Hereditary Endocrine Tumour Registries

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ABSTRACT

Introduction and hypothesis:

Endocrine neoplasia syndromes are phenotypically complex and there is a misconception that they are universally rare. Genetic alterations are increasingly recognized, however true prevalence is unknown. The purpose of a clinical registry is to monitor the quality of health care delivered to a specified group of patients through the collection, analysis and reporting of relevant health-related information. This leads to improved clinical practice, decision making, patient satisfaction and outcome. This review aims to identify, compare and contrasts active registries worldwide that capture data relevant to HET (hereditary endocrine tumours).

Methods:

Clinical registries were identified using a systematic approach from publications (Ovid MEDLINE, EMBASE) peer consultation, clinical trials and web searches. Inclusion criteria were hereditary endocrine tumours, clinical registries and English language. Exclusion criteria were institutional audits, absence of clinical data or inactive. Details surrounding general characteristics, funding, data fields, collection periods and entry methods were collated.

Results:

Fifteen registries specific for HET were shortlisted with 136 affiliated peer reviewed manuscripts.

Conclusions:

There are few clinical registries specific to HET. Most of these are European and the data collected is highly variable. Further research into their effectiveness is warranted. We note the
absence of an Australian registry for all HET, where potential health and economic gains may be possible. This review presents a unique opportunity to harmonize registry data for HET locally and further afield.

INTRODUCTION

Hereditary tumour syndromes are increasingly recognized in patients with endocrine cancers. There is a misconception that they are universally rare, whereas true prevalence is unknown. Depending on the tumour type, 10-40% may occur in association with a germline alteration, such as multiple endocrine neoplasia syndrome\textsuperscript{1-5}. This has implications on the clinical assessment, immediate care, counselling and long-term follow-up for the index patient and their relatives\textsuperscript{6}.

Hereditary Endocrine Tumours (HET) are phenotypically complex and frequently present variably with de novo mutations. Classic red flags for familial disease (early onset, family history, multifocal neoplasia and multiorgan involvement) can be difficult to recognize in patients with HET. Therefore, it is important to have a high index of suspicion for a hereditary syndrome when managing patients with endocrine tumours in order to avoid incomplete or misdiagnosis. Failure to make the connection between an isolated endocrine tumor and a hereditary syndrome is potentially a lost opportunity for patients and their family members\textsuperscript{7}.

The utility of genetic awareness is that it enables targeted treatment at an earlier stage, screening for other disease manifestations, and family cascade gene testing. Furthermore, approach to treatment, in particular surgery, may be different in a patient with a known genetic syndrome where multiple surgeries are anticipated. Surveillance plays a vital role in the management of
patients with hereditary syndromes. The key aspect of care is balancing the risks of early intervention versus disease-related morbidity (and mortality) from repeated interventions.

Clinical quality registries (CQRs) are organised systems that collect, handle and disseminate information on particular cohorts of interest who either have a disease, a risk factor that predisposes them to a health-related event or prior exposures suspected to cause adverse outcomes. CQRs are designed to systematically collect, analyse and report risk-adjusted outcomes that inform the appropriateness and effectiveness of care. Ongoing reporting of clinical data from the registry completes the clinical outcome feedback loop in a real world setting and is a cost-effective way of addressing significant gaps in current health information. Disease specific clinical quality registries and associated research are an important adjunct for healthcare providers.

In Australia there are currently about 90 clinical registries at some level of development or use. The Australian Register of Clinical Registries has recently been published to make information on all clinical registries widely available and to facilitate collaboration and awareness of registry activity among key stakeholders.

The aim of this review was to (1) identify clinical registries worldwide specific for HET and describe their general characteristics, (2) to inform the development of a HET CQR in Australia.
MATERIALS AND METHODS

a) Protocol and registration

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) format.

b) Information sources

- Electronic databases: EMBASE and MEDLINE
- Clinical Trials: www.clinicaltrials.gov
- Specialist societies: American Association of Endocrine Surgeons (AAES), American Thyroid Association (ATA), British Association of Endocrine and Thyroid Surgeons (BAETS), Australia and New Zealand Endocrine Surgeons (ANZES)
- Peer consultations

c) Search strategy

A search of articles was performed using EMBASE and MEDLINE between 1900 and 2021. The search terms were registries AND hereditary AND thyroid neoplasms, OR medullary thyroid cancer, OR medullary thyroid neoplasms, OR Hyperparathyroidism, OR adrenocortical neoplasms, OR adrenocortical cancer, OR adrenal cortex neoplasms, OR thyroid cancer papillary, OR non-medullary thyroid cancer, OR non-medullary thyroid neoplasms, OR neuroendocrine tumours, OR MEN1, OR multiple endocrine neoplasia Type 1, OR MEN2, OR multiple endocrine neoplasia type 2a, OR MEN3, OR multiple endocrine neoplasia, OR MEN4, OR FAP, OR familial adenomatous polyposis, OR adenomatous polyposis coli, OR Cowden syndrome, OR multiple hamartoma syndrome, OR neurofibromatosis 1, OR paraganglioma, OR
SDHx, OR on Hippel-Lindau Disease, OR tuberous sclerosis, OR Hyperparathyroid jaw tumour syndrome, OR Li Fraumeni syndrome, OR lynch syndrome, OR colorectal neoplasms hereditary non-polyposis, OR endocrine gland neoplasms, OR endocrine tumours, including variable spellings. Following this, a supplementary search was conducted via clinicaltrials.gov for observational patients registries relevant to HET and of relevant professional societies for clinical practice guidelines. Figure 1 shows a schematic of the search strategy.

d) Eligibility Criteria

The search was limited to English language only. Exclusion criteria were institutional audits, absence of clinical data, not relevant to HET or inactive.

e) Study Selection

The shortlisted papers were reviewed for relevance first by title and abstract and subsequently by full text appraisal. Duplicates were excluded.

f) Data management and analysis

Each shortlisted registry was independently investigated for additional information. The data dictionary was accessed, compared and contrasted. The principal investigator for each registry was also contacted and where possible interviewed via zoom with a standardised set of questions. The list of references was managed digitally within Mendeley (version 1.19.4).
RESULTS

1.0 Identification of HET Registries

1.1 General description

A total of 802 manuscripts were initially identified via electronic databases (n=595) and clinical trials (n=207). There were 140 duplicates which were excluded. 662 publications underwent preliminary screening for relevance by title and abstract. Of these, a further 521 were excluded (not relevant to HET n=428, non-English n=27, case report n=16, inactive n=23). The remaining 141 manuscripts underwent full text appraisal and a further 126 were excluded (not relevant to HET n=43, case report n=6, conference abstract n=5, no meaningful clinical data n=37, single institution audit n=13, inactive n=22). The final number of active patient registries relevant to HET was 15. The number of peer reviewed manuscripts affiliated with these shortlisted registries, independent of the search strategy, was 136.

2.0 Characteristics of identified HET Registries

2.1 Geographic coverage

All of the 15 included registries incorporated data from multiple institutions (multicentric). Of these eight of were national and the remainder were international (>1 country). Most of the registries were hosted in Europe (n=9, 60%), whereas the remainder were from North America (n=4, 26.7%) and Oceania (n=2, 13.3%). Table 1 presents a summary of the shortlisted registries with respect to organisation and structure.
2.2 Designation

The most common type of registry included in this study was an observational patient registry (6/15). Other registry designs were longitudinal study (3/15), clinical data repository (3/155), non-randomized interdisciplinary trial (2/15), and clinical quality registry (1/15).

2.3 Number of patients and years established

The total number of patients within all 15 of the shortlisted registries (at the time of analysis) was 179,155 (range 165 to 132,336). The average age of the shortlisted registries was 17.2 years. The ‘National VHL Research Database’ was the oldest registry, established in 1930 by Dr Kai Albrechtsen and now forms part of the national archives. By contrast, the newest registry was the ‘Registry of Li Fraumeni and Li Fraumeni Like Syndromes (ReLF)’, established in 2020. After adjusting for year established, the average number of patients recruited per year per registry was approximately 2372.

2.4 Funding

Data pertaining fiscal support was poorly described overall. Nine (60%) of the shortlisted registries were publicly funded whereas the remainder were funded in equal proportion by private enterprise (n=3, 20%) or a combination from public and private sources (n=3, 20%). Most of the registries hosted by European countries were publicly funded. Six registries required a paid membership by clinicians or academics. The amount and allocation of funding was not disclosed. Four registries ENS@T, Eurocrine, MyVHL and PlaNET are listed as a registered charities and actively accept donations.
2.5 Website

More than half of the registries (8/15) have an online presence i.e., dedicated website. Of those registries, English was the most common language. The SwissNET website is available in four languages (English, German, French and Italian). Standard information available online included an introductory statement, details of the disease, details of the executive committee, upcoming events, patient resources, physician resources, sponsorship, clinical trials, linked publications and contact details. Most websites included links to various social media platforms such as Instagram, Facebook, Twitter, YouTube and LinkedIn.

2.6 Recruitment

The mode of patient recruitment was generally similar. Typically, patients are referred to the registry by treating physicians (family medicine, internal medicine, surgery, genetics), and recruited following informed consent and direct contact with study nurses. Other sources of referral included pathology institutes, researchers, allied health professionals and patient initiated. Four registries were rebranded and include data from other projects, these were PlaNET (previously Unicorn), ITANET (previously ENTS), ENS@T (previously three adrenal networks in Italy, France and Germany) and National VHL Research database (previously works of Dr Albrechtsen). Table 2 presents a summary of the shortlisted Registries in terms of Data Management.

2.7 Data collection periods

All of the shortlisted registries included baseline data from the point of referral. The most common intervals thereafter were periodically (i.e., at planned follow-up (8/15)) and annually.
(7/15). Other data collection periods were pre-operatively, post-operatively or other unspecified times.

2.8 Data Entry Methods

Predominantly, data entry was prospective, by trained staff and stored online (12/15). Typically, this included mixed entry methods such as examination of hospital records from scheduled medical appointments and or registry specific questionnaires and patient interviews. Both PlaNET and MyVHL also feature patient portals for direct self-determined data entry. There was limited information pertaining to data assessment for internal consistency by external reviewers.

2.9 Patient demographics and background clinical data

All of the registries listed age and gender as core demographic data. EURReCA also listed current gender and gender at birth. Other demographics collected with variable frequency included date of registration, date of diagnosis, country of birth, country of residence, BMI, allergies, comorbidities and disability profile. EUROCRINE, one of the large international registries, specified three sets of data elements - core (all participating sites), national (all participating sites within in a single country) and own (institution specific).

2.10 Genetics

There were 14 primary genes of interest (VHL, RET, NF1, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, MAX, MENIN, TP-53, TSC1/TSC2 and other). The most commonly represented gene was VHL which was incorporated into 9 distinct registries. There was no
available information pertaining to specific variants. Figure 2 is a pie chart of the most commonly represented genes amongst the shortlisted registries.

2.11 Syndromes

Seven registries were specific for a single endocrine syndrome eg. Study and Monitoring of MEN1 (MEN1 only), whereas the remainder were umbrella registries for multiple endocrine syndromes and or tumour types eg. EUROCRINE Registry of Endocrine Tumours (rare endocrine tumours of the thyroid, parathyroid, adrenal gland and gastrointestinal tract eg. MEN1, MEN2, VHL, TS, Paragangliomas, Phaeochromocytomas and NETs).

2.12 Clinical/Diagnostic Variables

There was scant overlap across registries in terms of clinical data collected. Overall, the data captured may be classified into three groups:

1. Clinical diagnosis (age of first manifestation, symptoms at diagnosis, time between symptoms and diagnosis, associated syndromes),
2. Primary tumour (site, size, CT and other imaging characteristics, TNM classification, cytology, histology, grade) and
3. Biochemistry (timepoint, significance (unknown, normal, abnormal clinically insignificant, abnormal clinically significant)).

2.13 Treatment and Procedural Variables

Treatment and procedural variables were the most poorly defined data elements across all 15 registries. They were not included in five registries and unknown in a further two registries. Of
the remainder, surgery was the most described treatment related variable, including age at
surgery, aim of surgery (unknown, curative, palliative), extent of surgery (R0/R1/R2) and type of
surgery (open or laparoscopic, primary or revisional). Other treatments listed in broad terms
were radiotherapy, chemotherapy, molecular therapy and biotherapy.

2.14 Outcome Measures
There was no available outcome data for four registries. Commonly reported outcomes were
patient status (stable, progressive disease, responsive disease, dead, unknown), cause of death,
time to diagnosis, recurrence (age at recurrence, symptoms, number and site of recurrence),
surgical complications (Dindo Clavien classification) and, treatment suspension (unknown, as
prescribed, side effects, disease progression, patient choice, no response, alternative treatment).
Outcome measures were poorly described overall, however the PLANET registry records
multidisciplinary meeting recommendations (post diagnosis, during treatment, post-treatment
and following restaging).

2.15 Biomaterials
Six registries collected biomaterial however the nature and purpose of these was unclear.

2.16 Clinical Trials
Almost all of the registries (n=13, 87%) were involved with clinical trials. Via the MyVHL
patient app, participants can be immediately informed of new clinical trials via push
notifications.
2.17 Reporting/Publications

Data reporting was variable. Five registries published an annual report however one only (MyVHL) included fiscal information (revenue, expenses, assets and liabilities) and another two were only available for financial members. Reportable data included number of sites, number of patients, percent female, mean age at diagnosis, mean years involved, primary site, follow-up and new publications and or grant recipients. Overall, 136 peer reviewed publications based on registry data were identified. Of these, basic science was most commonly represented (80 papers\textsuperscript{15–94}) followed by clinical outcome (30 papers\textsuperscript{95–124}), quality and improvement (7 papers\textsuperscript{125–131}), treatment (6 papers\textsuperscript{132–137}) epidemiology (4 papers\textsuperscript{98,138–140}), PROMS (1 paper\textsuperscript{141}), and other (3 papers\textsuperscript{142–144}). Additionally, there were five registry issued clinical practice guidelines\textsuperscript{145–149} published in collaboration with other institutions and speciality societies. Table 3 presents a summary of relevant publications stratified by type and registry.

2.18 Patient reported outcomes (PROs)

Four registries collected data pertaining to patient-reported outcomes (PROs). This included socio-professional status and lifestyle (mobility, self-care, pain, activity and mental health). PlaNET reported using objective tools such as Eastern Co-operative Oncology Group (ECOG) performance scale, Bristol Stool Scale, QOL30, GINET51, whereas the other PRO tools were not defined.
2.19 Other

Eight principal investigators responded to an email sent by the primary author of this study regarding the structure and maintenance of their registries. There was no accessible information regarding data accuracy or completeness of data.

DISCUSSION

The purpose of this review was to present a summary of existing registries that capture data relevant to HET worldwide. In doing so, we aimed to compare and contrast these in order to inform the local development of a HET CQR. A secondary aim was to highlight the limitations of registry related activity in this field and identify potential mechanisms to overcome these.

Overall, we identified fifteen active, disease specific registries relevant to HET and 136 peer reviewed manuscripts associated with these. To our knowledge, this is the first scoping review of HET registries worldwide. This paper is a clinically relevant resource for clinicians managing these patients and presents a unique opportunity to identify areas of need in terms of registry-based research for patients with HET.

We have identified that there are few active registries and that the data collected is variable in terms of scope and methodology. There was a particular lack of standardisation with respect to patient eligibility criteria, recruitment, and data collection due to the heterogenous, multisystem nature of these disorders. We did not identify a single registry that encompasses all HET. The advantages of a narrow scope registry (i.e., a single tumour type or syndrome), is that more detailed data can be collected and analysed, although if the data points are too numerous, data
quality and completeness may be threatened. Furthermore, it is simpler to co-ordinate a single
disease entity compared with several. MyVHL is a natural history study of patients with VHL
only but is also part of the National Organization for Rare Diseases (NORD) IAMRARE registry
platform. My VHL has 3200 data elements for each patient and showcases the benefits of being a
single disease specific registry under the umbrella of a larger organisation. Ultimately, local
resources and specialist interest will be determining factors of scope and methodology.
Standardisation of data collection is important to enable multicentre and international
benchmarking, and collaboration via data harmonisation.

While there were some overlapping general principles of data collection and management, there
was vast disparity between what is relevant for different tumour types and syndromes and the
rationale for the research overall. For example, ENS@T is an international, longitudinal study of
adrenal tumours aiming to improve the understanding of genetics, tumorigenesis, hypersecretion
and risk of recurrence. The majority of their recent publications are related to basic science
concepts. By contrast, SwissNet is a national, clinical data repository for NET which aims to
provide the foundations for epidemiological studies and evidence for various treatment options.
While fewer in number, most of their recent publications are related to clinical and patient
reported outcomes. The rationale for a disease specific registry should be clearly defined at the
outset. Inevitably, this will have implications in terms of clinician involvement and published
research. The current lack of clinically – focused outcomes including research may not
encourage practicing clinicians in being involved.
We encountered (and eliminated) 45 manuscripts referring to registries that were inactive. Several registries were periodically inactive between projects. Overall, the most common reason for inactivity was lack of funding. The costs involved to run a registry are highly variable but intrinsically are not extravagant. The bulk of expenses pertain to wages for data entry and IT for data storage. Among the shortlisted registries most were partially funded by government, but the amount and longevity of this arrangement was not defined. Financial planning is equally as important as acquiring data, in terms of perceived registry success (internal review growth and improvement). The source of funding (industry, insurance, government) is also important and should align with the research aims and outcome measures.

It was interesting to note the absence of specialty society endorsement for any of the shortlisted registries. The reasons for this are unknown but could potentially represent conflict of interest, lack of awareness, or cost. The purpose of a specialty society is essentially a forum to exchange ideas amongst specialist clinicians. They rely and thrive on collaboration. Ideally, links to a disease specific registry would be available (and promoted) via a specialty society website. For example, the British Association of Endocrine and Thyroid Surgeons (BAETS) owns and manages the UK Registry of Endocrine and Thyroid Surgery (UKRETS) which is an electronic audit of endocrine operations performed in the UK. Participation in the UKRETS is considered an obligatory requirement for BAETS full members. This is a simple yet effective measure to safeguard uptake, quality and in turn clinical utility of registry related research. Amongst the publications which we identified in affiliation with the shortlisted registries, there were few which reported against standards and quality of care.
A particular hurdle for multi-institutional research is ethics approval, as identified during online discussions with numerous HET registry PIs. Typically, this has to be obtained at each participating site, which is time consuming and complex. Different privacy laws in different countries may impact the nature of data collected and importantly data sharing. For example, European countries are now subject to the General Data Protection Regulation (GDPR), which was initiated in May 2018. Application of the GDPR implies that personal data may only be used for medical research after informing patients and obtaining their explicit consent, which may affect the ability of European countries to report and share clinical data before 2018. In the United States, the Health Insurance Portability and Accountability Act (HIPAA) and its implementing regulations have created similar legal protections for the privacy of individually identifiable health information. The rule defines the conditions when health information is protected by law and how protected health information can be de-identified for secondary use. Institutions with clinical registries need to follow these rules and guidelines closely to successfully protect patient privacy. However, they also need to be supported in their de-identification efforts, in order to promote national and international academic alliances. Ethics and governance are a burden for many researchers in terms of time and cost, and the complexities of legislation associated with international registry data sharing is an even more significant challenge.

In considering the need for a national disease specific registry for HET an important starting point is to review existing information and any comparable local or international activities, such as the findings of this review. Successful measures such as opt out consent, trained data managers, and feedback loops to participating clinicians should be considered. Depending on
resources, it may be appropriate to commence with a limited set of data elements, informed via a consensus process (i.e., Delphi method), for a single hereditary syndrome. Ideally, patients would be identified at the point of gene testing with an automated referral mechanism by the diagnosing clinician, with the potential to use secondary data sources for case ascertainment. Thereafter, patients would be contacted by trained staff at baseline and other predetermined intervals, for prospective data collection and online data entry. A dedicated registry websites to increase awareness, information sharing, and credibility is essential. Furthermore, periodical data reporting is fundamental to the registry longevity and credibility.

This study has several minor limitations which we acknowledge. First of all, the methodology relied on appropriate acknowledgement of registry data in peer reviewed publications. As it is virtually impossible to identify a registry if it is not named, some registries may have been overlooked because of this search strategy. Secondly, we excluded single institution databases and hospital audits because typically they are low volume. This potentially excluded databases that had productive academic outputs. Thirdly, our search was limited to English publications only and therefore introduces language bias into our conclusions.

This is the first review of clinical registries for HET worldwide. We anticipate that our work will enhance awareness of existing resources and prompt collaboration between colleagues and institutions, with the overall aim to enhance patient care and outcome.
CONCLUSION

There is a paucity of clinical registries for HET worldwide and the information collected is highly variable. A lack of standardisation towards patient eligibility, recruitment and data collection methods currently limits the potential of registry data harmonisation and collaboration. Furthermore, a paucity of clinically focused outcomes may reduce clinician uptake. Additionally, labour intense ethics and governance applications and inconsistent financial support present unique challenges for registry related work. In order to enhance the impact of HET registries we recommend subspecialty society endorsement, varied funding models (private and public) and aggressive promotion of registry related activities and outputs (website, social media, peer reviewed publications). Ultimately, interdisciplinary and interinstitutional collaboration is necessary in the planning, establishment and maintenance of a nationally co-ordinated clinical registry for HET.

DATA AVAILABILITY STATEMENT

Original data generated and analysed during this study are included in this published article or in the data repositories listed in References.

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doi:10.1530/EJE-16-0467

Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration
G1-G46. doi:10.1530/EJE-18-0608

and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the
doi:10.1002/BJS.10414


**TABLE & FIGURES LEGEND**

Table 1: Summary of Shortlisted Registries - Organisation and Structure

Table 2: Summary of Shortlisted Registries - Data Management

Table 3: Summary of Published Data

Figure 1: PRISMA Summary of search strategy

Figure 2: Pie chart of most commonly represented genes
<table>
<thead>
<tr>
<th>Name</th>
<th>Website</th>
<th>Designation</th>
<th>Year Established</th>
<th>Funding</th>
<th>Host Country</th>
<th>Geographic Coverage</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>National VHL Research Database <em>(based on older works from Dr Kai Albrechtsen and Dr Rosenberg)</em></td>
<td>No</td>
<td>Longitudinal study</td>
<td>1930</td>
<td>Public</td>
<td>Denmark</td>
<td>National</td>
<td>165 in 2016</td>
</tr>
<tr>
<td>GPOH-MET Registry: Registry for children and adolescents with malignant endocrine tumour</td>
<td>No</td>
<td>Interdisciplinary non-randomized trial</td>
<td>1980</td>
<td>Public</td>
<td>Germany</td>
<td>National</td>
<td>875 in 2021</td>
</tr>
<tr>
<td>International Paediatric Adrenocortical Tumour Registry</td>
<td>No</td>
<td>Observational cohort study</td>
<td>2001</td>
<td>Mixed</td>
<td>USA</td>
<td>International</td>
<td></td>
</tr>
<tr>
<td>ENS@T: European Network for the Study of Adrenal Tumours <em>(based on merging of data from Italy, France and Germany)</em></td>
<td><a href="http://www.ensat.org">www.ensat.org</a></td>
<td>Longitudinal study</td>
<td>2002</td>
<td>Mixed</td>
<td>France</td>
<td>International</td>
<td>21,675* in 2022</td>
</tr>
<tr>
<td>SwissNET: Registry for Neuroendocrine Tumours in Switzerland</td>
<td><a href="http://www.swissnet.net">www.swissnet.net</a></td>
<td>Clinical data repository</td>
<td>2005</td>
<td>Private</td>
<td>Switzerland</td>
<td>National</td>
<td>2774 in 2021</td>
</tr>
<tr>
<td>Genetic Analysis of Phaeochromocytomas (PCC) and paragangliomas (PPGL) and associated conditions</td>
<td>No</td>
<td>Observational cohort study</td>
<td>2005</td>
<td>Public</td>
<td>USA</td>
<td>International</td>
<td>43. Aiming for 300</td>
</tr>
<tr>
<td>Clinical and Genetic Studies in Familial Non-medullary Thyroid Cancer</td>
<td>No</td>
<td>Observational cohort study</td>
<td>2010</td>
<td>Public</td>
<td>USA</td>
<td>National</td>
<td>1052 in 2022</td>
</tr>
<tr>
<td>MyVHL <em>(part of IAMRARE)</em></td>
<td><a href="http://www.vhl.org">www.vhl.org</a></td>
<td>Longitudinal study</td>
<td>2012</td>
<td>Private</td>
<td>USA</td>
<td>National</td>
<td>17,025 in 2019</td>
</tr>
<tr>
<td>ICCoN: Inherited Cancer Connect database</td>
<td>No</td>
<td>Clinical data repository</td>
<td>2013</td>
<td>Public</td>
<td>Australia</td>
<td>National</td>
<td>132,336 in 2022</td>
</tr>
<tr>
<td>EUROCINER: Registry of Endocrine Tumours</td>
<td><a href="http://www.eurocrine.eu">www.eurocrine.eu</a></td>
<td>Surgical quality registry</td>
<td>2015</td>
<td>Mixed</td>
<td>France</td>
<td>International</td>
<td>17,025 in 2022</td>
</tr>
<tr>
<td>EURReCA: European Registry for Rare Endocrine Conditions</td>
<td><a href="http://www.eurreca.net">www.eurreca.net</a></td>
<td>Interdisciplinary non-randomized trial</td>
<td>2018</td>
<td>Public</td>
<td>UK</td>
<td>International</td>
<td>710 in 2021</td>
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<tr>
<td>Study and Monitoring of MEN1</td>
<td>No</td>
<td>Observational cohort study</td>
<td>2019</td>
<td>Public</td>
<td>France</td>
<td>National</td>
<td>1600</td>
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<tr>
<td>ITANET <em>(previously ENETS)</em></td>
<td>No</td>
<td>Observational cohort study</td>
<td>2019</td>
<td>Public</td>
<td>Italy</td>
<td>National</td>
<td>3600</td>
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<tr>
<td>ReLF: Registry of Li Fraumeni and Li Fraumeni Like Syndromes</td>
<td>No</td>
<td>Observational cohort study</td>
<td>2020</td>
<td>Public</td>
<td>Italy</td>
<td>National</td>
<td>200</td>
</tr>
</tbody>
</table>
UK - unknown
* - total number of adrenal patients. Hereditary proportion UK.

4 Table 2: Summary of Shortlisted Registries – Data Management

<table>
<thead>
<tr>
<th>Name</th>
<th>Patient Recruitment</th>
<th>Timing of Data Collection*</th>
<th>Data Entry Methods</th>
<th>Data Reporting</th>
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</thead>
<tbody>
<tr>
<td>National VHL Research Database (based on older works from Dr Kai Albrechtsen and Dr Rosenberg)</td>
<td>Treating physicians</td>
<td>periodical</td>
<td>Mixed: Interviews and hospital records. Stored online.</td>
<td>Multiple peer reviewed publications</td>
</tr>
<tr>
<td>ENS@T: European Network for the Study of Adrenal Tumours (based on merging of data from Italy, France and Germany)</td>
<td>Treating physicians, pathologists, geneticists, researchers</td>
<td>periodical</td>
<td>Prospective. Stored online. Data accessible by contributors. Paid membership.</td>
<td>Multiple peer reviewed publications</td>
</tr>
<tr>
<td>EURReCA: European Registry for Rare Endocrine Conditions</td>
<td>Treating physicians</td>
<td>periodical</td>
<td>Prospective. Stored online. Data accessible by contributors.</td>
<td>Biannual report since 2020. Available online. Multiple peer reviewed publications</td>
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<tr>
<td>GPOH-MET Registry: Registry for children and adolescents with malignant endocrine tumour</td>
<td>Unknown</td>
<td>pre-operative, post-operative, follow-up unspecified</td>
<td>Prospective. Data accessible by members.</td>
<td>Multiple peer reviewed publications</td>
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<tr>
<td>SwissNET: Registry for Neuroendocrine Tumours in Switzerland</td>
<td>Treating physicians, pathology institutes and GPs</td>
<td>annual</td>
<td>Prospective. Stored online. Data accessible by members.</td>
<td>Annual report since 2012. Available online. Multiple peer reviewed publications</td>
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<tr>
<td>EUROCRINE: Registry of Endocrine Tumours</td>
<td>All nationally registered endocrine surgery</td>
<td>annual</td>
<td>Prospective. Stored online. Paid membership. Data accessible by members.</td>
<td>Annual report for members only. Multiple peer reviewed publications</td>
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<tr>
<td>MyVHL (part of IAMRARE)</td>
<td>Self-referral</td>
<td>annual</td>
<td>Prospective. Stored online. Patient entered data cross referenced by data manager (from medical records).</td>
<td>Annual report avail since 2014 (financial data only). Peer reviewed publication.</td>
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<td>Genetic Analysis of Phaeochromocytomas (PCC)</td>
<td>Treating physicians</td>
<td>annual</td>
<td>Prospective</td>
<td>Peer reviewed publication</td>
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<td>Registry and associated conditions</td>
<td>Treating physicians</td>
<td>Frequency</td>
<td>Data Collection Type</td>
<td>Data Access and Storage</td>
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<tr>
<td>International Paediatric Adrenocortical Tumour Registry</td>
<td>Treating physicians</td>
<td>annual</td>
<td>Prospective</td>
<td>Peer reviewed publication</td>
</tr>
<tr>
<td>Study and Monitoring of MEN1</td>
<td>Treating physicians</td>
<td>annual</td>
<td>Prospective. Stored online</td>
<td>Peer reviewed publication</td>
</tr>
<tr>
<td>ITANET (previously ENETS)</td>
<td>Treating physicians</td>
<td>annual</td>
<td>Prospective. Data accessible by members.</td>
<td>Peer reviewed publication</td>
</tr>
<tr>
<td>Clinical and Genetic Studies in Familial Non-medullary Thyroid Cancer</td>
<td>Treating physicians</td>
<td>periodical</td>
<td>Mixed: Interviews and hospital records. Stored online.</td>
<td>Peer reviewed publication</td>
</tr>
<tr>
<td>ReLF: Registry of Li Fraumeni and Li Fraumeni Like Syndromes</td>
<td>Treating physicians</td>
<td>periodical</td>
<td>Mixed.</td>
<td>Nil</td>
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<tr>
<td>PlaNET Registry (previously UNICORN foundation)</td>
<td>Treating physicians (at included sites)</td>
<td>periodical</td>
<td>Prospective. Manual entry via health professionals (data manager, nurse, fellow, clinician). Stored online. Only accessible by members.</td>
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<tr>
<td>ICCoN: Inherited Cancer Connect database</td>
<td>Familial cancer clinics</td>
<td>periodical</td>
<td>Retrospective. Stored online. Progeny database on hospital server. Data entry manager collates, cleans and formats data entries supplied by FCC. Funding lost from 2016 until 2022. Data entry suspended until recently. Aiming for prospective from now.</td>
<td>Multiple peer reviewed publications. Annual report to funding bodies where applicable. HREC and research governance.</td>
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</tbody>
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*All registries collected baseline data*
### Table 3: Summary of Published Data

<table>
<thead>
<tr>
<th>Name</th>
<th>Basic Science</th>
<th>Clinical Outcome</th>
<th>Practice Guidelines</th>
<th>Epidemiology</th>
<th>Quality and Improvement</th>
<th>PROMS</th>
<th>Treatment</th>
<th>Other</th>
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<tr>
<td>National VHL Research Database (<em>based on older works from Dr Kai Albrechtsen and Dr Rosenberg</em>)</td>
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<td>415-98</td>
<td>1145</td>
<td>3139,140,152</td>
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<td>International Paediatric Adrenocortical Tumour Registry</td>
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<td>Study and Monitoring of MEN1</td>
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<tr>
<td>ReLF: Registry of LiFraumeni and LiFraumeni Like Syndromes</td>
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<td>PlaNET Registry (previously UNICORN foundation)</td>
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<td><strong>TOTAL</strong> (n = 136)</td>
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Figure 2
147x110 mm (3.3 x DPI)