Prevalence and re-classification Variants of Uncertain Significance (VUS): experience of a breast cancer center in northeastern Mexico.

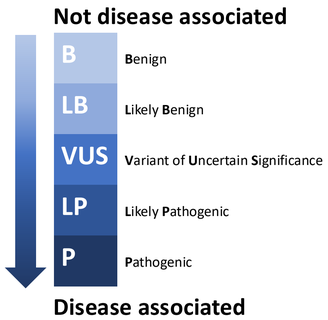
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Introduction

- **Variants of Uncertain Significance (VUS)** are **genomic alterations** for which **current evidence is insufficient to determine** whether they represent **a benign OR pathogenic change.**
- In **hereditary breast and ovarian cancer (HBOC)** genes:
  - **~23% of reported variants are VUS**
  - **19–27% are later reclassified**
  - **Reclassification rates vary by ancestry and database representation**
- This **uncertainty** complicates **clinical management, risk assessment, and surveillance planning.**
- The challenge is amplified in **underrepresented populations**, where limited **ancestry-specific** data **prolongs diagnostic uncertainty**.

Figure 1. Genetic variants associated with cancer classified by ACMG/AMP



Methods

We conducted a **retrospective clinical-genomic review**, including **only patients diagnosed with breast cancer** between **2018 and 2024** at the **Breast Cancer Institute of Zambrano Hellion Hospital.**

Results

- **Cohort Overview**
  - 1014 breast cancer patients included
  - **334 VUS identified**
  - **19 breast cancer–related VUS found in 9 patients**
- **Reclassification Outcomes**
  - **10** total reclassifications:
    - **Benign: 6**
    - **Likely pathogenic: 3**
    - **Pathogenic: 1**
- **Time to Reclassification**
  - Mean: **26.44** ± 12.6 months (**range 7–52**)
- **Clinical Characteristics**
  - **All** patients were **female.**
  - **Mean age** at breast cancer diagnosis: 40.3 ± 5.32 years.
  - All cases presented with **unilateral disease.**
  - **Triple-negative breast cancer** (TNBC) was observed in **44% of patients.**

Table 1. VUS identified in breast cancer patients and their reclassification outcome

Patient ID	Identified VUS (gene)	Time to reclassification (months)	Reclassification outcome
1	BRCA1	56	Pathogenic
	RET	81	Bening
2	NF1	21	Likely pathogenic
	BRCA1		VUS
3	NF1	52	Bening
4	NF1	15	Bening
5	NF1	18	Bening
	BRCA1		VUS
6	BRCA2	30	Likely pathogenic
	DICER1		VUS
7	POLE	26	Likely pathogenic
	ATM		VUS
8	NF1	38	Bening
9	BRCA2	7	Bening
	ATM		VUS
	BRCA1		VUS
	BMPR1A		VUS
	MEN1		VUS
	TMEM127		VUS

Table 2. Distribution of Reclassified Variants by Gene and Final Classification

Gene	Benign	Likely Pathogenic	Pathogenic	Total Reclassified
NF1	4	1	0	5
BRCA2	1	1	0	2
BRCA1	0	0	1	1
POLE	0	1	0	1
RET	1	0	0	1
Total	6	3	1	10

Discussion

- Underrepresentation of Mexican ancestry in genomic databases increases the likelihood of reporting variants as **VUS**.
- Similar to Arab and Hispanic cohorts, this reflects **structural—not biological—disparities** in genomic data.
- Most reclassified VUS were **benign**, suggesting uncertainty driven by limited population-specific evidence.
- Reclassification delays (up to **52 months**) highlight gaps in **systematic re-analysis** and follow-up.
- High VUS rates contribute to **clinical uncertainty**, **patient anxiety**, and **inconsistent management**.
- Findings support improving **genomic representation**, expanding **genetic counseling**, and implementing **recontact systems**.

Conclusions

- Nearly half of the VUS in this cohort were **reclassified**, confirming that variant interpretation is **dynamic** and evolves with new evidence.
- Reclassification patterns are influenced by the **underrepresentation of Hispanic populations** in genomic databases and by **limited access to genetic services** in Mexico.
- Improving VUS interpretation requires:
  - Incorporation of **population-specific genomic data**
  - **Functional assays**
  - **Co-segregation analyses**
  - Assessment of **co-occurrence** with known pathogenic variants
- Strengthening these elements will enhance **classification accuracy**, **reduce uncertainty**, and support **more precise genetic counseling**, particularly in **underrepresented populations.**

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