based cancer surveillance strategies.

In conclusion, over the past two decades, advances in genomic sequencing technologies have led to a substantial increase in the generation of clinically relevant genetic data. In this

context, active variant reclassification has emerged as a key component of genetic testing for hereditary cancer predisposition. This practice has demonstrated a positive clinical impact by enabling new therapeutic options, surveillance strategies, and personalized genetic counseling over time.

The experience of Grupo Fleury Laboratory, one of the pioneers in implementing an active reclassification model in Brazil, highlights the importance of continuously updating public databases such as ClinVar and ClinGen, alongside the scientific literature. A critical element in this process has been the development of an internal pipeline (unpublished data) designed to actively identify updates in these databases and flag potentially reclassifiable variants. This tool has proven essential in determining which variants are eligible for re-evaluation, ensuring that new evidence is systematically incorporated into clinical decision-making, with a direct impact on patient care.

When combined with technical expertise in the ACMG-AMP guidelines and clinical support for phenotype-genotype correlation, this model has resulted in a measurable increase in the number of reclassified variants, particularly evident in the first two quarters of 2023.

Therefore, active reclassification is a feasible practice with high clinical value and should be adopted as a standard in genetic follow-up programs. Furthermore, it underscores the need for continuous integration among laboratories, clinicians, and patients in the ongoing monitoring of genetic variants to fully realize the benefits of genomic medicine.

Author contributions

T.H.A.L.: provided the conception and design of the study, and acquisition of data. T.H.A.L., C.A.S.C., J.E.P.C., E.N.F., F.H.S., M.C.T.P., O.J.E.P., C.M.M., R.A.S., A.R.M., I.G., M.M.N., W.A.R.B. and D.P.: performed the analysis. T.H.A.L. wrote the manuscript with support from D.P., E.N.F. and C.M.M. revised it critically for important intellectual content. All authors read and approved the final version.

Ethics Statement

The study protocol was reviewed and approved by the Human Research Ethics Committee of Fleury Group (protocol number NP_779 and NP_614); Plataforma Brasil CAAE# 56961222.6.0000.5474; Fleury# 5.833.008). All procedures were conducted in accordance with applicable local regulations and institutional guidelines for research involving human participants. Written informed consent was obtained from all individuals before their inclusion in the study.

Conflict of Interest

All authors, except Miguel Mitne-Neto and Israel Gomy, are employees of Genesis Genomics. These authors receive salary and employment-related benefits from the institution. Miguel Mitne-Neto and Israel Gomy declare no competing interests.

Data Availability Statement

The datasets generated and analyzed during the current study are currently in the process of being submitted to the ClinVar repository and will be made available upon completion of the submission process.

Funding Declaration

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