Journal of the Endocrine Society, 2023, **7**, 1–13
https://doi.org/10.1210/jendso/bvac194
Advance access publication 23 December 2022
Research Article

Hereditary Endocrine Tumor Registries

Edwina C. Moore,[1] Liane Ioannou,[2] Rasa Ruseckaite,[2] Jonathan Serpell,[3] and Susannah Ahern[2]

[1]Department of Endocrine Surgery, Peninsula Private Hospital and Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria 3800, Australia
[2]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria 3800, Australia
[3]Department of Breast, Endocrine and General Surgery, Alfred Health, Monash University, Melbourne, Victoria 3800, Australia

Correspondence: Edwina C. Moore, MBBS (HONS), BMedSci, Peninsula Private Hospital, 525 McClelland Dr, Ste 16, Langwarrin, VIC, 3199, Australia. Email: edwina.bolshinsky@gmail.com.

Abstract

Context: 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.

Objective: This review aims to identify, compare, and contrast active registries worldwide that capture data relevant to hereditary endocrine tumors (HETs).

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 tumors, clinical registries, and English language. Exclusion criteria were institutional audits, absence of clinical data, or inactivity. 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.

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

Key Words: hereditary, endocrine tumors, endocrine cancers, clinical quality registries, database

Abbreviations: BAETS, British Association or Endocrine and Thyroid Surgeons; CQR, clinical quality registry; HET, hereditary endocrine tumor; PI, principal investigator; PRO, patient-recorded outcome.

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

Hereditary endocrine tumors (HETs) 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 tumors 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 [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 for which 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 vs disease-related morbidity (and mortality) from repeated interventions.

Clinical quality registries (CQRs) are organized 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 [8]. CQRs are designed to systematically collect, analyze, and report risk-adjusted outcomes that inform the appropriateness and effectiveness of care [9, 10]. 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 health care providers [11, 12].

Received: 21 October 2022. **Editorial Decision:** 15 December 2022. **Corrected and Typeset:** 6 January 2023

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 [13, 14].

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 an HET CQR in Australia.

Materials and Methods

Protocol and Registration

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

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 or Endocrine and Thyroid Surgeons (BAETS), Australia and New Zealand Endocrine Surgeons (ANZES)
- Peer consultations

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 *von 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. Fig. 1 shows a schematic of the search strategy.

Eligibility Criteria

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

Study Selection

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

Data Management and Analysis

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

Results

Identification of Hereditary Endocrine Tumor Registries

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. There were 662 publications that 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.

Characteristics of Identified Hereditary Endocrine Tumor Registries

Geographic coverage

All of the 15 included registries incorporated data from multiple institutions (multicentric). Of these, 8 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 organization and structure.

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), nonrandomized interdisciplinary trial (2/15), and clinical quality registry (1/15).

Number of patients and years established

The total number of patients within all 15 of the shortlisted registries (at time of analysis) was 179 155 (range, 165-132 336). 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 which 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

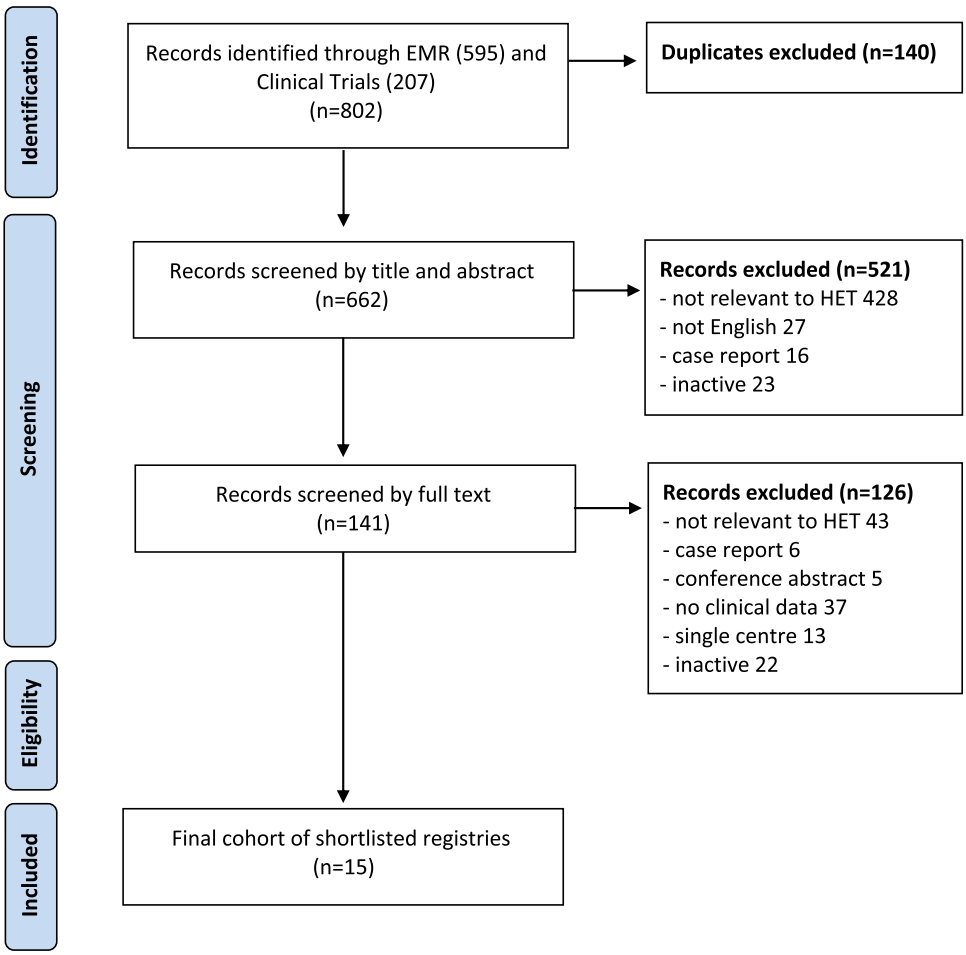

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) summary of search strategy.

year established, the average number of patients recruited per year per registry was approximately 2372.

Funding

Data pertaining to 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 of 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.

Websites

More than half of the registries (8/15) have an online presence, such as a dedicated website. Of those registries, English was the most common language. The SwissNET website is available in 4 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.

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: PlaNET (previously Unicorn), ITANET (previously ENTS), ENS@T (previously 3 adrenal networks in Italy, France, and Germany), and the National VHL Research database (previously works of Dr Albrechtsen). Table 2 presents a summary of the shortlisted registries in terms of data management.

Data collection periods

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

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

Table 1. Summary of shortlisted registries—organization and structure

Name	Website	Designation	Year established	Funding	Host country	Geographic coverage	No. of patients
National VHL Research Database (based on older works from Dr Kai Albrechtsen and Dr Rosenberg)	No	Longitudinal study	1930	Public	Denmark	National	165 in 2016
GPOH-MET Registry: Registry for children and adolescents with malignant endocrine tumor	No	Interdisciplinary nonrandomized trial	1980	Public	Germany	National	875 in 2021
International Paediatric Adrenocortical Tumour Registry	No	Observational cohort study	2001	Mixed	USA	International	*UK. Aiming for 9999*
ENS@T: European Network for the Study of Adrenal Tumours (based on merging of data from Italy, France and Germany)	www.ensat.org	Longitudinal study	2002	Mixed	France	International	21 675[a] in 2022
SwissNET: Registry for Neuroendocrine Tumours in Switzerland	www.swissnet.net	Clinical data repository	2005	Private	Switzerland	National	2774 in 2021
Genetic Analysis of Phaeochromocytomas (PCC) and paragangliomas (PPGL) and associated conditions	No	Observational cohort study	2005	Public	USA	International	*UK. Aiming for 2000*
Clinical and Genetic Studies in Familial Non-medullary Thyroid Cancer	No	Observational cohort study	2010	Public	USA	National	*43. Aiming for 300*
MyVHL (part of IAMRARE)	www.vhl.org	Longitudinal study	2012	Private	USA	National	1052 in 2022
ICCoN: Inherited Cancer Connect database	No	Clinical data repository	2013	Public	Australia	National	17 025 in 2019
EUROCRINE: Registry of Endocrine Tumours	www.eurocrine.eu	Surgical quality registry	2015	Mixed	France	International	132 336 in 2022
PlaNET Registry *(previously UNICORN foundation)*	www.neuroendocrine.org.au	Clinical data repository	2015	Private	Australia	National	2500
EURReCA: European Registry for Rare Endocrine Conditions	www.eurreca.net	Interdisciplinary nonrandomized trial	2018	Public	UK	International	710 in 2021
Study and Monitoring of MEN1	No	Observational cohort study	2019	Public	France	National	*UK. Aiming for 1600*
ITANET (previously ENETS)	No	Observational cohort study	2019	Public	Italy	National	*UK. Aiming for 3600*
ReLF: Registry of Li Fraumeni and Li Fraumeni-like Syndromes	No	Observational cohort study	2020	Public	Italy	National	*UK. Aiming for 200*

Abbreviations: UK, unknown; USA, United States of America.
[a]Total number of adrenal patients. Hereditary proportion UK.

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.

Patient demographics and background clinical data

All of the registries listed age and sex 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, body mass index, allergies, comorbidities, and disability profile. EUROCRINE, one of the large international registries, specified 3 sets of data elements—core (all participating sites), national (all participating sites within in a single country), and own (institution specific).

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. Fig. 2 is a pie chart of

the most commonly represented genes among the shortlisted registries.

Syndromes

Seven registries were specific for a single endocrine syndrome, such as Study and Monitoring of MEN1 (MEN1 only), whereas the remainder were umbrella registries for multiple endocrine syndromes and or tumor types, such as EUROCRINE Registry of Endocrine Tumours (rare endocrine tumors of the thyroid, parathyroid, adrenal gland, and gastrointestinal tract, eg, MEN1, MEN2, VHL, TS, paragangliomas, phaeochromocytomas, and neuroendocrine tumors).

Clinical/Diagnostic variables

There was scant overlap across registries in terms of clinical data collected. Overall, the data captured may be classified into 3 groups:

1. Clinical diagnosis (age of first manifestation, symptoms at diagnosis, time between symptoms and diagnosis, associated syndromes);
2. Primary tumor (site, size, computed tomography and other imaging characteristics, TNM classification, cytology, histology, grade); and
3. Biochemistry (time point, significance [unknown, normal, abnormal clinically insignificant, abnormal clinically significant]).

Treatment and procedural variables

Treatment and procedural variables were the most poorly defined data elements across all 15 registries. They were not included in 5 registries and unknown in a further 2 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.

Outcome measures

There were no available outcome data for 4 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).

Biomaterials

Six registries collected biomaterial; however, the nature and purpose of these were unclear.

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.

Reporting/Publications

Data reporting was variable. Five registries published an annual report; however, only one (MyVHL) included fiscal information (revenue, expenses, assets, and liabilities) and another 2 were available only for financial members. Reportable data included number of sites, number of patients, percentage female, mean age at diagnosis, mean years involved, primary site, follow-up, 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 [15-94]) followed by clinical outcome (30 papers [95-124]), quality and improvement (7 papers [125-131]), treatment (6 papers [132-137]), epidemiology (4 papers [98, 138-140]), patient-reported outcome (PRO) measure (1 paper [141]), and other (3 papers [142-144]). Additionally, there were 5 registry-issued clinical practice guidelines [145-149] published in collaboration with other institutions and specialty societies. Table 3 presents a summary of relevant publications stratified by type and registry.

Patient-reported outcomes

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

Other

Eight PIs responded to an email sent by the primary author of this study (ECM) 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 to inform the local development of an 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 15 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 vary in terms of scope and methodology. There was a particular lack of standardization with respect to patient eligibility criteria, recruitment, and data collection because of the heterogeneous, multisystem nature of these disorders. We did not identify a single registry that encompasses all HETs. The advantages of a narrow-scope registry (ie, a single tumor type or syndrome), is that more detailed

Table 2. Summary of shortlisted registries—data management

Name	Patient recruitment	Timing of data collection[a]	Data entry methods	Data reporting
National VHL Research Database (based on older works from Dr Kai Albrechtsen and Dr Rosenberg)	Treating physicians	Periodical	Mixed: interviews and hospital records. Stored online	Multiple peer-reviewed publications
ENS@T: European Network for the Study of Adrenal Tumours (based on merging of data from Italy, France and Germany)	Treating physicians, pathologists, geneticists, researchers	Periodical	Prospective. Stored online. Data accessible by contributors. Paid membership	Multiple peer-reviewed publications
EURReCA: European Registry for Rare Endocrine Conditions	Treating physicians	Periodical	Prospective. Stored online. Data accessible by contributors	Biannual report since 2020. Available online. Multiple peer-reviewed publications
GPOH-MET Registry: Registry for children and adolescents with malignant endocrine tumour	Unknown	Preoperative, postoperative, follow-up unspecified	Prospective. Data accessible by members	Multiple peer-reviewed publications
SwissNET: Registry for Neuroendocrine Tumours in Switzerland	Treating physicians, pathology institutes, and GPs	Annual	Prospective. Stored online. Data accessible by members	Annual report since 2012 Available online. Multiple peer-reviewed publications
EUROCRINE: Registry of Endocrine Tumours	All nationally registered endocrine surgery	Annual	Prospective. Stored online. Paid membership. Data accessible by members	Annual report for members only. Multiple peer-reviewed publications
MyVHL (part of IAMRARE)	Self-referral	Annual	Prospective. Stored online. Patient-entered data cross-referenced by data manager (from medical records)	Annual report available since 2014 (financial data only). Peer-reviewed publication
Genetic Analysis of Phaeochromocytomas (PCC) and paragangliomas (PPGL) and associated conditions	Treating physicians	Annual	Prospective	Peer-reviewed publication
International Paediatric Adrenocortical Tumour Registry	Treating physicians	Annual	Prospective	Peer-reviewed publication
Study and Monitoring of MEN1	Treating physicians	Annual	Prospective. Stored online	Peer-reviewed publication
ITANET (previously ENETS)	Treating physicians	Annual	Prospective. Data accessible by members	Peer-reviewed publication
Clinical and Genetic Studies in Familial Non-medullary Thyroid Cancer	Treating physicians	Periodical	Mixed: interviews and hospital records. Stored online	Peer-reviewed publication
ReLF: Registry of Li Fraumeni and Li Fraumeni-like Syndromes	Treating physicians	Periodical	Mixed	Nil
PlaNET Registry (previously UNICORN foundation)	Treating physicians (at included sites)	Periodical	Prospective. Manual entry via health professionals (data manager, nurse, fellow, clinician). Stored online. Only accessible by members	Nil
ICCoN: Inherited Cancer Connect database	FCCs	Periodical	Retrospective. Stored online. Progeny database on hospital server. Data entry manager collates, cleans, and formats data entries supplied by FCCs. Funding lost from 2016 until 2022. Data entry suspended until recently. Aiming for prospective from now.	Multiple peer-reviewed publications. Annual report to funding bodies where applicable. HREC and research governance.

Abbreviations: FCC, familial cancer centers; GPs, general practitioners; HREC, human research ethics committees.
[a]All registries collected baseline data

data can be collected and analyzed, although if the data points are too numerous, data quality and completeness may be threatened. Furthermore, it is simpler to coordinate 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)

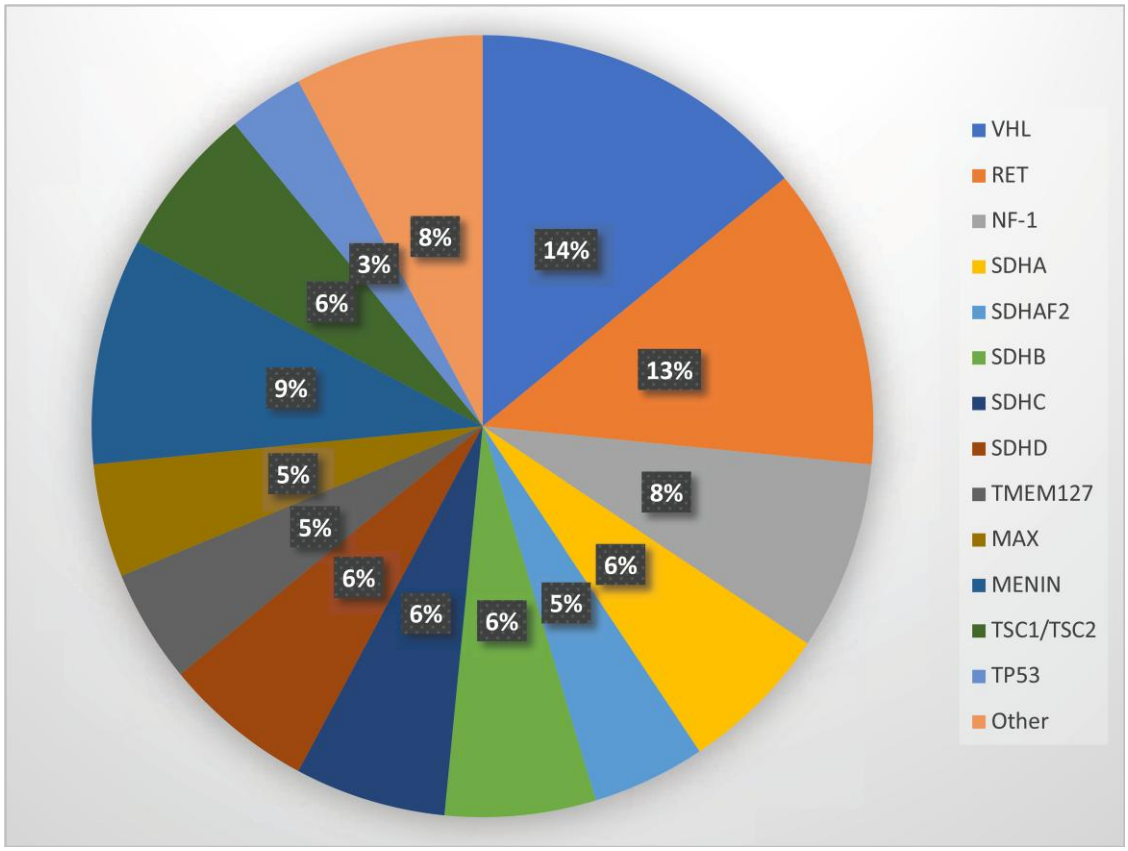

Figure 2. Pie chart of the most commonly represented genes.

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 organization. Ultimately, local resources and specialist interest will be determining factors of scope and methodology. Standardization of data collection is important to enable multicenter and international benchmarking, and collaboration via data harmonization.

While there were some overlapping general principles of data collection and management, there was vast disparity between what is relevant for different tumor types and syndromes and the rationale for the research overall. For example, ENS@T is an international, longitudinal study of adrenal tumors aiming to improve the understanding of genetics, tumorigenesis, hypersecretion, and risk of recurrence. The majority of its recent publications are related to basic science concepts. By contrast, SwissNet is a national, clinical data repository for neuroendocrine tumors that 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 outcomes and PROs. 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 to be 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 information technology 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 among 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 BAETS owns and manages the UK Registry of Endocrine and Thyroid Surgery, which is an electronic audit of endocrine operations performed in the United Kingdom. Participation in the UK Registry of Endocrine and Thyroid Surgery is considered a 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. Among the publications that we identified in affiliation with the shortlisted registries, there were few that 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 affect the

Table 3. Summary of published data

Name	Basic science	Clinical outcome	Practice guidelines	Epidemiology	Quality and improvement	PROMs	Treatment	Other
National VHL Research Database (based on older works from Dr Kai Albrechtsen and Dr Rosenberg)	1 [15]	4 [95-98]	1 [145]	3 [139, 140]				1 [142]
ENS@T: European Network for the Study of Adrenal Tumours (based on merging of data from Italy, France and Germany)	77 [18-94]		4 [146-149]					
EURReCA: European Registry for Rare Endocrine Conditions					6 [126-131]			
GPOH-MET Registry: Registry for children and adolescents with malignant endocrine tumour		6 [118-120, 122, 123, 133]					2 [132, 133]	
SwissNET: Registry for Neuroendocrine Tumours in Switzerland		4 [99-102]				1 [141]	2 [134, 135]	1 [144]
EUROCRINE: Registry of Endocrine Tumours		6 [103-108]					2 [136, 137]	1 [143]
MyVHL (part of IAMRARE)		1 [114]						
Genetic Analysis of Phaeochromocytomas (PCC) and paragangliomas (PPGL) and associated conditions	1 [16]							
International Paediatric Adrenocortical Tumour Registry	1 [17]							
Study and Monitoring of MEN1								
ITANET (previously ENETS)		6 [109-113, 124]						
Clinical and Genetic Studies in Familial Non-medullary Thyroid Cancer		3 [115-117]		1 [138]				
ReLF: Registry of Li Fraumeni and Li Fraumeni-like Syndromes								
PlaNET Registry (previously UNICORN foundation)								
ICCoN: Inherited Cancer Connect database					1 [125]			
TOTAL (n = 136)	80	30	5	4	7	1	6	3

Abbreviation: PROMs, patient-reported outcome measures.

nature of data collected and importantly data sharing. For example, European countries are now subject to the General Data Protection Regulation, which was initiated in May 2018 [150]. Application of the General Data Protection Regulation implies that personal data may be used for medical research only 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, HIPAA (the Health Insurance Portability and Accountability Act) and its implementing regulations have created similar legal protections for the privacy of individually identifiable health information [151]. The rule defines the conditions when health information is protected by law and how protected health information can be deidentified 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 deidentification efforts 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 substantial 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 [12]. Depending on resources, it may be appropriate to commence with a limited set of data elements, informed via a consensus process (ie, 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 website to increase awareness, information sharing, and credibility is essential. Furthermore, periodical data reporting is fundamental to registry longevity and credibility.

This study has several minor limitations that we acknowledge. First, 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. Second, we excluded single-institution databases and hospital audits because typically they are low volume. This potentially excluded databases that had productive academic outputs. Third, our search was limited to English-language 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 standardization toward patient eligibility, recruitment, and data-collection methods currently limits the potential of registry data harmonization and collaboration. Furthermore, a paucity of clinically focused outcomes may reduce clinician uptake. Additionally, labor-intense ethics and governance applications and inconsistent financial support present unique challenges for registry-related work. To enhance the effect of HET registries, we recommend subspecialty society endorsement, varied funding models (private and public), and aggressive promotion of registry-related activities and output (website, social media, peer-reviewed publications). Ultimately, interdisciplinary and interinstitutional collaboration is necessary in the planning, establishment, and maintenance of a nationally coordinated clinical registry for HET.

Disclosures

The authors have nothing to disclose.

Data Availability

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

References

1. Dadu R, Bagheri-Yarmand R, Ringel MD, *et al.* Hereditary endocrine tumours: current state-of-the-art and research opportunities: the state of science in medullary thyroid carcinoma: current challenges and unmet needs. *Endocr Relat Cancer*. 2020;27(8):T27-T39.
2. Perrier ND, Arnold A, Costa-Guda J, *et al.* Hereditary endocrine tumours: current state-of-the-art and research opportunities: new and future perspectives for parathyroid carcinoma. *Endocr Relat Cancer*. 2020;27(8):T53-T63.
3. Dahia PLM, Clifton-Bligh R, Gimenez-Roqueplo AP, Robledo M, Jimenez C. Hereditary endocrine tumours: current state-of-the-art and research opportunities: metastatic pheochromocytomas and paragangliomas: proceedings of the MEN2019 workshop. *Endocr Relat Cancer*. 2020;27(8):T41-T52.
4. Grubbs EG, Lechan RM, Edeiken-Monroe B, *et al.* Hereditary endocrine tumours: current state-of-the-art and research opportunities: early thyroidectomy in multiple endocrine neoplasia: a four-decade experience. *Endocr Relat Cancer*. 2020;27(8):T1-T8.
5. Pieterman CRC, Sadowski SM, Maxwell JE, *et al.* Hereditary endocrine tumours: current state-of-the-art and research opportunities: MEN1-related pancreatic NETs: identification of unmet clinical needs and future directives. *Endocr Relat Cancer*. 2020;27(8):T9-T25.
6. Brock P, Geurts JL, van Galen P, *et al.* Hereditary endocrine tumours: current state-of-the-art and research opportunities: challenges and opportunities in genetic counseling for hereditary endocrine neoplasia syndromes. *Endocr Relat Cancer*. 2020;27(8):T65-T75.
7. Petr EJ, Else T. Genetic predisposition to endocrine tumors: diagnosis, surveillance and challenges in care. *Semin Oncol*. 2016;43(5):582-590.
8. Registries for Evaluating Patient Outcomes: A User's Guide—PubMed. Accessed August 16, 2022. https://pubmed.ncbi.nlm.nih.gov/24945055/
9. Wilcox N, McNeil JJ. Clinical quality registries have the potential to drive improvements in the appropriateness of care. *Med J Aust*. 2016;205(S10):S27-S29.
10. McNeil JJ, Evans SM, Johnson NP, Cameron PA. Clinical-quality registries: their role in quality improvement. *Med J Aust*. 2010;192(5):244-245.

11. Evans SM, Scott IA, Johnson NP, Cameron PA, McNeil JJ. Development of clinical-quality registries in Australia: the way forward. *Med J Aust*. 2011;194(7):360-363.
12. Hoque DME, Kumari V, Hoque M, Ruseckaite R, Romero L, Evans SM. Impact of clinical registries on quality of patient care and clinical outcomes: a systematic review. *PLoS One*. 2017;12(9):e0183667.
13. Australian Commission on Safety and Quality in Health Care. Prioritised list of clinical domains for clinical quality registry development: final report. Published online 2020. Accessed May 10, 2022. https://www.safetyandquality.gov.au/sites/default/files/2020-08/prioritisation_criteria.pdf
14. Ahern S, Evans S, Hopper I, Zalcberg J. Towards a strategy for clinical quality registries in Australia. *Aust Health Rev*. 2019;43(3):284-287.
15. Alosi D, Bisgaard M, Hemmingsen S, Krogh L, Mikkelsen H, Binderup M. Management of gene variants of unknown significance: analysis method and risk assessment of the *VHL* mutation p.P81S. (c.241C > T). *Curr Genomics*. 2017;18(1):93-103.
16. Dahia PLM. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. *Nat Rev Cancer*. 2014;14(2):108-119.
17. Pinto EM, Maxwell KN, Halalsheh H, *et al*. Clinical and functional significance of TP53 exon 4-intron 4 splice junction variants. *Mol Cancer Res*. 2022;20(2):207-216.
18. Lalli E, Doghman M, Latre de Late P, El Wakil A, Mus-Veteau I. Beyond steroidogenesis: novel target genes for SF-1 discovered by genomics. *Mol Cell Endocrinol*. 2013;371(1-2):154-159.
19. Doghman M, Figueiredo BC, Volante M, Papotti M, Lalli E. Integrative analysis of SF-1 transcription factor dosage impact on genome-wide binding and gene expression regulation. *Nucleic Acids Res*. 2013;41(19):8896-8907.
20. Custódio G, Parise GA, Filho NK, *et al*. Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors. *J Clin Oncol*. 2013;31(20):2619-2626.
21. Duregon E, Volante M, Giorcelli J, Terzolo M, Lalli E, Papotti M. Diagnostic and prognostic role of steroidogenic factor 1 in adrenocortical carcinoma: a validation study focusing on clinical and pathologic correlates. *Hum Pathol*. 2013;44(5):822-828.
22. Kreissl MC, Schirbel A, Fassnacht M, *et al*. [^{123}I] Iodometomidate imaging in adrenocortical carcinoma. *J Clin Endocrinol Metab*. 2013;98(7):2755-2764.
23. Peitzsch M, Prejbisz A, Kroiß M, *et al*. Analysis of plasma 3-methoxytyramine, normetanephrine and metanephrine by ultraperformance liquid chromatography-tandem mass spectrometry: utility for diagnosis of dopamine-producing metastatic phaeochromocytoma. *Ann Clin Biochem*. 2013;50(Pt 2):147-155.
24. Letouzé E, Martinelli C, Loriot C, *et al*. SDH mutations establish a hypermethylator phenotype in paraganglioma. *Cancer Cell*. 2013;23(6):739-752.
25. Rao JU, Engelke UFH, Rodenburg RJT, *et al*. Genotype-specific abnormalities in mitochondrial function associate with distinct profiles of energy metabolism and catecholamine content in pheochromocytoma and paraganglioma. *Clin Cancer Res*. 2013;19-(14):3787-3795.
26. Doghman M, Lalli E. Lack of long-lasting effects of mitotane adjuvant therapy in a mouse xenograft model of adrenocortical carcinoma. *Mol Cell Endocrinol*. 2013;381(1-2):66-69.
27. Pinzani P, Scatena C, Salvianti F, *et al*. Detection of circulating tumor cells in patients with adrenocortical carcinoma: a monocentric preliminary study. *J Clin Endocrinol Metab*. 2013;98(9):3731-3738.
28. Peitzsch M, Pelzel D, Glöckner S, *et al*. Simultaneous liquid chromatography tandem mass spectrometric determination of urinary free metanephrines and catecholamines, with comparisons of free and deconjugated metabolites. *Clin Chim Acta*. 2013;418:50-58.
29. Poli G, Guasti D, Rapizzi E, *et al*. Morphofunctional effects of mitotane on mitochondria in human adrenocortical cancer cells. *Endocr Relat Cancer*. 2013;20(4):537-550.
30. Chortis V, Taylor AE, Schneider P, *et al*. Mitotane therapy in adrenocortical cancer induces CYP3A4 and inhibits 5α-reductase, explaining the need for personalized glucocorticoid and androgen replacement. *J Clin Endocrinol Metab*. 2013;98(1):161-171.
31. Barreau O, Assié G, Wilmot-Roussel H, *et al*. Identification of a CpG island methylator phenotype in adrenocortical carcinomas. *J Clin Endocrinol Metab*. 2013;98(1):E174-E184.
32. de Cubas AA, Leandro-García LJ, Schiavi F, *et al*. Integrative analysis of miRNA and mRNA expression profiles in pheochromocytoma and paraganglioma identifies genotype-specific markers and potentially regulated pathways. *Endocr Relat Cancer*. 2013;20(4):477-493.
33. Gaujoux S, Hantel C, Launay P, *et al*. Silencing mutated β-catenin inhibits cell proliferation and stimulates apoptosis in the adrenocortical cancer cell line H295R. *PLoS One*. 2013;8(2):e55743.
34. Eisenhofer G, Lenders JWM, Siegert G, *et al*. Plasma methoxytyramine: a novel biomarker of metastatic pheochromocytoma and paraganglioma in relation to established risk factors of tumour size, location and SDHB mutation status. *Eur J Cancer*. 2012;48-(11):1739-1749.
35. de Krijger RR, Papathomas TG. Adrenocortical neoplasia: evolving concepts in tumorigenesis with an emphasis on adrenal cortical carcinoma variants. *Virchows Arch*. 2012;460(1):9-18.
36. Doghman M, Lalli E. Efficacy of the novel dual PI3-kinase/mTOR inhibitor NVP-BEZ235 in a preclinical model of adrenocortical carcinoma. *Mol Cell Endocrinol*. 2012;364(1-2):101-104.
37. Barreau O, de Reynies A, Wilmot-Roussel H, *et al*. Clinical and pathophysiological implications of chromosomal alterations in adrenocortical tumors: an integrated genomic approach. *J Clin Endocrinol Metab*. 2012;97(2):E301-E311.
38. Assie G, Giordano TJ, Bertherat J. Gene expression profiling in adrenocortical neoplasia. *Mol Cell Endocrinol*. 2012;351(1):111-117.
39. Letouzé E, Rosati R, Komechen H, *et al*. SNP array profiling of childhood adrenocortical tumors reveals distinct pathways of tumorigenesis and highlights candidate driver genes. *J Clin Endocrinol Metab*. 2012;97(7):E1284-E1293.
40. Beuschlein F, Galac S, Wilson DB. Animal models of adrenocortical tumorigenesis. *Mol Cell Endocrinol*. 2012;351(1):78-86.
41. Luconi M, Mannelli M. Xenograft models for preclinical drug testing: implications for adrenocortical cancer. *Mol Cell Endocrinol*. 2012;351(1):71-77.
42. Mulatero P, Tauber P, Zennaro MC, *et al*. KCNJ5 mutations in European families with nonglucocorticoid remediable familial hyperaldosteronism. *Hypertension*. 2012;59(2):235-240.
43. Boulkroun S, Beuschlein F, Rossi GP, *et al*. Prevalence, clinical, and molecular correlates of KCNJ5 mutations in primary aldosteronism. *Hypertension*. 2012;59(3):592-598.
44. Burnichon N, Cascoń A, Schiavi F, *et al*. MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. *Clin Cancer Res*. 2012;18(10):2828-2837.
45. Mariniello B, Rosato A, Zuccolotto G, *et al*. Combination of sorafenib and everolimus impacts therapeutically on adrenocortical tumor models. *Endocr Relat Cancer*. 2012;19(4):527-539.
46. Doghman M, El Wakil A, Cardinaud B, *et al*. Regulation of insulin-like growth factor-mammalian target of rapamycin signaling by microRNA in childhood adrenocortical tumors. *Cancer Res*. 2010;70(11):4666-4675.
47. Stell A, Sinnott R, Jiang J. Enabling secure, distributed collaborations for adrenal tumor research. *Stud Health Technol Inform*. 2010;159:259-263.
48. Arlt W, Biehl M, Taylor AE, *et al*. Urine steroid metabolomics as a biomarker tool for detecting malignancy in adrenal tumors. *J Clin Endocrinol Metab*. 2011;96(12):3775-3784.

49. Comino-Méndez I, Gracia-Aznárez FJ, Schiavi F, *et al.* Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. *Nat Genet*. 2011;43(7):663-667.
50. Doghman M, Axelson M, Lalli E. Potent inhibitory effect of the cyclolignan picropodophyllin (PPP) on human adrenocortical carcinoma cells proliferation—PubMed. Accessed August 3, 2022. https://pubmed.ncbi.nlm.nih.gov/21968616/
51. Papathomas TG, Gaal J, Corssmit EPM, *et al.* Non-pheochromocytoma (PCC)/paraganglioma (PGL) tumors in patients with succinate dehydrogenase-related PCC-PGL syndromes: a clinicopathological and molecular analysis. *Eur J Endocrinol*. 2013;170(1):1-12.
52. Pezzani R, Rubin B, Redaelli M, *et al.* The antiproliferative effects of ouabain and everolimus on adrenocortical tumor cells. *Endocr J*. 2014;61(1):41-53.
53. Därr R, Pamporaki C, Peitzsch M, *et al.* Biochemical diagnosis of phaeochromocytoma using plasma-free normetanephrine, metanephrine and methoxytyramine: importance of supine sampling under fasting conditions. *Clin Endocrinol (Oxf)*. 2014;80(4):478-486.
54. Morin A, Letouzé E, Gimenez-Roqueplo AP, Favier J. Oncometabolites-driven tumorigenesis: from genetics to targeted therapy. *Int J Cancer*. 2014;135(10):2237-2248.
55. Ragazzon B, Libé R, Assié G, *et al.* Mass-array screening of frequent mutations in cancers reveals RB1 alterations in aggressive adrenocortical carcinomas. *Eur J Endocrinol*. 2014;170(3):385-391.
56. Beuschlein F, Fassnacht M, Assié G, *et al.* Constitutive activation of PKA catalytic subunit in adrenal Cushing's syndrome. *N Engl J Med*. 2014;370(11):1019-1028.
57. Eisenhofer G, Tischler AS. Neuroendocrine cancer. Closing the GAPP on predicting metastases. *Nat Rev Endocrinol*. 2014;10(6):315-316.
58. di Dalmazi G, Kisker C, Calebiro D, *et al.* Novel somatic mutations in the catalytic subunit of the protein kinase A as a cause of adrenal Cushing's syndrome: a European multicentric study. *J Clin Endocrinol Metab*. 2014;99(10):E2093-E2100.
59. de Late PL, El Wakil A, Jarjat M, *et al.* Vanin-1 inactivation antagonizes the development of adrenocortical neoplasia in SF-1 transgenic mice. *Endocrinology*. 2014;155(7):2349-2354.
60. Lu H, Papathomas TG, van Zessen D, *et al.* Automated selection of hotspots (ASH): enhanced automated segmentation and adaptive step finding for Ki67 hotspot detection in adrenal cortical cancer. *Diagn Pathol*. 2014;9(1):216.
61. Castro-Vega LJ, Buffet A, de Cubas AA, *et al.* Germline mutations in FH confer predisposition to malignant pheochromocytomas and paragangliomas. *Hum Mol Genet*. 2014;23(9):2440-2446.
62. Assié G, Letouzé E, Fassnacht M, *et al.* Integrated genomic characterization of adrenocortical carcinoma. *Nat Genet*. 2014;46(6):607-612.
63. Qin N, de Cubas AA, Garcia-Martin R, *et al.* Opposing effects of HIF1α and HIF2α on chromaffin cell phenotypic features and tumor cell proliferation: insights from MYC-associated factor X. *Int J Cancer*. 2014;135(9):2054-2064.
64. Oudijk L, de Krijger RR, Rapa I, *et al.* H-RAS mutations are restricted to sporadic pheochromocytomas lacking specific clinical or pathological features: data from a multi-institutional series. *J Clin Endocrinol Metab*. 2014;99(7):E1376-E1380.
65. Hantel C, Jung S, Mussack T, Reincke M, Beuschlein F. Liposomal polychemotherapy improves adrenocortical carcinoma treatment in a preclinical rodent model. *Endocr Relat Cancer*. 2014;21(3):383-394.
66. Richter S, Peitzsch M, Rapizzi E, *et al.* Krebs cycle metabolite profiling for identification and stratification of pheochromocytomas/paragangliomas due to succinate dehydrogenase deficiency. *J Clin Endocrinol Metab*. 2014;99(10):3903-3911.
67. Rubin B, Monticelli H, Redaelli M, *et al.* Mitogen-activated protein kinase pathway: genetic analysis of 95 adrenocortical tumors. *Cancer Invest*. 2015;33(10):526-531.
68. Heck D, Wortmann S, Kraus L, *et al.* Role of endocrine gland-derived vascular endothelial growth factor (EG-VEGF) and its receptors in adrenocortical tumors. *Horm Cancer*. 2015;6(5-6):225-236.
69. Ruggiero C, Doghman M, Lalli E. How genomic studies have improved our understanding of the mechanisms of transcriptional regulation by NR5A nuclear receptors. *Mol Cell Endocrinol*. 2015;408:138-144.
70. Bertoin F, Letouzé E, Grignani P, *et al.* Genome-wide paternal uniparental disomy as a cause of Beckwith-Wiedemann syndrome associated with recurrent virilizing adrenocortical tumors. *Horm Metab Res*. 2015;47(7):497-503.
71. Niemeijer ND, Papathomas TG, Korpershoek E, *et al.* Succinate dehydrogenase (SDH)-deficient pancreatic neuroendocrine tumor expands the SDH-related tumor spectrum. *J Clin Endocrinol Metab*. 2015;100(10):E1386-E1393.
72. Loriot C, Domingues M, Berger A, *et al.* Deciphering the molecular basis of invasiveness in Sdhb-deficient cells. *Oncotarget*. 2015;6(32):32955-32965.
73. Lepoutre-Lussey C, Thibault C, Buffet A, *et al.* From Nf1 to Sdhb knockout: successes and failures in the quest for animal models of pheochromocytoma. *Mol Cell Endocrinol*. 2016;421:40-48.
74. van Berkel A, Rao JU, Lenders JWM, *et al.* Semiquantitative 123I-metaiodobenzylguanidine scintigraphy to distinguish pheochromocytoma and paraganglioma from physiologic adrenal uptake and its correlation with genotype-dependent expression of catecholamine transporters. *J Nucl Med*. 2015;56(6):839-846.
75. Weismann D, Peitzsch M, Raida A, *et al.* Measurements of plasma metanephrines by immunoassay vs liquid chromatography with tandem mass spectrometry for diagnosis of pheochromocytoma. *Eur J Endocrinol*. 2015;172(3):251-260.
76. Peitzsch M, Adaway JE, Eisenhofer G. Interference from 3-O-methyldopa with ultra-high-performance LC-MS/MS measurements of plasma metanephrines: chromatographic separation remains important. *Clin Chem*. 2015;61(7):993-996.
77. Oudijk L, van Nederveen F, Badoual C, *et al.* Vascular pattern analysis for the prediction of clinical behaviour in pheochromocytomas and paragangliomas. *PLoS One*. 2015;10(3):e0121361.
78. Papathomas TG, Oudijk L, Persu A, *et al.* SDHB/SDHA immunohistochemistry in pheochromocytomas and paragangliomas: a multicenter interobserver variation analysis using virtual microscopy: a multinational study of the European Network for the Study of Adrenal Tumors (ENS@T). *Mod Pathol*. 2015;28(6):807-821.
79. de Cubas AA, Korpershoek E, Inglada-Pérez L, *et al.* DNA methylation profiling in pheochromocytoma and paraganglioma reveals diagnostic and prognostic markers. *Clin Cancer Res*. 2015;21(13):3020-3030.
80. Oudijk L, Neuhofer CM, Lichtenauer UD, *et al.* Immunohistochemical expression of stem cell markers in pheochromocytomas/paragangliomas is associated with SDHx mutations. *Eur J Endocrinol*. 2015;173(1):43-52.
81. Evenepoel L, Papathomas TG, Krol N, *et al.* Toward an improved definition of the genetic and tumor spectrum associated with SDH germ-line mutations. *Genet Med*. 2015;17(8):610-620.
82. Poli G, Ceni E, Armignacco R, *et al.* 2D-DIGE proteomic analysis identifies new potential therapeutic targets for adrenocortical carcinoma. *Oncotarget*. 2015;6(8):5695-5706.
83. Sue M, Martucci V, Frey F, *et al.* Lack of utility of SDHB mutation testing in adrenergic metastatic phaeochromocytoma. *Eur J Endocrinol*. 2015;172(2):89-95.
84. Gimenez-Roqueplo AP, Lehnert H, Mannelli M, *et al.* Phaeochromocytoma, new genes and screening strategies. *Clin Endocrinol (Oxf)*. 2006;65(6):699-705.
85. Papathomas TG, de Krijger RR, Tischler AS. Paragangliomas: update on differential diagnostic considerations, composite tumors, and recent genetic developments. *Semin Diagn Pathol*. 2013;30(3):207-223.

86. Oudijk L, Gaal J, Korpershoek E, *et al*. SDHA mutations in adult and pediatric wild-type gastrointestinal stromal tumors. *Mod Pathol*. 2013;26(3):456-463.
87. Gimenez-Roqueplo AP, Dahia PL, Robledo M. An update on the genetics of paraganglioma, pheochromocytoma, and associated hereditary syndromes. *Horm Metab Res*. 2012;44(5):328-333.
88. Bertherat J. Adrenocortical cancer in Carney complex: a paradigm of endocrine tumor progression or an association of genetic predisposing factors? *J Clin Endocrinol Metab*. 2012;97(2):387-390.
89. Timmers HJLM, Chen CC, Carrasquillo JA, *et al*. Staging and functional characterization of pheochromocytoma and paraganglioma by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography. *J Natl Cancer Inst*. 2012;104(9):700-708.
90. Assié G, Jouinot A, Bertherat J. The "omics" of adrenocortical tumours for personalized medicine. *Nat Rev Endocrinol*. 2014;10(4):215-228.
91. van Berkel A, Rao JU, Kusters B, *et al*. Correlation between in vivo 18F-FDG PET and immunohistochemical markers of glucose uptake and metabolism in pheochromocytoma and paraganglioma. *J Nucl Med*. 2014;55(8):1253-1259.
92. Castro-Vega LJ, Letouzé E, Burnichon N, *et al*. Multi-omics analysis defines core genomic alterations in pheochromocytomas and paragangliomas. *Nat Commun*. 2015;6(1):6044.
93. Rao JU, Engelke UFH, Sweep FCGJ, *et al*. Genotype-specific differences in the tumor metabolite profile of pheochromocytoma and paraganglioma using untargeted and targeted metabolomics. *J Clin Endocrinol Metab*. 2015;100(2):E214-E222.
94. Beuschlein F, Weigel J, Saeger W, *et al*. Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. *J Clin Endocrinol Metab*. 2015;100(3):841-849.
95. Binderup MLM. Von Hippel-Lindau disease: diagnosis and factors influencing disease outcome. *Dan Med J*. 2018;65(3):B5461.
96. Binderup MLM, Budtz-Jørgensen E, Bisgaard ML. New Von Hippel-Lindau manifestations develop at the same or decreased rates in pregnancy. *Neurology*. 2015;85(17):1500-1503.
97. Binderup MLM, Gimsing S, Kosteljanetz M, Thomsen C, Bisgaard ML. Von Hippel-Lindau disease: deafness due to a non-MRI-visible endolymphatic sac tumor despite targeted screening. *Int J Audiol*. 2013;52(11):771-775.
98. Binderup MLM, Jensen AM, Budtz-Jørgensen E, Bisgaard ML. Survival and causes of death in patients with von Hippel-Lindau disease. *J Med Genet*. 2017;54(1):11-18.
99. Refardt J, Zandee WT, Brabander T, *et al*. Inferior outcome of neuroendocrine tumor patients negative on somatostatin receptor imaging. *Endocr Relat Cancer*. 2020;27(11):615-624.
100. Sadowski SM, Christ E, Bédat B, *et al*. Nationwide multicenter study on the management of pulmonary neuroendocrine (carcinoid) tumors. *Endocr Connect*. 2018;7(1):8-15.
101. Kollár A, Blank A, Perren A, Bütikofer L, Stettler C, Christ E. Additional malignancies in patients with neuroendocrine tumours: analysis of the SwissNET registry. *Swiss Med Wkly*. 2016;146:w14362.
102. Merola E, Rinke A, Partelli S, *et al*. Surgery with radical intent: is there an indication for G3 neuroendocrine neoplasms? *Ann Surg Oncol*. 2020;27(5):1348-1355.
103. Greilsamer T, Nomine-Criqui C, Thy M, *et al*. Robotic-assisted unilateral adrenalectomy: risk factors for perioperative complications in 303 consecutive patients. *Surg Endosc*. 2019;33(3):802-810.
104. Bergenfelz A, van Slycke S, Makay Ö, Brunaud L. European multicentre study on outcome of surgery for sporadic primary hyperparathyroidism. *Br J Surg*. 2020;108(6):675-683.
105. van Beek DJ, Almquist M, Bergenfelz AO, Musholt TJ, Nordenström E; EUROCRINE® Council. Complications after medullary thyroid carcinoma surgery: multicentre study of the SQRTPA and EUROCRINE® databases. *Br J Surg*. 2021;108(6):691-701.
106. Staubitz JI, Watzka F, Poplawski A, *et al*; EUROCRINE® Council. Effect of intraoperative nerve monitoring on postoperative vocal cord palsy rates after thyroidectomy: European multicentre registry-based study. *BJS Open*. 2020;4(5):821-829.
107. Albers MB, Almquist M, Bergenfelz A, Nordenström E. Complications of surgery for gastro-entero-pancreatic neuroendocrine neoplasias. *Langenbecks Arch Surg*. 2020;405(2):137-143.
108. Mihai R, Donatini G, Vidal O, Brunaud L. Volume-outcome correlation in adrenal surgery—an ESES consensus statement. *Langenbecks Arch Surg*. 2019;404(7):795-806.
109. Panzuto F, Massironi S, Partelli S, *et al*. Gastro-entero-pancreatic neuroendocrine neoplasia: the rules for non-operative management. *Surg Oncol*. 2020;35:141-148.
110. Panzuto F, Campana D, Massironi S, *et al*. Tumour type and size are prognostic factors in gastric neuroendocrine neoplasia: a multicentre retrospective study. *Dig Liver Dis*. 2019;51(10):1456-1460.
111. Rossi RE, Milanetto AC, Andreasi V, *et al*. Risk of preoperative understaging of duodenal neuroendocrine neoplasms: a plea for caution in the treatment strategy. *J Endocrinol Invest*. 2021;44-(10):2227-2234.
112. Massironi S, Rossi RE, Milanetto AC, *et al*. Duodenal gastric metaplasia and duodenal neuroendocrine neoplasms: more than a simple coincidence? *J Clin Med*. 2022;11(9):2658.
113. Panzuto F, Maccauro M, Campana D, *et al*. Impact of the SARS-CoV2 pandemic dissemination on the management of neuroendocrine neoplasia in Italy: a report from the Italian Association for Neuroendocrine Tumors (ItaNet). *J Endocrinol Invest*. 2021;44(5):989-994.
114. Larcher A, Rowe I, Belladelli F, *et al*. Von Hippel-Lindau disease-associated renal cell carcinoma: a call to action. *Curr Opin Urol*. 2022;32(1):31-39.
115. Vriens MR, Suh I, Moses W, Kebebew E. Clinical features and genetic predisposition to hereditary nonmedullary thyroid cancer. *Thyroid*. 2009;19(12):1343-1349.
116. Ito Y, Kakudo K, Hirokawa M, *et al*. Biological behavior and prognosis of familial papillary thyroid carcinoma. *Surgery*. 2009;145(1):100-105.
117. Klubo-Gwiezdzinska J, Yang L, Merkel R, *et al*. Results of screening in familial non-medullary thyroid cancer. *Thyroid*. 2017;27(8):1017-1024.
118. Redlich A, Wechsung K, Boxberger N, Leuschner I, Vorwerk P. Extra-appendiceal neuroendocrine neoplasms in children—data from the GPOH-MET 97 study. *Klin Padiatr*. 2013;225(6):315-319.
119. Redlich A, Lessel L, Petrou A, Mier P, Vorwerk P. Multiple endocrine neoplasia type 2B: frequency of physical stigmata—results of the GPOH-MET registry. *Pediatr Blood Cancer*. 2020;67(2):e28056.
120. Kuhlen M, Frühwald MC, Dunstheimer DPA, Vorwerk P, Redlich A. Revisiting the genotype-phenotype correlation in children with medullary thyroid carcinoma: a report from the GPOH-MET registry. *Pediatr Blood Cancer*. 2020;67(4):e28171.
121. Redlich A, Boxberger N, Schmid KW, Frühwald M, Rohrer T, Vorwerk P. Sensitivity of fine-needle biopsy in detecting pediatric differentiated thyroid carcinoma. *Pediatr Blood Cancer*. 2012;59(2):233-237.
122. Redlich A, Pamporaki C, Lessel L, Frühwald MC, Vorwerk P, Kuhlen M. Pseudohypoxic pheochromocytomas and paragangliomas dominate in children. *Pediatr Blood Cancer*. 2021;68(7):e28981.
123. Boxberger N, Redlich A, Böger C, *et al*. Neuroendocrine tumors of the appendix in children and adolescents. *Pediatr Blood Cancer*. 2013;60(1):65-70.
124. Massironi S, Campana D, Pusceddu S, *et al*; ItaNet (Italian Association for Neuroendocrine Tumours) Study Group. Second primary neoplasms in patients with lung and gastroenteropancreatic neuroendocrine neoplasms: data from a retrospective multicentric study. *Dig Liver Dis*. 2021;53(3):367-374.
125. Forrest L, Mitchell G, Thrupp L, *et al*. Consumer attitudes towards the establishment of a national Australian familial cancer

research database by the Inherited Cancer Connect (ICCon) partnership. *J Community Genet*. 2018;9(1):57-64.
126. Ali SR, Bryce J, Smythe C, *et al*. Supporting international networks through platforms for standardised data collection—the European Registries for Rare Endocrine Conditions (EuRRECa) model. *Endocrine*. 2021;71(3):555-560.
127. Ali SR, Bryce J, Tan LE, *et al*. The EuRRECa project as a model for data access and governance policies for rare disease registries that collect clinical outcomes. *Int J Environ Res Public Health*. 2020;17(23):8743.
128. de Vries F, Bruin M, Cersosimo A, *et al*. An overview of clinical activities in Endo-ERN: the need for alignment of future network criteria. *Eur J Endocrinol*. 2020;183(2):141-148.
129. Ali SR, Bryce J, Cools M, *et al*. The current landscape of European registries for rare endocrine conditions. *Eur J Endocrinol*. 2019;180(1):89-98.
130. Ali SR, Bryce J, Kodra Y, Taruscio D, Persani L, Ahmed SF. The quality evaluation of rare disease registries—an assessment of the essential features of a disease registry. *Int J Environ Res Public Health*. 2021;18(22):11968.
131. Kodra Y, Weinbach J, Posada-De-La-Paz M, *et al*. Recommendations for improving the quality of rare disease registries. *Int J Environ Res Public Health*. 2018;15(8):1644.
132. Redlich A, Boxberger N, Strugala D, *et al*. Systemic treatment of adrenocortical carcinoma in children: data from the German GPOH-MET 97 trials. *Klin Padiatr*. 2012;224(6):366-371.
133. Hubertus J, Boxberger N, Redlich A, von Schweinitz D, Vorwerk P. Surgical aspects in the treatment of adrenocortical carcinomas in children: data of the GPOH-MET 97 trial. *Klin Padiatr*. 2012;224(3):143-147.
134. Kollár A, Bütikofer L, Ochsenbein A, Stettler C, Trepp R. Treatment sequence in patients with neuroendocrine tumours: a nationwide multicentre, observational analysis of the Swiss Neuroendocrine Tumour Registry. *Swiss Med Wkly*. 2020;150:w20176.
135. Kaderli RM, Spanjol M, Kollár A, *et al*. Therapeutic options for neuroendocrine tumors: a systematic review and network meta-analysis. *JAMA Oncol*. 2019;5(4):480-489.
136. Vatansever S, Nordenström E, Raffaelli M, Brunaud L, Makay Ö; EUROCRINE Council. Robot-assisted versus conventional laparoscopic adrenalectomy: results from the EUROCRINE surgical registry. *Surgery*. 2022;171(5):1224-1230.
137. Hallin Thompson L, Makay Ö, Brunaud L, Raffaelli M, Bergenfelz A; EUROCRINE Council. Adrenalectomy for incidental and symptomatic phaeochromocytoma: retrospective multicentre study based on the Eurocrine® database. *Br J Surg*. 2021;108(10):1199-1206.
138. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. *Cancer*. 2009;115(16):3801-3807.
139. Binderup MLM, Galanakis M, Budtz-Jørgensen E, Kosteljanetz M, Bisgaard ML. Prevalence, birth incidence, and penetrance of von Hippel-Lindau disease (vHL) in Denmark. *Eur J Hum Genet*. 2017;25(3):301-307.
140. Binderup MLM, Stendell AS, Galanakis M, Møller HU, Kiilgaard JF, Bisgaard ML. Retinal hemangioblastoma: prevalence, incidence and frequency of underlying von Hippel-Lindau disease. *Br J Ophthalmol*. 2018;102(7):942-947.
141. Krug S, Khosravian M, Weissbach J, *et al*. The patient's point of view: COVID-19 and neuroendocrine tumor disease. *Cancers (Basel)*. 2022;14(3):613.
142. Binderup MLM, Budtz-Jørgensen E, Bisgaard ML. Risk of new tumors in von Hippel-Lindau patients depends on age and genotype. *Genet Med*. 2016;18(1):89-97.
143. Inabnet WB III, Palazzo F, Sosa JA, *et al*. Correlating the Bethesda system for reporting thyroid cytopathology with histology and extent of surgery: a review of 21,746 patients from four endocrine surgery registries across two continents. *World J Surg*. 2020;44(2):426-435.
144. Gouffon M, Iff S, Ziegler K, *et al*. Diagnosis and workup of 522 consecutive patients with neuroendocrine neoplasms in Switzerland. *Swiss Med Wkly*. 2014;144:w13924.
145. Mølgaard Binderup ML, Bisgaard ML, Harbud V, *et al*; Danish vHL Coordination Group. Von Hippel-Lindau disease (vHL). National clinical guideline for diagnosis and surveillance in Denmark. 3rd edition. *Dan Med J*. 2013;60(12):B4763.
146. Plouin PF, Amar L, Dekkers OM, *et al*; Guideline Working Group. European Society of Endocrinology clinical practice guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. *Eur J Endocrinol*. 2016;174(5):G1-G10.
147. Fassnacht M, Arlt W, Bancos I, *et al*. Management of adrenal incidentalomas: European Society of Endocrinology clinical practice guideline in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol*. 2016;175(2):G1-G34.
148. Fassnacht M, Dekkers OM, Else T, *et al*. European Society of Endocrinology clinical practice guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol*. 2018;179(4):G1-G46.
149. Gaujoux S, Mihai R; Joint Working Group of ESES and ENSAT. European Society of Endocrine Surgeons (ESES) and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the surgical management of adrenocortical carcinoma. *Br J Surg*. 2017;104(4):358-376.
150. Wierda E, Eindhoven D, Schalij MJ, *et al*. Privacy of patient data in quality-of-care registries in cardiology and cardiothoracic surgery: the impact of the new general data protection regulation EU-law. *Eur Heart J Qual Care Clin Outcomes*. 2018;4(4):239-245.
151. Kayaalp M. Patient privacy in the era of big data. *Balkan Med J*. 2018;35(1):8-17.