Preventable

SUSTAINABLE CARE FOR RARE TUMOUR RISK SYNDROMES

Deliverable D3.2 (WP3)

Cost-benefit model care pathways of RTRS and per RTRS 1

20 November 2024

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Document Control Sheet

PROJECT INFORMATION

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WP-Leader (Name and Short Org. Name)	Céu Mateus (LU)
Task No	Task 3.2
Task Title	Use multicentric clinical data (WP1) to model the disease progression in RTRS patients receiving primary/secondary prevention measures and/or treatment.
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Reviewer	Date	Reviewer Name (Short Organisation Name)
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2	27/06/2024	Carla Oliveira (i3S), Sara Pereira (i3S)
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Legal disclaimer

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ABBREVIATIONS

Abbreviation	Definition
BHD	Birt-Hogg Dubé syndrome
ERN GENTURIS	European Reference Network Genetic Tumour Risk Syndromes
FMM	Familial Malignant Melanoma
GIST	Gastrointestinal Stromal Tumour syndrome
HDGC	Hereditary Diffuse Gastric Cancer
HLRCC	Hereditary Leiomyomatosis and Renal Cell Carcinoma
LFS	Li-Fraumeni Syndrome
PHTS	PTEN Hamartoma Tumour Syndrome
PJS	Peutz-Jeghers Syndrome
RTRS	Rare Tumour Risk Syndromes
WP	Work Package

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Executive Summary

Deliverable D3.2 of the PREVENTABLE project (***Cost-benefit model care pathways of RTRS and per RTRS 1***) is part of the work carried out by **WP3**, in coordination with the rest of the WPs of the project. Deliverable D3.2 is led by the **LU** (**Lancaster University**).

This deliverable, is part of a set of deliverables describing the steps to develop the cost-benefit model for the 8 RTRS included in PREVENTABLE: HDGC- Hereditary Diffuse Gastric Cancer, GIST- Gastrointestinal Stromal Tumour syndrome, BHD- Birt-Hogg Dubé syndrome, HLRCC- Hereditary Leiomyomatosis and Renal Cell Carcinomas, LFS- Li-Fraumeni Syndrome, PHTS- PTEN Hamartoma Tumour Syndrome, FMM- Familial Malignant Melanoma, and PJS- Peutz-Jeghers Syndrome. Despite associated with task 3.2, the current document refers to both tasks 3.1 and 3.2 from WP3. This report summarises the literature review that is an essential step to develop the cost-benefit model.

The conclusions from this deliverable will be highly relevant to the health economic cost analysis of the different clinical pathways of care for each RTRS.

About the project

The **PREVENTABLE** project was created to address the existing knowledge gap regarding the costs of the pathways of care in patients with **Rare Tumour Risk Syndromes (RTRS)**, namely when comparing prevention with therapeutical approaches. The project **main aim** is to **assess the clinical, social and financial impact of applying multidisciplinary and specialized care to prevent advanced disease in families suffering from RTRS**.

RTRS are a **group of rare diseases** genetically determined by birth, which predispose patients to high susceptibility to develop cancers during their whole life and to transmit the disease to their offspring. Since the genetic and heritable defects responsible for causing RTRS are already known for many of the syndromes, there is the opportunity to spot high-risk carriers before the disease progresses and define trajectories for tumour onset and development. This knowledge is particularly relevant since RTRS disease onset is relatively random: besides being gender-specific in some cases, cancers may develop in organs at different orders, with diverse recurrence patterns, and at different ages.

In this sense, PREVENTABLE is focused on the **pathways of care of eight RTRS**, in which cancer onset is known to affect both males and females, some of them during childhood, to define and evaluate specific conditions for these pathways, including prevention, diagnosis or therapeutic protocols. An integrative **comparison between cumulative health costs of prevention versus treatment pathways** across all PREVENTABLE participating hospitals will **allow tailoring specific pathways of care to prevent advanced disease in RTRS-carrying families while reducing the economic burden** associated with hospitalization and treatment of clinically expressed cancers.

PREVENTABLE is a **36-month Horizon Europe project under the call HORIZON-HLTH-2022-CARE-08 and Grant Agreement 101095483**, funded by the European Health and Digital Executive Agency (HADEA). The project integrates several EU and two non-EU partners, including ten healthcare centres experts in the eight RTRS from **Portugal**, **Spain**, **France**, **the Netherlands**, **Norway, Sweden** and **Germany**, and Healthcare Providers of the European Reference Network on Tumour Risk Syndromes (ERN GENTURIS). The consortium is also composed of experts in the fields of health economics and behavioural science models, multidisciplinary innovation and organisational networking.

Overall, PREVENTABLE will enable the **implementation of cost-effective RTRS patient-centred care with long-term clinical, social and financial benefits across Europe, and a long-lasting impact on all RTRS patients and their families**.

Chapter number

D3.2 – Cost-benefit model care pathways of RTRS and per RTRS 1

Preventable
SUSTAINABLE CARE FOR RARE TUMOR RISK SYNDROMES

1. Introduction

Rare tumour risk syndromes (RTRS) are a series of rare diseases, affecting 5 or less per 10.000 people and caused by heritable genetic variants, that predispose individuals to the development of cancer throughout life. Besides this high-risk of developing various cancers across their lifetime, which can be as high as 100%, these individuals have a 50% chance of transmitting the disease to their offspring.

RTRS constitute a fraction of heritable cancers which are rare, neglected, and need specialised care. Despite the fact that there is considerable diversity in the organ systems that may be involved, individuals affected by these conditions share similar challenges: Delay in diagnosis, lack of prevention for patients and healthy relatives, and therapeutic mismanagement. When undiagnosed or not surveilled, many asymptomatic RTRS patients can develop aggressive cancers, leading to premature death, severely impacting theirs and their families' health and quality of life.

Cancers in RTRS can be prevented and survival rates maximized if asymptomatic patients are involved in intensive surveillance programs, cancer-prone organs are surgically removed prior to disease development, or very small cancerous or precancerous lesions are removed or treated. RTRS concurrently provides a unique and powerful context for cancer prevention, early diagnosis, and treatment, from which both symptomatic and asymptomatic patients would benefit immensely.

2. Literature review

2.1 Objectives:

Main objectives of WP3 are:

- To collect data from the literature to model the natural progression of diseases occurring in RTRS patients, by conducting a specific literature review for each of the eight syndromes involved in the project.

- To collect mainly retrospective observational data (published), including estimation of cancer incidence, pre-cancer mortality and post-cancer mortality rates among carriers who do not opt for preventative surgery or surveillance programs but also for those participating in specific clinical vigilance programs.

- Subsequently, to use multicentric real clinical data to model the disease onset and progression, and to model the differences in outcomes and costs in RTRS patients receiving primary/secondary prevention measures and/or treatment, taking forward the work developed in WP1 and WP2.

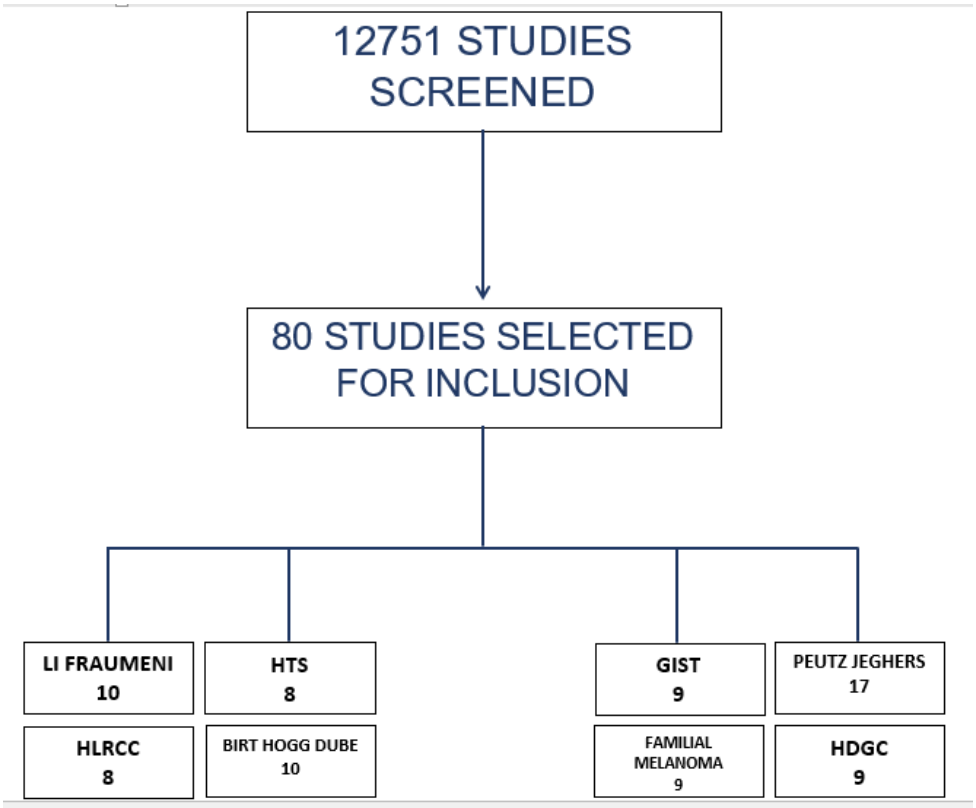
2.2 Summary of progress

A systematic literature review was performed for each syndrome considered in the project. Two major databases, one medical, PubMed and one general, Embase, were searched to locate studies about the syndromes, their clinical manifestations, diagnosis, treatments and surveillance programs. Database search was accompanied by hand searching of reference lists and citations of relevant publications to identify any additional studies.
Searches were focused on patients with specific RTRS, carriers of a germline pathogenic or likely pathogenic variant in the disease-causing gene, that can be either asymptomatic (considered as a carrier individual who has not (yet) developed any manifestation of the disease), or symptomatic (considered as a carrier individual who has developed disease within the RTRS spectrum).
Only studies written in English, Portuguese or Spanish, published from 2010 to date (May 2024) were considered. Specifically, research papers involving studies performed in humans were included. Studies without published results, those regarding specific treatments, diagnostic methods or features of the syndrome, single case/family reports or reviews/meta-analysis were excluded (*see Appendix for complete Data Searches*).

2.3 Results

Eight PRISMA flow diagrams (*See Appendix*) were created to record the different stages of the literature search and to improve the transparency and the scientific methodology applied.

In total, more than 12.000 studies were screened and finally 80 papers were selected for data extraction. Covidence was used as a screening tool; and retrieved data was organized and data extraction tables created using Microsoft Excel.



Li-Fraumeni Syndrome; HTS: PTEN Hamartoma Tumour Syndrome; GIST: Gastrointestinal Stromal Tumour; HLRCC: Hereditary Leiomyomatosis and Renal Cell Cancer; HDGC: Hereditary Diffuse Gastric Cancer; Birt-Hogg Dubé syndrome; FMM- Familial Malignant Melanoma and Peutz-Jeghers Syndrome.

Figure 1. Workflow of literature review for the 8 RTRS included in preventable

2.4 More significative results:

Eighty high quality, peer reviewed papers were selected and eight data extraction tables (*See Appendix*) were created. Sufficient data was obtained to model the disease onset and progression.

2.5 Impact of results:

Having collected high quality, mainly retrospective observational data, including cancer incidence, overall and organ-specific mortality rates, surveillance programs diagnostic and survival outcomes, will allow the team to model disease onset and progression.

Next step is to include multicentric real clinical and economic data of patients receiving primary/secondary prevention measures and/or treatment, computing the differences in outcomes and costs, and taking forward the work developed in WP1 and WP2.

2.6 Literature collection strategy

2.6.1 Search strategies

A - Peutz-Jeghers Syndrome

Databases: PubMed and Embase
"Peutz-Jeghers" *OR* "STK11" *OR* "LKB1"
Studies published between January 1st, 2010 to February 29th, 2024
Inclusion: Research papers, with published results, in vivo studies, studies in humans.
Exclusion: Specific treatments or diagnostic methods, studies performed in vitro or in animals, reviews and metaanalysis, single case reports.
Languages: Spanish, English and Portuguese
Last search performed March 26th, 2024

B - Birt-Hogg-Dube Syndrome

Databases: PubMed and Embase
“Birt-Hogg-Dubé” *OR* “Hornstein-Knickenberg” *OR* Folliculin OR FCNL
Studies published between January 1st, 2010 to March 31th, 2024
Inclusion: Research papers, with published results, in vivo studies, studies in humans.
Exclusion: Specific treatments or diagnostic methods, studies performed in vitro or in animals, reviews and metaanalysis, single case reports.
Languages: Spanish, English and Portuguese
Last search performed April 1st, 2024

C - Hereditary Leiomyomatosis and Renal Cell Cancer

Databases: PubMed and Embase
"Hereditary Leiomyomatosis and Renal Cell Cancer" *OR* "Hereditary leiomyomatosis" *OR* "FH tumour predisposition syndrome" *OR* "HLRCC"
Studies published between January 1st, 2010 to May 31th, 2024
Inclusion: Research papers, with published results, in vivo studies, studies in humans.
Exclusion: Specific treatments or diagnostic methods, studies performed in vitro or in animals, reviews and metaanalysis, single case reports.
Languages: Spanish, English and Portuguese
Last search performed April 24th, 2024

D - Familial Melanoma

Databases: PubMed and Embase
"Familial melanoma" *OR* "Familial malignant melanoma" *OR* "Familial atypical multiple mole melanoma" *OR* "FAMMM"
Studies published between January 1st, 2010 to April 30th, 2024
Inclusion: Research papers, with published results, in vivo studies, studies in humans.

Exclusion: Specific treatments or diagnostic methods, studies performed in vitro or in animals, reviews and metaanalysis, single case reports.
Languages: Spanish, English and Portuguese
Last search performed May 06th, 2024

E - Hereditary Diffuse Gastric Cancer

Databases: PubMed and Embase
"Hereditary diffuse gastric cancer" *OR* "Hereditary lobular breast cancer" *OR* "HDGC" *OR* "Germline CDH1"
Studies published between January 1st, 2010 to April 30th, 2024
Inclusion: Research papers, with published results, in vivo studies, studies in humans.
Exclusion: Specific treatments or diagnostic methods, studies performed in vitro or in animals, reviews and metaanalysis, single case reports.
Languages: Spanish, English and Portuguese
Last search performed May 15th, 2024

F - GIST - GastroIntestinal Stromal Tumour

Databases: PubMed and Embase
(KIT OR PDGFRA) *AND* (GIST OR "Gastrointestinal stromal tumour" *OR* "gastrointestinal stromal tumor" *OR* "familial gist")
Studies published between January 1st, 2010 to April 30th, 2024
Inclusion: Research papers, with published results, in vivo studies, studies in humans.
Exclusion: Specific treatments or diagnostic methods, studies performed in vitro or in animals, reviews and metaanalysis, single case reports.
Languages: Spanish, English and Portuguese
Last search performed May 27th, 2024

G - PTEN Hamartoma Tumour Syndrome

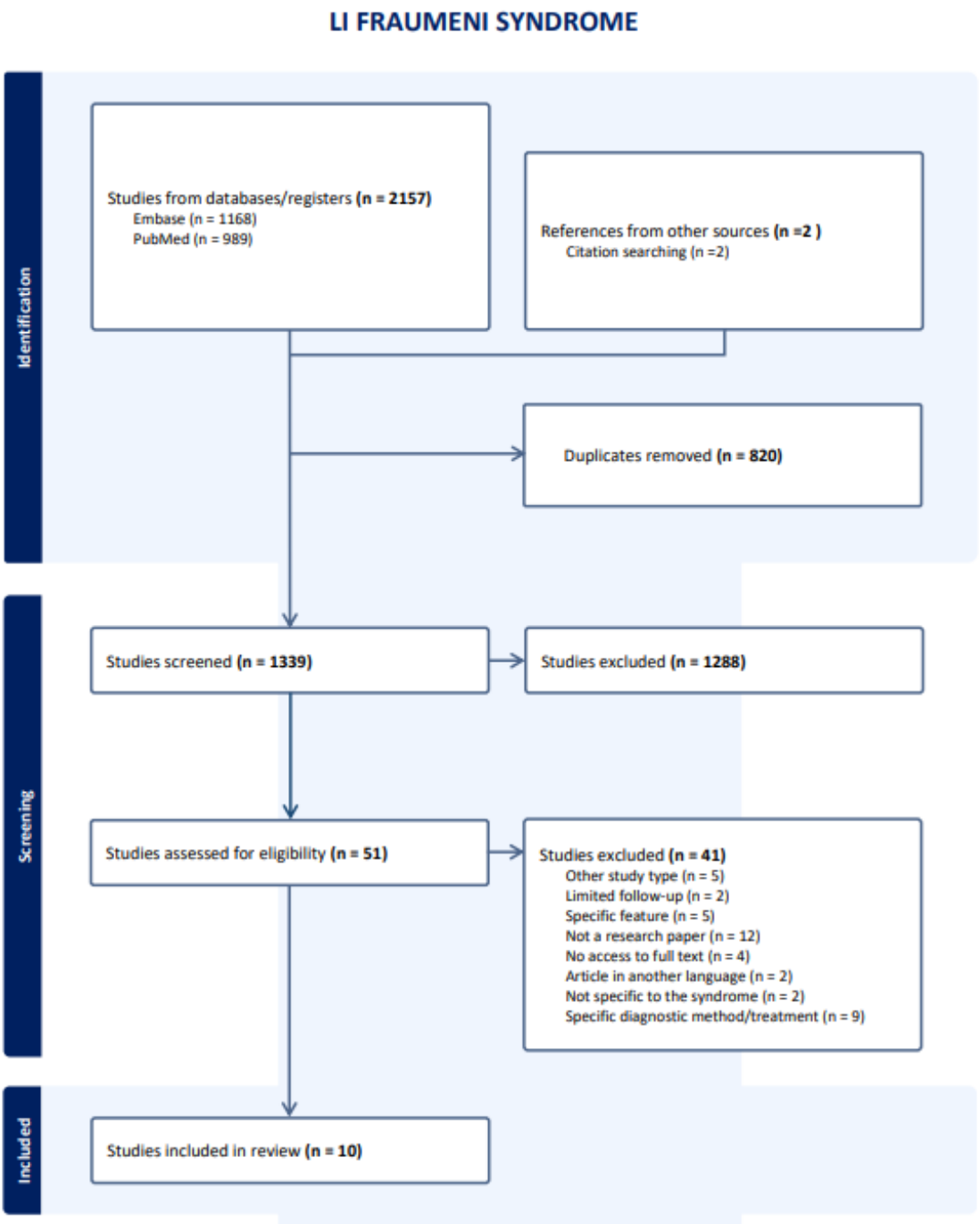
Databases: PubMed and Embase
"PTEN Hamartoma Tumour Syndrome" *OR* PHTS *OR* "Hamartoma Tumour Syndrome" *OR* "GERMLINE PTEN"
Studies published between January 1st, 2010 to May 31th, 2024
Inclusion: Research papers, with published results, in vivo studies, studies in humans.
Exclusion: Specific treatments or diagnostic methods, studies performed in vitro or in animals, reviews and metaanalysis, single case reports.
Languages: Spanish, English and Portuguese
Last search performed June 6th, 2024.

H - Li Fraumeni Syndrome

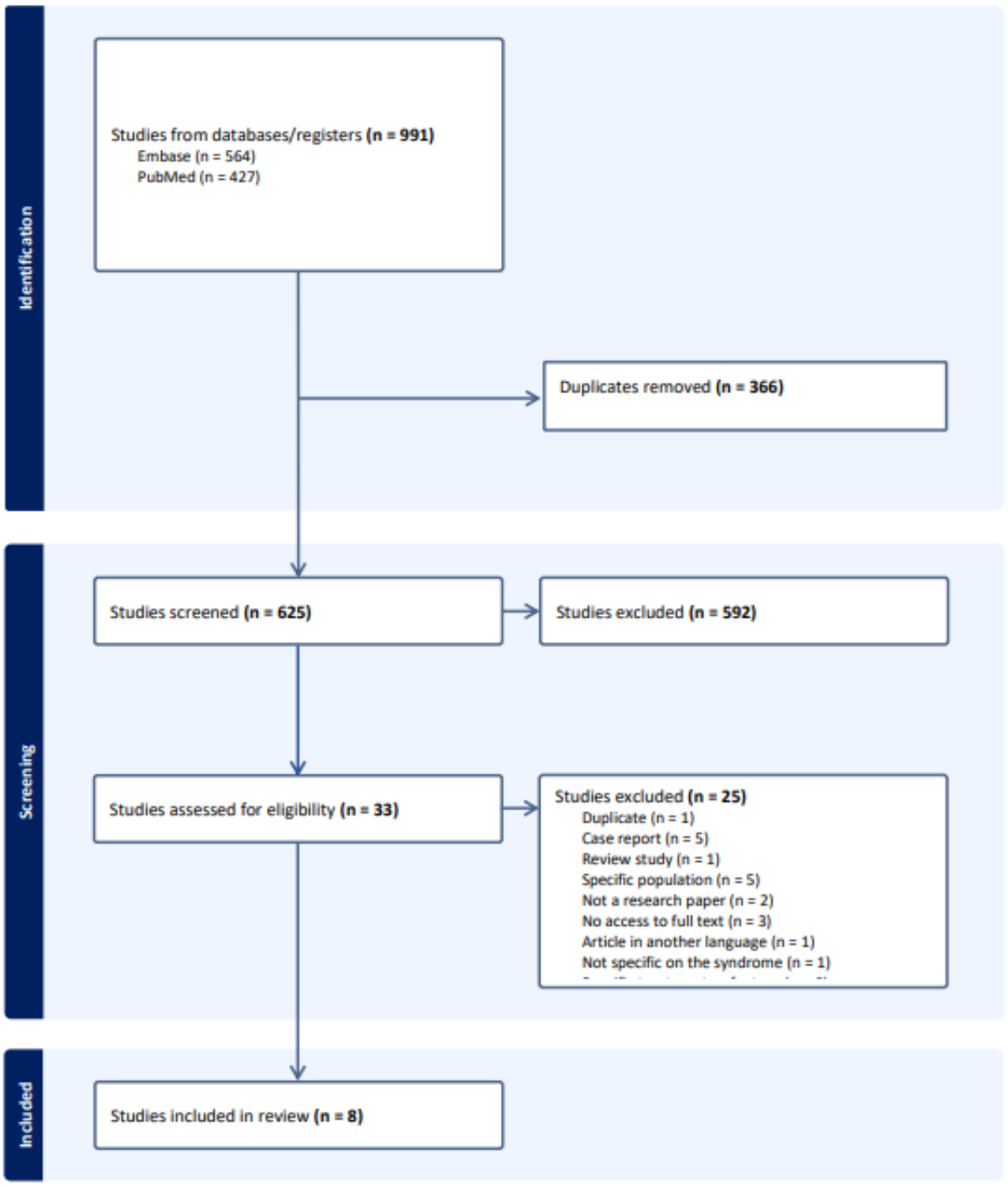
Databases: PubMed and Embase
"Li Fraumeni" OR "Germline PT53"
Studies published between January 1st, 2010 to May 31th, 2024

Inclusion: Research papers, with published results, in vivo studies, studies in humans.
Exclusion: Specific treatments or diagnostic methods, studies performed in vitro or in animals, reviews and metaanalysis, single case reports.
Languages: Spanish, English and Portuguese
Last search performed June 6th, 2024

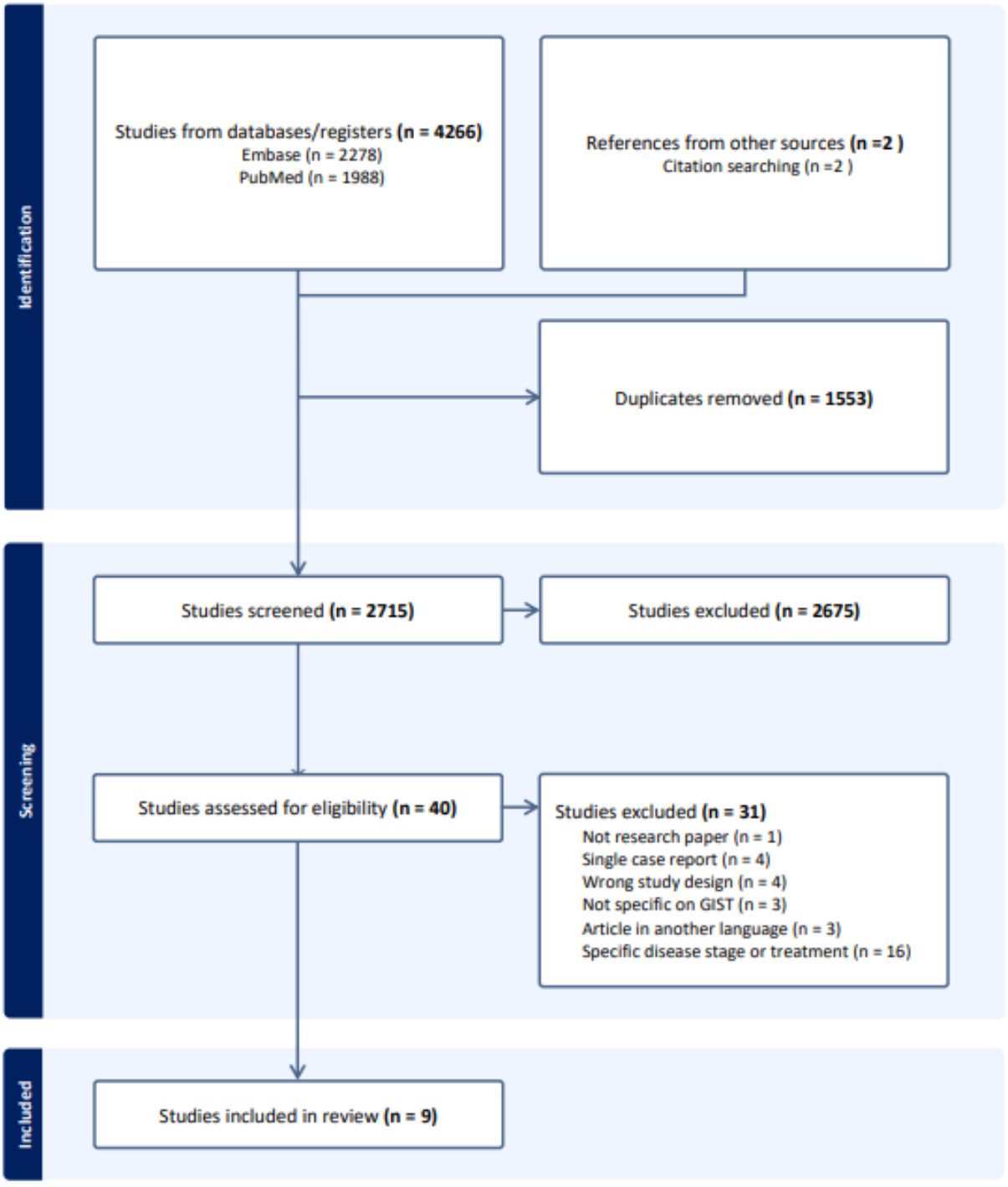
2.6.2 PRISMA Flow diagrams



PTEN - HAMARTOMA TUMOUR SYNDROME



GIST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Embase (n = 2278)
PubMed (n = 1988)
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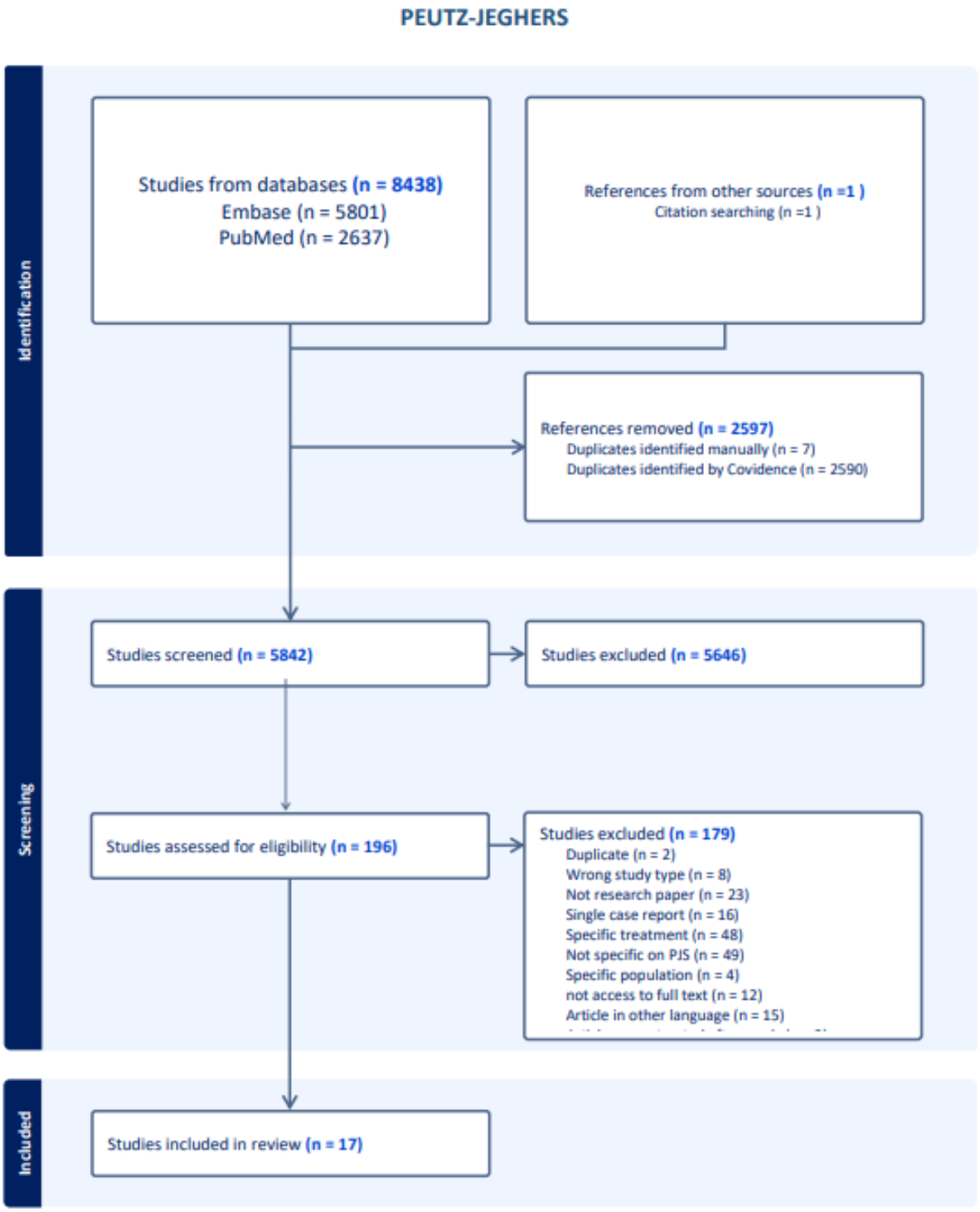
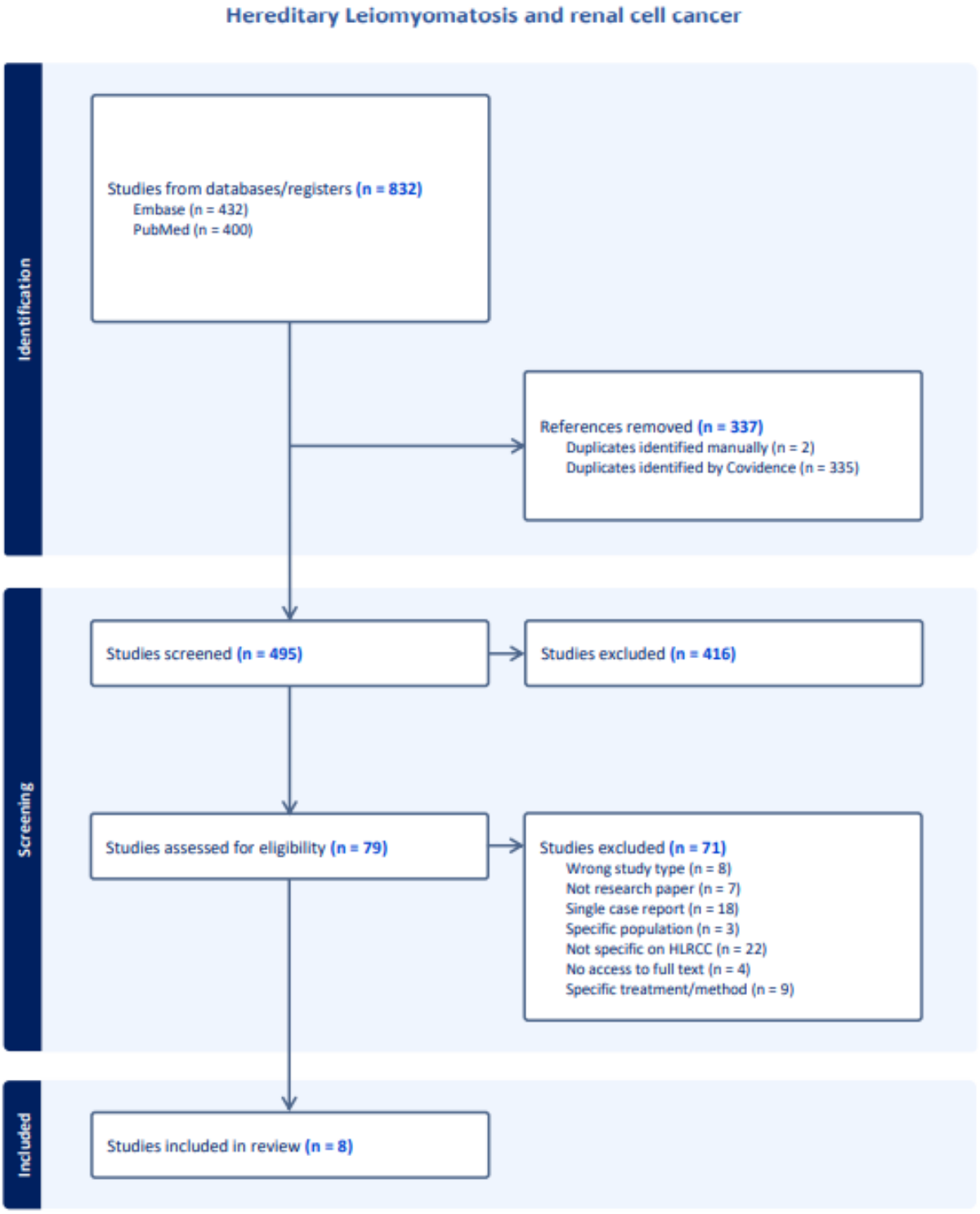
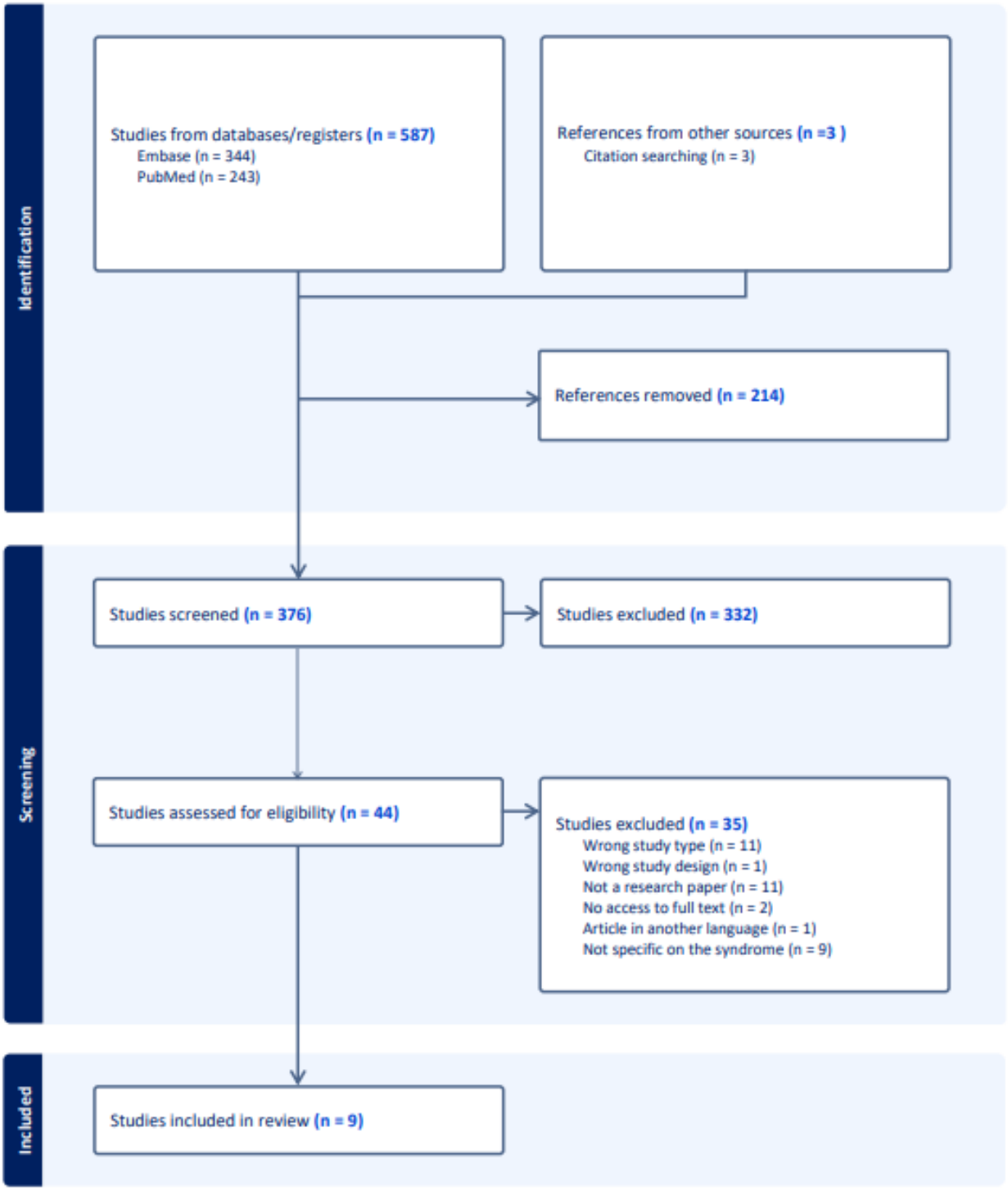
Citation searching (n =2)
Duplicates removed (n = 1553)
Screening
Studies screened (n = 2715)
Studies excluded (n = 2675)
Studies assessed for eligibility (n = 40)
Studies excluded (n = 31)
Not research paper (n = 1)
Single case report (n = 4)
Wrong study design (n = 4)
Not specific on GIST (n = 3)
Article in another language (n = 3)
Specific disease stage or treatment (n = 16)
Included
Studies included in review (n = 9)

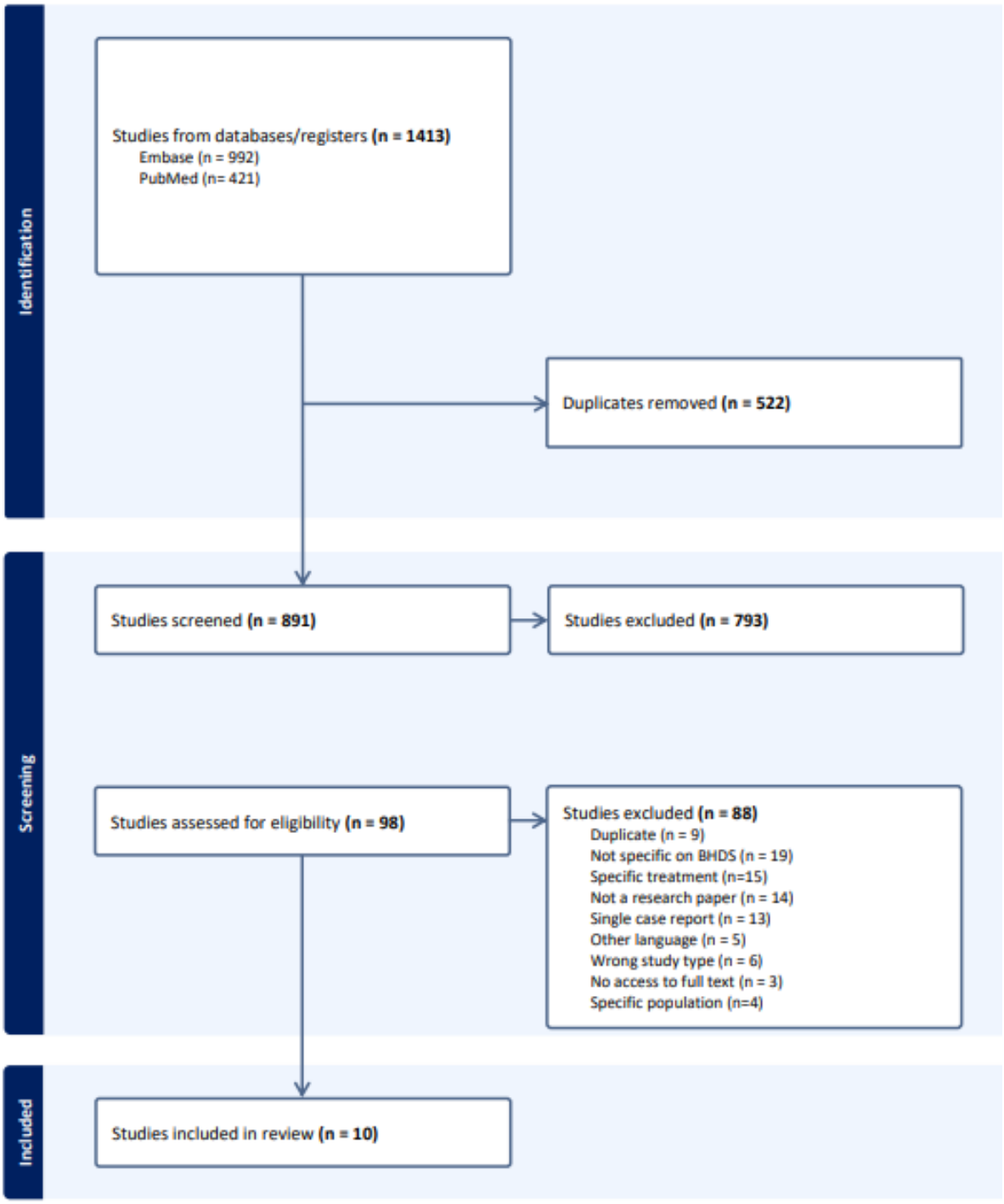

PEUTZ-JEGHERS
Identification
Studies from databases (n = 8438)
Embase (n = 5801)
PubMed (n = 2637)
References from other sources (n =1)
Citation searching (n =1)
References removed (n = 2597)
Duplicates identified manually (n = 7)
Duplicates identified by Covidence (n = 2590)
Screening
Studies screened (n = 5842)
Studies excluded (n = 5646)
Studies assessed for eligibility (n = 196)
Studies excluded (n = 179)
Duplicate (n = 2)
Wrong study type (n = 8)
Not research paper (n = 23)
Single case report (n = 16)
Specific treatment (n = 48)
Not specific on PJS (n = 49)
Specific population (n = 4)
not access to full text (n = 12)
Article in other language (n = 15)
Included
Studies included in review (n = 17)

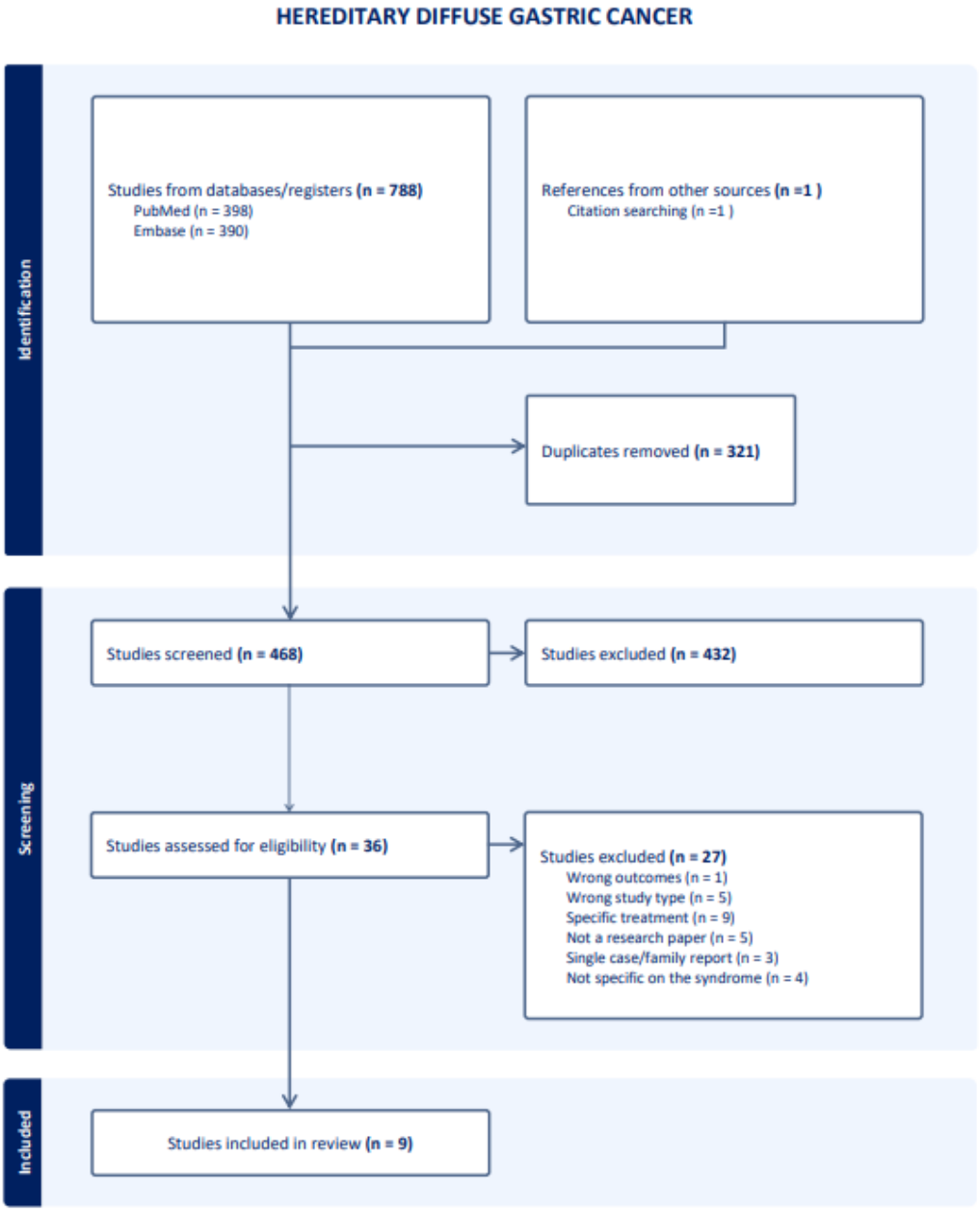

Hereditary Leiomyomatosis and renal cell cancer
Identification
Studies from databases/registers (n = 832)
Embase (n = 432)
PubMed (n = 400)
References removed (n = 337)
Duplicates identified manually (n = 2)
Duplicates identified by Covidence (n = 335)
Screening
Studies screened (n = 495)
Studies excluded (n = 416)
Studies assessed for eligibility (n = 79)
Studies excluded (n = 71)
Wrong study type (n = 8)
Not research paper (n = 7)
Single case report (n = 18)
Specific population (n = 3)
Not specific on HLRCC (n = 22)
No access to full text (n = 4)
Specific treatment/method (n = 9)
Included
Studies included in review (n = 8)

FAMILIAL MELANOMA



BIRT HOGG DUBE




HEREDITARY DIFFUSE GASTRIC CANCER
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Embase (n = 390)
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Duplicates removed (n = 321)
Screening
Studies screened (n = 468)
Studies excluded (n = 432)
Studies assessed for eligibility (n = 36)
Studies excluded (n = 27)
Wrong outcomes (n = 1)
Wrong study type (n = 5)
Specific treatment (n = 9)
Not a research paper (n = 5)
Single case/family report (n = 3)
Not specific on the syndrome (n = 4)
Included
Studies included in review (n = 9)

2.7 references

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