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Germline BRCA - Lynch Syndrome MINAS: Report of Six Argentinian families and a systematic review of the literature

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Abstract

The co-occurrence of germline BRCA and Lynch Syndrome (gBRCA-LS MINAS) in a single individual is an infrequent overlap of the two most frequent hereditary cancer syndromes. Recent reviews have attempted to determine whether the cancer risk profile in gBRCA-LS carriers is independent for both syndromes or if the presence of both germline variants act as mutual modifying factors (synergistic effect). This study aims to describe and expand the knowledge on gBRCA-LS and describe the gBRCA-LS phenotype by reporting six affected Argentinian families and performing a systematic review of the literature. A total of 92 patients from 69 families who are carriers of pathogenic and/or likely pathogenic variants in both BRCA1 or BRCA2 and LS genes are described in the literature to date. BRCA1 was detected in 58% of families and MSH6 and PMS2 in 60,9%. Female to male ratio was 2:1. Overall, 81% (n = 75) of patients were diagnosed with at least one tumor. Median age of onset of breast cancer was 36,5 years in BRCA1 carriers and 40 years in BRCA2 carriers. Germline BRCA2 was overrepresented in patients with colorectal cancer and BRCA1 in patients with endometrial cancer. gBRCA-MLH1 was present in 44% (n = 4) of patients with ovarian cancers, with one gBRCA1-MLH1 carrier having a very early age of onset. Our findings suggest that the co-occurrence of gBRCA and LS may define a distinct hereditary cancer phenotype with synergistic features beyond those observed in either syndrome separately, although further studies are required to validate these observations.

Introduction

Multi-locus Inherited Neoplasia Allele Syndrome (MINAS) refers to the co-occurrence of two or more germline pathogenic or likely pathogenic variants (PVs) in cancer susceptibility genes (CSG) in the same individual, regardless of the genes, genetic variants or phenotypes involved [1]. The use of multigene panel testing (MGPT) as a standard of care in the clinical setting for hereditary cancer has led to the identification of a growing number of patients with MINAS [2].

Evidence about whether MINAS may have a unique (synergistic) or independent (additive) effect is scarce and limited mainly to BRCA1/BRCA2 given its high relative frequency [3–4]. Other MINAS combinations have been reported in isolation and aggregated data is lacking. The spectrum of possible synergistic effects includes varying degrees of severity, age of onset, and the presence of tumors outside of the established spectrum.

The co-occurrence of Hereditary Breast-Ovarian Cancer due to PVs in BRCA1 or BRCA2 and Lynch Syndrome (LS) due to PVs in MLH1, MSH2, MSH6, PMS2 and 3’ EPCAM deletions (gBRCA-LS MINAS) is the second most common MINAS combination [1]. To date, 29 patients have been described and analyzed in a review by Yuen et al [5], although the data about the phenotype is limited. Its prevalence is estimated to be between 4 to 5.6 per million people in diverse populations [6–8] and higher in Ashkenazi Jewish [9]. A cohort of over 250,000 individuals tested with multi-gene panel (MGPT) in a clinical setting established a frequency of 0,28% among mutation-positive patients [10].

The objectives of this work are (1) to report six new families with gBRCA-LS, and (2) to characterize the phenotype associated with this co-occurrence by conducting a systematic review of the literature.

Patients and Methods

Systematic review of the literature

This systematic review was conducted in accordance with the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [11]. We included observational studies—specifically case reports, case series, and cohort studies—reporting gBRCA-LS MINAS patients with detailed molecular and clinical information as specified below.

A comprehensive search of PubMed and Embase was conducted on November 28 2025, with no date restriction. The search was limited to articles in English and Spanish. The following search strategy was used: “("BRCA1" OR "BRCA2") AND ("MLH1" OR "MSH2" OR "MSH6" OR "PMS2" OR "EPCAM" OR "MMR" OR "Mismatch Repair" OR "Lynch") AND ("germline mutation" OR "germline" OR "germ-line" OR "genetic predisposition" OR "inherited mutation" OR "cancer susceptibility genes" OR "double heterozygosity" OR "double heterozygotes" OR "double heterozygous" OR "double pathogenic" OR "double pathogenic variants" OR "double mutations" OR "double variants" OR "double germline mutations" OR "Co-Occurrence" OR "Concurrent" OR "Transheterozygotes" OR "Transheterozygous" OR "Transheterozygosity" OR "Co-inheritance" OR "Coinheritance" OR "Co-dominance" OR "Codominance" OR "Co-existence" OR "Coexistence" OR "MINAS" OR "multilocus inherited neoplasia") AND ("Cancer")”.

Study Selection

Two reviewers independently screened titles and abstracts for relevance, followed by full-text review. Inclusion criteria were met if the studies described cases with confirmed gBRCA-LS MINAS detailing both the patients’ phenotypes and genetic variants involved. We excluded reports that lacked the description of the phenotype or genetic variants or included variants of uncertain significance. When the genetic variants were absent, attempts were made to contact corresponding authors for clarification. Discrepancies were resolved by consensus between the reviewers. Additional cases were identified after the date of the systematic review by screening the MINAS section of LOVD [12] and by reviewing references from the included studies.

National and institutional databases

We retrospectively identified additional gBRCA-LS MINAS cases from institutional and national sources. Molecular reports from the SITHER (Hereditary Tumor Information System) [13] public database were reviewed, and a call for cases was issued through the Argentinian Familial Cancer Network (RACAF)

clinical registries. Participating medical geneticists or oncologic genetic counselors provided anonymized data on family history, cancer diagnoses, and demographic characteristics.

Data extraction, categorization and statistical analysis

For each reported patient (from publications and local records), we collected the following data: gender; age at report, death, or last tumor diagnosis; ethnicity; PVs; clinical status (affected/unaffected, number and type of tumors, age of onset); histopathological and molecular details; and any additional relevant clinical information (including other diseases or genetic variants). Current NCCN criteria for BRCA and LS testing were assessed for every patient [14–15].

Affected individuals were classified into the following phenotypic categories based on their cancer diagnoses:

- *BRCA-related*: breast cancer (BC) and melanoma;
- *LS-related*: colorectal cancer (CRC), endometrial cancer, sebaceous acanthomas, gastric, small bowel, biliary tract, bladder and central nervous system tumors;
- *Overlapping tumors*: ovarian (OC), pancreatic, and/or prostate cancer;
- *Other*: tumors outside the BRCA and LS spectra.

To compare the groups, we constructed 2×2 contingency tables (events/non-events) and estimated the odds ratio (OR) with its 95% confidence interval using the two-tailed Fisher's exact test, setting $\alpha = 0.05$. When zero cells were present, the Haldane–Anscombe correction (+ 0.5) was applied prior to calculation. Analyses were performed in R (R Foundation for Statistical Computing) using the fisher.test() function (conf.level = 0.95).

Results

gBRCA-LS patients reported in this study

Six families with gBRCA-LS MINAS were identified in the institutional records with diagnoses between the years 2012 to 2025. Pedigrees are shown in Online Resource 1.

Family 1

A 29-year-old female was diagnosed with stage II (T3N0M0) moderately differentiated CRC adenocarcinoma showing mismatch repair deficiency (dMMR) due to loss of MSH2 and MSH6 expression on immunohistochemistry (IHC). She underwent sigmoidectomy. Single-gene sequencing detected a PV in MSH2: c.2539_2542del p.(Lys847Profs*44). At age 32 a unilateral hormone receptor (HR) positive ductal carcinoma in situ (DCIS) was detected and treated with quadrantectomy, radiotherapy, and tamoxifen for 5 years. Its microsatellite stable status (MSS) was discordant with a

total loss of MMR protein expression on IHC. Complete sequencing and MLPA of BRCA1/BRCA2 identified an intronic PV in BRCA2 (c.8755-1G > A). To date, no other family member has been tested for both variants.

Family 2

A 41-year-old female from a family with a previously known PV in BRCA1: c.211A > G, p.(Arg71Gly) on the maternal side was diagnosed with a dMMR (isolated PMS2 deficiency), microsatellite instability-high (MSI-H) sigmoid CRC. She underwent left hemicolectomy. Histology revealed areas of mucinous carcinoma, signet-ring cells, and poorly differentiated medullary features with lymphovascular invasion and positive lymph nodes (1/35). A second primary CRC was diagnosed in the transverse colon within the first year of follow-up and a transverse colectomy was offered. Histology confirmed a moderately differentiated mucinous adenocarcinoma with signet-ring features and lymphovascular invasion. BRAF V600E testing was negative but IHC was not performed. MGPT confirmed the presence of the familial BRCA1 pathogenic variant and identified an additional PV in PMS2 (c.1687C > T, p.Arg563*). Familial segregation of the PMS2 variant has not yet been confirmed.

Family 3

The index case is a 44-year-old female diagnosed with a stage IIIC2 (pT3a N2 M0), MSH2 and MSH6 deficient endometrial adenocarcinoma (EC) and a metachronous, stage I (pT1 N0 M0) uterine, spindle-cell leiomyosarcoma with fumarate hydratase deficient by IHC. A panel testing of 8 genes (including FH) detected PVs in BRCA1: c.68_69del p.(Glu23Valfs*17) and MSH2: c.1906G > C p.(Ala636Pro). She underwent total anexo-hysterectomy, adjuvant chemotherapy (paclitaxel-carboplatin), pelvic radiotherapy and intravaginal brachytherapy. After one year she progressed with thoracic and abdominal lymph nodes and received immunotherapy with pembrolizumab. An unaffected sister and their mother, also with EC at age 58, were subsequently diagnosed as double heterozygotes while a sister with ovarian and CRC only carries the MSH2 variant and is a true negative for BRCA1.

Family 4

A 48-year-old female was diagnosed with triple-negative invasive breast ductal carcinoma (TNBC) with negative axillary lymph nodes. She underwent mastectomy followed by adjuvant chemotherapy. BRCA1 and BRCA2 sequencing revealed a pathogenic variant in BRCA1: c.5123C > A p.(Ala1708Glu). She underwent risk-reducing contralateral mastectomy, hysterectomy and bilateral salpingo-oophorectomy and has been disease free for 14 years. Given her family history of cancer in both sides of her family and the finding of four non-dysplastic polyps on a colonoscopy, a MGPT was ordered which confirmed the presence of the BRCA1 variant and revealed an additional variant in PMS2: c.137G > T p.(Ser46Ile). An unaffected son inherited both variants.

Family 5

The index case is a 72-year-old male diagnosed with a stage II (T1 N1 M0) HR positive, Her2 negative mucinous and micropapillary invasive breast carcinoma. He underwent unilateral mastectomy and adjuvant chemotherapy. Germline NGS detected PVs in BRCA2: c.5946del (p.Ser1982Argfs*22) and a deletion of exons 1 to 15 in PMS2 confirmed by MLPA. His maternal aunt had been diagnosed with breast cancer at age 40 and was previously known to carry the BRCA2 PV. His mother with BC at the age of 55 is an obligate carrier of this variant. A brother with prostate cancer had tumor NGS testing that included BRCA2 and PMS2 genes that only detected the BRCA2 PV with a 50% allele frequency. A sister with endometrial cancer was negative for BRCA2 and is currently untested for PMS2.

Family 6

The proband is a 60-year-old male with a previous diagnosis of an MMR proficient (pMMR), rectal adenocarcinoma at age 55 and was treated with Dixon surgery followed by concurrent radiotherapy and adjuvant chemotherapy. Family history included a maternal aunt with four primary tumors who had previously tested positive for a PV in MSH6: c.3959_3962 del (p.Ala1320Glufs*6) and a niece with a triple negative breast cancer who had tested positive for a PV in BRCA1: c.68_69del p.(Glu23Valfs*17). MGPT revealed the presence of both familial variants in the proband. His two daughters are currently untested, an unaffected brother only inherited the BRCA1 PV and his mother is an obligate carrier for the MSH6 variant.

Systematic review

Forty publications meeting inclusion criteria were retrieved by systematic review and referenced articles [2; 5–9; 12; 16–49]. The flow of study selection is depicted in Fig. 1 (see Online Resource 2 for excluded studies). Including patients retrieved from the systematic review (81 patients), the LOVD MINAS database (2 patients) and the six previously unreported families described in this report (9 patients), a total of 92 individuals with gBRCA-LS MINAS have been reported to date.

The included studies span publication years from 2000 to 2025 and represent cases from a broad geographic distribution, including Asia (28,2%), Europe (28,2%), North America (25,6%), Latin America (15,4%), and Oceania (2.6%).

Clinical and molecular characteristics of gBRCA-LS MINAS patients.

A total of 92 gBRCA-LS carriers (median age: 50 years; range 22–91 years) from 69 families were identified (Online Resource 3), 65% (n = 53) female and 35% (n = 29) male (n = 10 gender not reported). Overall, 81% (n = 75) were cancer-affected and 19% (n = 17) were non-affected carriers. Testing criteria according to NCCN current guidelines were fulfilled in 93% of patients for BRCA testing, 80% for LS and 73% for both.

Among 75 cancer-affected patients, there was sufficient clinical information from 68 individuals to determine the number of tumors per patient: 1 (n = 42; 62%), 2 (n = 17; 25%) and ≥ 3 (n = 9; 13%) tumors.

Phenotypic categories of these patients were: 23 BRCA-only (34%); 21 LS-only (31%); 22 with both BRCA and LS tumors or at least one overlapping tumor (32%); and 2 with non-related tumors (3%).

Genotypic composition of the cohort revealed that BRCA1 PVs were present in 58% (n = 40) of families and LS genes showed a predominance of MSH6 and PMS2 (60,9%; n = 42). An EPCAM deletion was detected only once. One patient had triple MINAS (BRCA2-MLH1-MSH6). Three patients carried a third heterozygous PV (2 NBN and 1 MUTYH). Gene combination can be found in Table 1.

Type of genetic variants for BRCA1 and 2 were 77% (n = 53) frameshift or truncating, 11% (n = 8) missense, 6% (n = 4) intronic and 6% (n = 4) BRCA1 intragenic deletions. For LS genes there were 53% (n = 37) frameshift or truncating, 23% (n = 16) missense, 11% (n = 8) large genomic rearrangements, 10% (n = 7) intronic variants and 3% (n = 2) single-codon in-frame deletion and start loss variants.

Excluding the case with triple MINAS, carriers of MSH6 and PMS2 were less likely to be diagnosed with two or more tumors (10/53; 18,9%) than MLH1, MSH2 and EPCAM carriers (17/37; 45,9%) [OR 0,40 (IC95 0,17 – 0,91) p = 0.0486]. Six of the nine (66,6%) patients with 3 or more tumors were MLH1 or MSH2 carriers.

Table 1
"Genotypic combination of gBRCA-LS MINAS"

Genes	BRCA1	BRCA2	Total
MLH1	8 (11,6%)	4 (5,8%)*	12 (17,4%)
MSH2	6 (8,7%)	7 (10,2%)	13 (18,9%)
MSH6	13 (18,9%)▯	9 (13%)	22 (31,9%)
PMS2	12 (17,4%)	8 (11,6%)	20 (29%)
EPCAM	1 (1,4%)	-	1 (1,4%)
MLH1 & MSH6	-	1 (1,4%)	1 (1,4%)
Total	40 (58%)	29 (42%)	69 (100%)

* 2 patients from one family carried a third heterozygous PV in NBN: c.2140C > T p.(Arg714*)

▯1 patient carried a third heterozygous PV in MUTYH: c.536A > G p.(Tyr179Cys)

Tumor analysis

A total of 120 tumors were diagnosed in this cohort of gBRCA-LS patients: 37% (n = 45) BRCA-related, 39% (n = 47) LS-related, 13% (n = 16) overlapping tumors, and 10% (n = 12) were not related to BRCA nor LS.

Prevalence of gBRCA1 carriers in BC patients (52%; n = 20) was similar to gBRCA2 (48%; n = 17). Median age at first BC diagnosis was younger in BRCA1 carriers compared to BRCA2 (36,5 years vs 40 years respectively). A second BC (contralateral or side N/R) was diagnosed in five females: two carried BRCA1 (combined with MLH1 and MSH2) and three BRCA2 (two alongside MSH6 and one MSH2). TNBC was found in BRCA1 carriers in 80% of breast tumors (n = 8) (3 MLH1, 4 MSH6, and 1 PMS2). BRCA2 was carried by both males with BC (1 MSH6 and 1 PMS2) and the three patients diagnosed with melanoma (2 MSH2 and 1 MSH6).

Distribution of LS-only related tumors showed 44% (n = 21) CRC, 34% (n = 16) endometrial, 9% (n = 4) bladder and urinary tract, 6% (n = 3) gastric, 4% (n = 2) sebaceous carcinoma, and 2% (n = 1) central nervous system cancer. gBRCA2 carriers were detected in 63% (n = 12) of CRC patients. gBRCA1-LS MINAS (4 MLH1, 4 MSH2, 2 MSH6, 2 MSH2) was carried by 70% (n = 12) of endometrial cancer patients and 30% (n = 4) carried BRCA2-LS MINAS (1 MSH2, 2 MSH6 and the patient with triple MINAS). One endometrial carcinosarcoma (BRCA1-PMS2) was MMRp and MSS. Overall, extracolonic tumors within the LS spectrum were more frequent in MLH1, MSH2 and EPCAM (21/37, 56,8%) than MSH6 and PMS2 carriers (15/53; 28,3%) [OR 3,28 (IC95 1,26 – 8,84) p = 0.0089].

In overlapping tumors, 78% (n = 7) of ovarian cancer cases were found in gBRCA1 carriers. gMLH1-BRCA MINAS was carried by 44% (n = 4) of OC patients (3 BRCA1, 1 BRCA2). One carrier of MLH1 and BRCA1 had an age of onset of OC of 31 years. BRCA2 was carried by 75% (n = 3) of males with prostate cancer (1 MSH2, 1 MSH6 and 1 PMS2). gBRCA2-PMS2 was carried by 67% (n = 2) of pancreatic cancer patients. Evidence about driver genes in overlapping tumors (n = 12) is scarce: 2 ovarian tumors had concordant MMRd (one of which was MSI-H and also had BRCA LOH) and 2 pancreatic tumors were microsatellite stable (one with an MMR deficiency concordant with its LS gene and no BRCA LOH; one with BRCA2 LOH).

Twelve tumors unrelated to the BRCA or LS spectra were detected in nine patients. Two female patients affected by more than one unrelated tumor (1 BRCA2-MLH1 and 1 BRCA2-MSH6) each had a hematological malignancy and a squamous cell carcinoma. Lung and kidney cancer were the only other type of tumors diagnosed more than one time within this category.

Tumor characteristics can be found in Table 2

Discussion

To our knowledge, this systematic review identifies the largest number of gBRCA-LS patients reported to date, including the detailed report of six new families from Argentina.

Previous studies have explored the clinical spectrum in individuals with gBRCA-LS MINAS. Harada et al. suggested a predominance of BRCA-associated tumors, while Yuen et al. reported a predominance of the overlapping phenotype over Lynch syndrome and BRCA-associated tumors. Additionally, Zhang et al. identified an earlier onset of gastric cancer in patients with Homologous Recombination Deficiency

(HRD)-LS MINAS. In our cohort, the phenotypic distribution of the patients was even among the three categories. We only detected three cases of gastric cancer in gBRCA-LS MINAS, making it not possible to establish an early age of onset in this group.

The difference in number of tumors among MLH1 and MSH2 in comparison with MSH6 and PMS2 carriers may reflect the differences in penetrance among these genes, producing a higher prevalence of LS-only tumors in patients with gMLHS1 and gMSH2 and of BRCA-only in patients carrying gPVs in MSH6 and PMS2.

gBRCA2 overrepresentation in CRC and of gBRCA1 in EC may indicate modifying factors and therefore a distinct risk profile in gBRCA-LS MINAS carriers that warrants further investigations. Similarly, the early age of onset observed in ovarian cancer —particularly among individuals with gBRCA1-MLH1 PVs— might be of importance regarding the optimal timing of risk-reducing salpingo-oophorectomy in this population. There are currently no specific guidelines for the management and surveillance of patients with MINAS.

Incorvaia et al [50] described the interactions between the MMR and HRD pathways involved in tumorigenesis that could be of importance for clinical and therapeutic purposes. Overlapping tumors represent a challenge in the understanding of the MINAS phenotype and are critical to establish the gBRCA-LS phenotype. Comprehensive somatic analyses (including MSI, IHC, LOH studies, and genomic profiling) in ovarian, prostate and pancreatic cancer are needed to clarify the interaction between BRCA and MMR pathways deriving in the tumors of gBRCA-LS MINAS carriers. In this review we found limited evidence regarding which pathways were involved in overlapping tumors: one of the ovarian tumors had both MMRd and BRCA LOH, providing conflicting information about its pathogenesis. A second ovarian tumor only showed MMRd, one pancreatic tumor exhibited both MMRd and MSS and a second pancreatic cancer only showed BRCA2 LOH.

The tumors outside the classical BRCA-LS spectrum seem to appear sporadically without a predominant tumor type, making it unlikely that the combined presence of BRCA and MMR PVs defines an expanded spectrum. Instead, these may represent coincidental findings not directly attributable to the MINAS context, although further studies are needed to establish the full extent of gBRCA-LS phenotype.

Despite reflecting a selection bias, 81% of the patients in the cohort had at least one cancer diagnosis, suggesting that the overall disease burden in gBRCA–LS MINAS may be higher than in either BRCA or LS carriers alone. All unaffected carriers were relatives identified through cascade testing. Considering the low prevalence of this condition and that a proportion of carriers would not have been detected using current NCCN testing criteria for BRCA or LS syndromes alone, we underscore the utility of broad MGPT approaches to improve detection.

This study has strengths and limitations. Among the strengths, we identified gBRCA-LS patients not included in previous systematic reviews, thereby expanding the current knowledge of this condition. To enhance data robustness and avoid duplication and the inclusion of VUS, we excluded reports lacking

detailed genetic variants and/or relevant clinical information. If such data had been available, up to 52 additional cases could have been included (ESM_2)

We also contribute to the literature with six previously unreported Argentinian gBRCA–LS MINAS families, including comprehensive clinical and molecular information. We underscore the importance of including underrepresented populations with diverse ethnic backgrounds, which remain largely absent from European and North American series.

A limitation lies in the heterogeneity of the included reports, which ranged from detailed case reports to large cohorts with variable depth and quality of clinical, familial, and genetic information. Histological and molecular information about the tumors identified in the review was available for approximately a third of them.

In conclusion, gBRCA-LS MINAS is an infrequent condition with multiple considerations regarding its prevalence, diagnosis, management and surveillance. Some elements of its phenotype may be distinctive enough from both syndromes individually to acknowledge a synergistic effect to a certain extent. Detailed case reports including tumor types, family history, genetic testing results and somatic studies are needed to advance the understanding on the subject.

Declarations

The authors declare no competing interests

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Author contributions:

All authors contributed to the study conception and design. Guillermo Alberto and Fernando Tortosa performed the data collection for the systematic review. Guillermo Alberto, Lucas Sebastián Sánchez, María Dolores Mansilla Figueroa and Luisina Bruno performed the study selection of the systematic review. Guillermo Alberto, Luisina Inés Bruno, Lina Matilde Nuñez, María Dolores Mansilla Figueroa, Lucas Sebastián Sánchez, Gabriela Norese, Mariana Hirst, Melina Winocur and María Ana Redal participated in the data collection and analysis for the families reported in this study. The first draft of the manuscript was written by Guillermo Alberto and Lina Matilde Nuñez and all authors commented on previous versions of the manuscript. All authors read and approved of the final manuscript.

Ethics Statements

This study was evaluated and approved by the Research Ethics Committee of Instituto Alexander Fleming with the registry code #18348. The study was designed and performed according to the 1964

Declaration of Helsinki and the national law for protection of personal data which sets the scope of use of anonymized personal data protection for scientific investigations.

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Table 2

Table 2 is available in the Supplementary Files section.

Figures

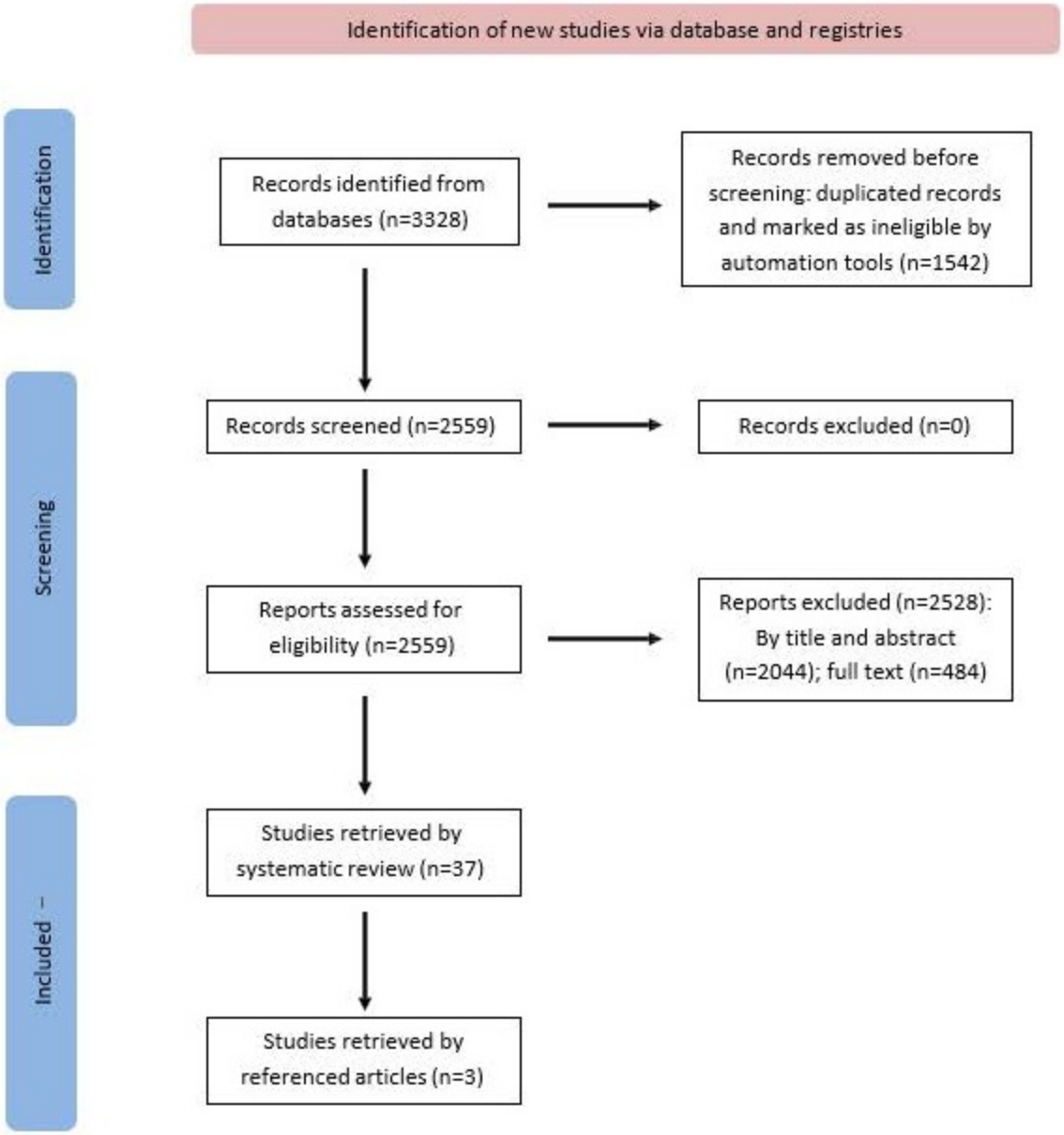


Figure 1

PRISMA flowchart of study selection in the systematic review

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