# Hereditary Breast Cancer Beyond BRCA1/2: Real-World Value of Cascade Testing in Southern Europe cohort

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## Abstract

In a Southern European cohort (n=387), we report a 23.5% diagnostic yield, validating the utility of multi-gene panels beyond BRCA1/2. Cascade testing proved critical, identifying 70.5% of high-penetrance and 72% of moderate-penetrance carriers (e.g., ATM, CHEK2), primarily among unaffected relatives.

These data challenge recommendations to limit moderate-risk gene testing, demonstrating that broad screening significantly expands prevention opportunities for at-risk families.

## Introduction

Multi-gene panel testing has expanded the identification of hereditary breast cancer syndromes. ESMO Precision Oncology Working Group recently published recommendations advising against routine testing of certain genes suggesting minimal mortality benefit (ATM, CHEK2).

We present the germline findings from a large, single institution cohort in Southern Europe, focusing on the diagnostic yield of high- and moderate-penetrance genes and the clinical context of variant identification.

## Methods and Materials

We conducted a retrospective analysis of patients (pts) referred to our Hereditary Cancer Genetic Counseling Unit between May 2023 and April 2025. Variant classification followed American College of Medical Genetics (ACMG) criteria.

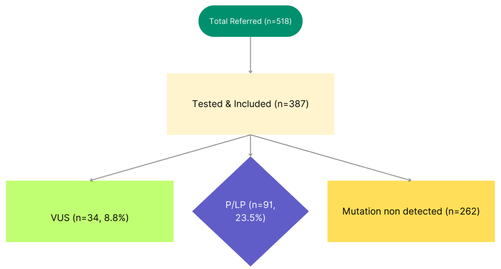



**Figure 1.** Study Flow and Patient Disposition

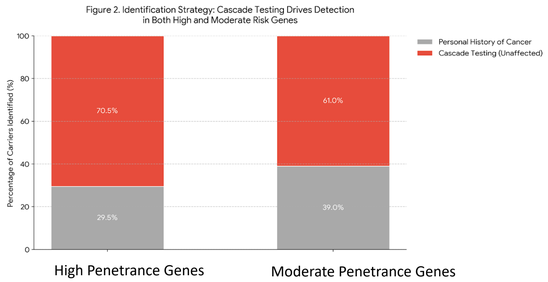



**Figure 2.** Identification Strategy: Cascade Testing Drives Detection in Both High and Moderate Risk Genes

## Results

From a total of 518 pts referred for counseling, 387 were tested and included in the analysis (median age 57).
Overall, 91 pts (23.5%) carried a pathogenic/likely pathogenic (P/LP) variant (Class 4/5) and 34 (8.8%) had a variant of uncertain significance (VUS). Among the 151 (39%) patients with a personal history of BC, the specific diagnostic yield for a P/LP variant was 14.56% (n=22), while the VUS rate was 15.2% (n=23).

Among P/LP carriers, 51 (56%) were in high-penetrance breast cancer genes: BRCA1 (n=24), BRCA2 (n=24) and PALB2, PTEN, CDH1 (n=1 each). 36 of 51 (70.5%) of these carriers were identified via cascade testing of healthy relatives. 18 of 91 pts (19.7%) P/LP variants were found in moderate-penetrance genes: ATM (n=9), CHEK2 (n=6), RAD51C (n=2), BRIP1 (n=1). Of note, 11 variants (61%) were identified through cascade testing rather than personal history of cancer.

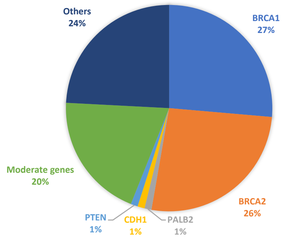



**Figure 3.** Gene Landscape

## Discussion

While ESMO focuses on the lack of mortality benefit for the cancer patient, our study highlights that the primary utility of finding ATM/CHEK2 is often for the healthy relative

## Conclusions

In this real-world cohort, nearly a quarter of individuals undergoing testing carried a clinically significant germline variant. While BRCA1/2 remain dominant, a substantial number of variants in genes like ATM, CHEK2, and RAD51C were discovered through cascade testing, mainly in unaffected carriers.

This highlights the clinical challenges surrounding the moderate penetrance genes, including appropriate follow-up and counseling strategies.

| Gene | Total carries (n) | BC Cases (n) | Multigene panel (n) | Cascade testing (n) (F;M) |
|---|---|---|---|---|
| BRCA1 | 24 | 8 | 8 | 16 (10;6) |
| BRCA2 | 24 | 7 | 5 | 19 (14;5) |
| PALB2 | 1 | 0 | 1 | 0 |
| PTEN | 1 | 0 | 1 | 0 |
| CDH1 | 1 | 0 | 0 | 1 (0;1) |
| ATM | 9 | 3 | 1 | 8 (7;1) |
| CHEK2 | 6 | 3 | 3 | 3 (3;0) |
| RAD51C | 2 | 0 | 0 | 2 (2;0) |
| BRIP1 | 1 | 1 | 1 | 0 |

*F: Female; M: Male*

**Table 1:** Pathogenic and Likely Pathogenic Germline Variants: Breast Cancer Cases and Detection Methods in a Hereditary Breast Cancer Cohort

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## References

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