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Rare and Complex Urology: Clinical Overview of ERN eUROGEN

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Abstract

Background: In 2017, the European Commission launched 24 European Reference Networks (ERNs). ERN eUROGEN is the network for urorectogenital diseases and complex conditions, and started with 29 full member healthcare providers (HCPs) in 11 countries. It then covered 19 different disease areas distributed over three workstreams (WSs).
Objective: To provide an overview and identify challenges in data collection at European level of the ERN eUROGEN patient population treated by HCPs in the network.
Design, setting, and participants: A retrospective cohort study was conducted of the 29 HCPs who were full members between 2013 and 2019.
Outcome measurements and statistical analysis: Data were extracted from the original HCP applications and the ERN continuous monitoring system. Patient volumes, new patient numbers, and procedures were compared between different WSs, countries, and HCPs. Discrepancies between monitoring and application data were identified.
Results and limitations: Between 2013 and 2019, 122 040 patients required long-term care within the 29 HCPs. The volume of patients treated and procedures undertaken per year increased over time. Large discrepancies were found between patient numbers contained in the application forms and those reported in the continuous monitoring system (0–1357% deviation).
Conclusions: Patient numbers and procedures increased across ERN eUROGEN HCPs. Reliable data extraction appeared challenging, illustrated by the patient volume discrepancies between application forms and the continuous monitoring data. Improved disease definitions, re-evaluation of affiliated HCPs, and valid data extraction are needed for future improvements.
Patient summary: We analysed the patient population with rare urorectogenital diseases or complex conditions within the ERN eUROGEN network between 2013 and 2019. Clinical activity was found to increase, but differences in patient numbers were evident between healthcare providers. In order to acquire valid patient numbers, both improved definitions of diagnostic codes and greater insight into the data-gathering process are required.

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‡ The list of the members of ERN eUROGEN is presented in the Supplementary material.
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1. Introduction

Very occasionally, every urologist will see a patient with a rare disease or complex condition. In these situations, it would be helpful for both the patient and the treating urologist to consult experts in other healthcare specialities that could offer advice and/or practical suggestions. These healthcare providers (HCPs) should be centres of expertise for rare diseases or complex conditions within their speciality.

This situation was discussed by European patient representatives, politicians, experts, and other specialists, resulting in a unique approach through the Cross-Border Healthcare Directive in 2011 followed by a Commission Decision on European Reference Networks (ERNs) in 2014.

The European Commission (EC) launched a call for ERNs in 2016, and leading European urological HCPs pooled their knowledge and expertise to form an ERN (ERN eUROGEN) focused on rare urorectogenital diseases and complex conditions. The aim was to build a European-level network to "care, share, and cure" from birth until end of life. The initial application consisted of recognition as centres for rare diseases by national ministries of health and extensive assessment of patient contacts, procedures, and involvement in research, education, and training. National experts applied for potential membership and were assessed by the independent assessment body and the European Board of Member State representatives (BoMS) for approval.

The 24 ERNs became operational in 2017, covering a broad range of rare diseases (Supplementary material). The ERNs' mission is to reduce healthcare inequalities for all patients with rare or complex conditions across Europe [1]. Initially, 29 HCPs in 11 countries met the member criteria and formed ERN eUROGEN, focusing on rare urorectogenital diseases and complex conditions. In 2019, affiliated partners were appointed in countries without existing full members, expanding the network to 44 HCPs from 19 EU countries [2].

The network aims to facilitate the exchange of clinical expertise through a clinical patient management system, and the development of clinical practice guidelines and clinical decision support tools. Other activities are education, training, research, innovation, and generation and sharing of evidence through a new registry. ERN eUROGEN has three workstreams (WSs) with their own disease areas (DAs; Fig. 1): WS1, rare congenital urorectogenital anomalies; WS2, functional urogenital conditions requiring highly specialised surgery; and WS3, rare urogenital tumours [3].

This study provides unique urological knowledge and data collected between 2013 and 2019 from recognised European HCPs with specific expertise; recommends future ways to extract more reliable, uniform data; and identifies barriers to extracting accurate information on patient numbers and surgical procedures.

2. Patients and methods

2.1. Analysis of ERN monitoring indicators during 2013–2019

To allow transparent follow-up and quality improvement of network activities, the EC developed a continuous monitoring system. This includes mandatory periodic reporting on 18 key performance indicators, including the number of new patients seen per year [4]. In addition, ERN eUROGEN collects the total number of patients seen and the number of complex surgical procedures undertaken each year. DAs 2.6, 2.7, and 3.5 were added recently and, due to the limited data, were not included in the analysis.

The following data were extracted: total number of patients requiring long-term care, total number of new patients, and total number of surgical procedures per year for the period 2013–2019, by WSs and DAs from the 29 full-member HCPs.

Total patients were defined as follows: "The total number of patients attending the ERNs' HCPs, regardless of age, within the specified timeframe, including visits to outpatient clinics, hospital discharges and emergencies, coming from both national and international referrals whose disease/condition falls within the codes listed. Every patient counts once within the specified timeframe, whether they were there more than once in that period."

New patients were defined as follows: "The total number of new patients attending the ERNs' HCPs for the first time, regardless of age, within the specified timeframe, including visits to outpatient clinics, hospital discharges and emergencies, coming from both national and international referrals whose disease/condition falls within the codes listed."

Complex surgical procedures were defined as "the number of (surgical) procedures/year including primary and secondary reconstructions needing general anaesthesia/year", reflecting the important impact on the patient and healthcare providers clinical care situation.

2.2. Definitions of DAs

In Europe, a disease is classed as rare when it affects one in 2000 persons. ERN eUROGEN suggests defining the term "complex condition" as a rare clinical complication involving more than two organ systems, based on the EU definition [2].

Monitoring of clinical activity within ERNs necessitates transparent definitions consistent with clinical practice and diagnosis registration. The World Health Organization (WHO) developed the International Classification of Diseases (ICD), the international standard for reporting diseases and health conditions [5]. The EC created Orphanet to collect knowledge on rare diseases. This resulted in the Orphanet nomenclature, a multilingual standardised system providing specific terminology for rare diseases [6].

To classify diseases, ICD-10 and Orphanet codes were combined to achieve full coverage and clarity on diagnoses of rare diseases and conditions within HCPs. This resulted in an initial classification of 114 diseases including their codes (Supplementary material). In 2019, the BoMS approved an expansion of disease coverage, resulting in 19 DAs in 36 specific Orphanet groupings [7].

2.3. Statistical analysis

The variables were described using descriptive statistics. The number of total patients from 2013 to 2015 was calculated, and compared according to the application forms and the continuous monitoring system. Incidences in ERN eUROGEN monitoring data were calculated using the relevant demographic data from Eurostat [8]. Comparative incidences were used from relevant literature or reports. For posterior hypospadias, data from multiple articles were used to determine the proportion of hypospadias that can be classified as posterior [9–12]. This resulted in a 9.4% of posterior hypospadias proportion of the total incidence of hypospadias. The total incidence of hypospadias that would be classified as posterior, according to the EUROCAT study by Bergman et al [9] and the study by Nordenvall et al [12], is estimated at 2.03 per 10

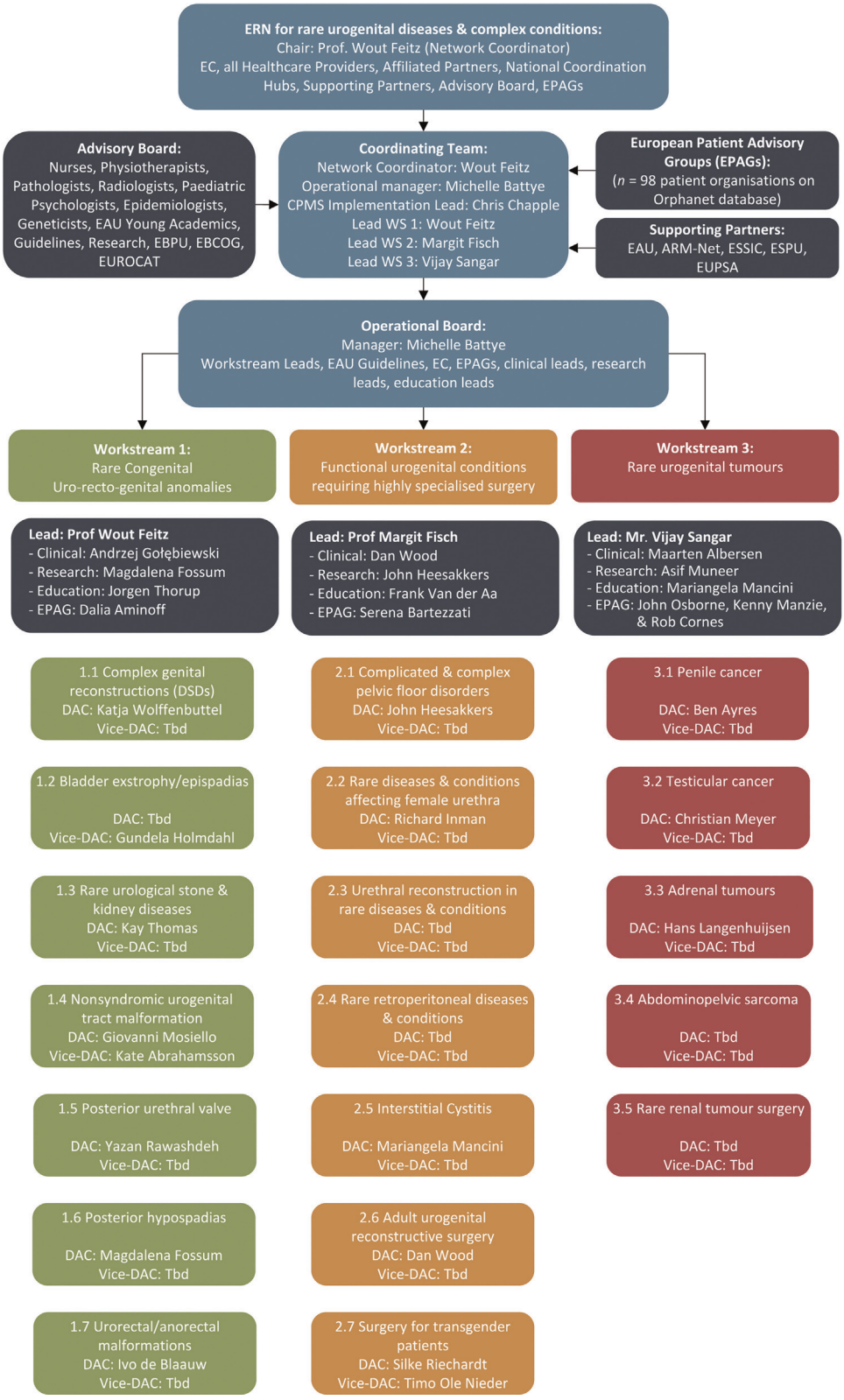


Fig. 1 – Organisational structure of ERN eUROGEN. Please note DAs 2.6, 2.7, and 3.6 were recently added DAs and are therefore not included in the analysis. CPMS = clinical patient management system; DA = disease area; EAU = European Association of Urology; EC = European Commission; EPAG = European Patient Advisory Group; ERN = European Reference Network; WS = workstream.

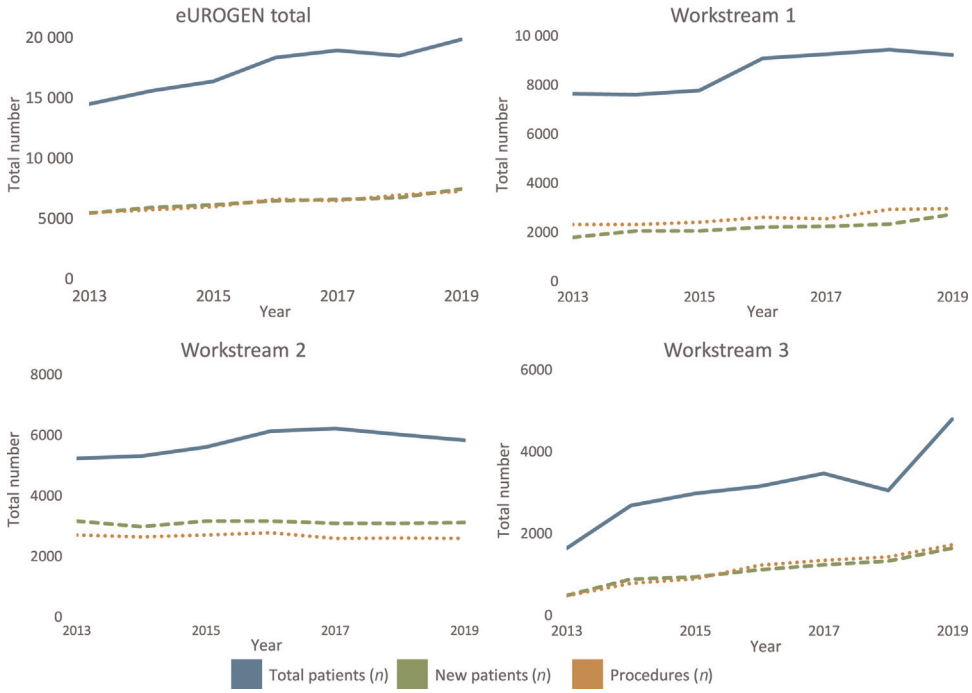


Fig. 2 – Overview of patient volumes in 2013–2019 per workstream.

000 live births. For interstitial cystitis, an incidence of 1.2 per 100 000 was estimated in the population aged 25–80 yr [13,14]. The incidence of penile cancer in Europe was estimated by calculating the weighted average from incidence rates by the report of the International Agency for Research on Cancer [15]. This resulted in a crude incidence ratio of 1.64 per 100 000; as ERN eUROGEN data were not standardised for age distribution, crude incidence ratios were used.

3. Results

3.1. Overview of clinical activities

From 2013 to 2019, a total of 122 040 patients were under long-term care, with a total of 44 700 new patients and 44 436 procedures (Fig. 2). A cumulative patient population of 59 998 was found, with the largest patient volume in WS1. WS2 saw the largest number of new patients, with an annual average of 3104. WS1 and WS3 showed increases in new patients per year of 52% and 337%, respectively. WS1 and WS3 showed increases of complex surgical procedures of 33% and 367%, respectively, whereas WS2 showed a minor decrease (–4% between 2013 and 2019).

3.2. Disease proportion

Figure 3 depicts the proportions of different DAs within the various WSs. In WS1, most patients had nonsyndromic urogenital tract malformations, hypospadias, or urorectal malformations. In WS2, DA 2.1 covered a large proportion, comprising multiple disorders combined with a relatively high volume of cases (further specification of diseases included per DA is provided in the Supplementary material). In WS3, penile cancer had the highest proportion, followed by testicular and adrenal tumours.

3.3. Number of patients per country

The UK and Germany had the most ERN eUROGEN members. Belgium registered the largest patient volumes, followed by The Netherlands and Italy (Fig. 4). In most countries, the majority of patients were classified in WS1. Belgium and Italy had the highest percentage of patients (67% and 52%) in WS2. Portugal was the only country fully focused on WS3 with 100% of patients, followed by the UK with 57% of patients in WS3.

3.4. Scattering of results

Total patient volumes and the number of procedures per disease were scattered widely among HCPs and countries (see the Supplementary material). To illustrate this, variances in new patients per centre are shown for WS1 as well as the number of members active in that DA (Fig. 5). The largest variability was found in DA 1.6. In total, 12 members were active in this area and reported nine to 182 new patients (median 37) between 2013 and 2019. The smallest variance was in DA 1.2, ranging from zero to 12 new cases (median six cases).

3.5. Incidences

Population size and live birth data from the Eurostat website were combined with the total number of new patients from ERN eUROGEN HCPs. These numbers were

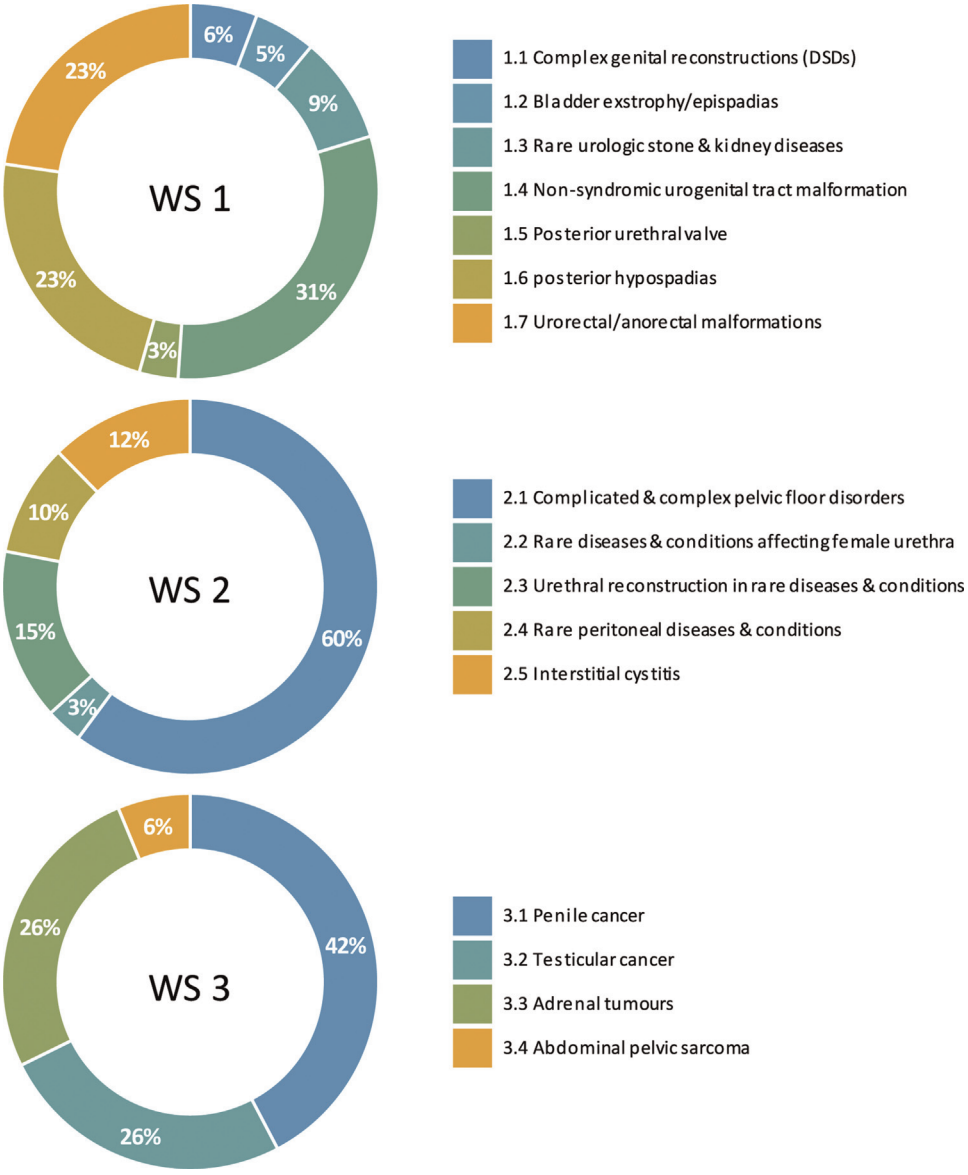


Fig. 3 – Proportions of patients per DA and WS for the year 2019. DAs 2.6, 2.7, and 3.5 are not included as these are currently under development. DA = disease area; WS = workstream.

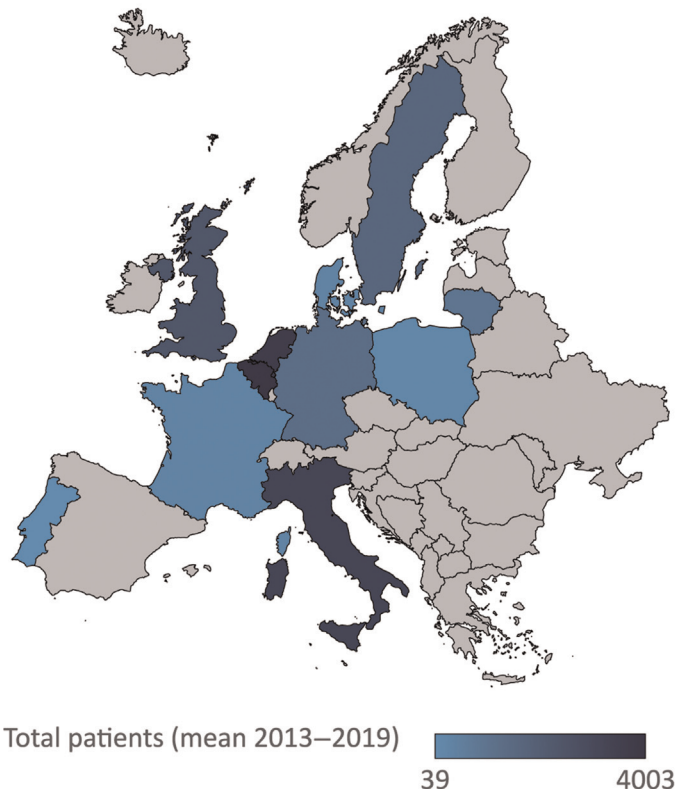
compared with the incidences found in the literature, which are presented in the Supplementary material, with examples for hypospadias, interstitial cystitis, and penile cancer.

3.6. Differences between application and monitoring

To analyse data collection reliability, total patient numbers according to the original HCP application forms were compared with the data from the continuous monitoring system from 2013 to 2015. Figure 6 shows the percentage deviation of total patient numbers. Overall, because the mean deviation for all WSs is positive (WS1: 35%, WS2: 15%, and WS3: 278%), patients were under-rated in the applications. Nevertheless, multiple HCPs were over-rated in their applications. Of the 29 HCPs, only two had corresponding numbers and scored a 0% difference.

4. Discussion

This article describes ERN eUROGEN's progress in collecting relevant and reliable performance data for rare and complex urorectogenital diseases. It presents valuable insights into clinical activities and their monitoring, alongside the other objectives of the ERNs. In 7 yr, 122 040 patients required long-term care within 29 HCPs, and clinical activity increased over time. Reliable data extraction appears challenging, as



Country	Centres	Total patients
UK	6	2396
Sweden	2	1663
Portugal	1	39
Poland	1	171
The Netherlands	2	3693
Lithuania	1	943
Italy	4	3240
France	1	318
Denmark	2	346
Germany	6	1296
Belgium	3	4003
Total	29	18 108

Fig. 4 – Distribution of patients between countries, with the number of full members displayed. The total mean patient numbers requiring long-term care between 2013 and 2019 are shown.

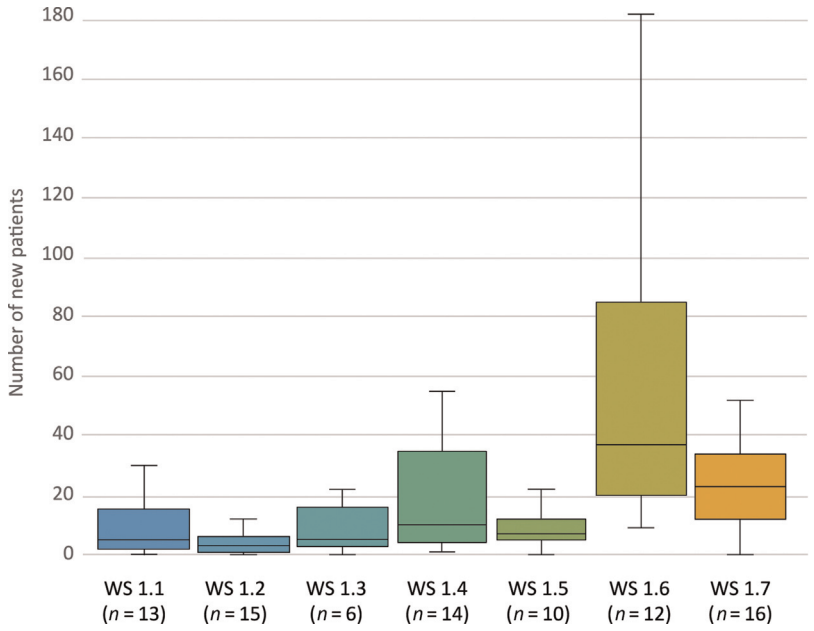


Fig. 5 – Box and whisker plots showing the variance in new patients between centres for WS1 in 2019. Data are shown per WS1 DA (number of affiliated HCPs). DA = disease area; HCP = healthcare provider; WS = workstream.

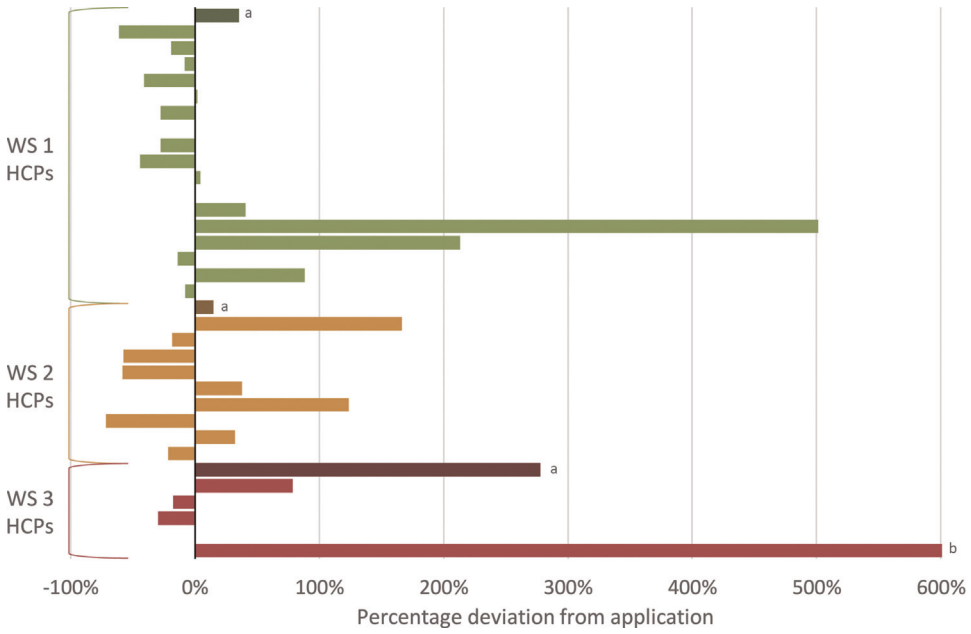


Fig. 6 – Percentage deviation of the number of patients between the continuous monitoring program and the original application. Results per WS are shown, with each bar representing an individual HCP (anonymous) with comparable data from 2013 to 2015. HCP = healthcare provider; WS = workstream. [a] Mean percentage deviation per WS. [b] Deviation of 1357%.

illustrated by the discrepancies between patient numbers registered in the ERN application forms and those in the continuous monitoring system. Clarification of the DAs is needed for further improvement.

4.1. *Expansion of the network*

The network will be expanding with additional HCPs, because ERNs aim to have a member in every EU member state to ensure full geographical coverage. Variability in patient numbers was seen between HCPs, and discrepancies were found between incidences according to the literature and the ERN eUROGEN population (Fig. 7). The variability was probably influenced by differences in referral population sizes. Although many patient numbers were registered using the continuous monitoring system, full coverage has not yet been achieved. This is probably because only a selection of European HCPs is active in this area and listed as ERN members. Local and national variations were found regarding diagnosis registration and methods of extracting patient numbers from hospital files or data warehouses despite the use of Orphanet and/or ICD-10 coding. Furthermore, the extent of centralisation differs between countries, which might partly explain the large variation [16].

4.2. *Clarification of definitions*

Although total patient numbers were comparable between the application forms and the continuous monitoring system, discrepancies exist within the different HCPs, up to 1357%.

These discrepancies might be caused partly by different definitions of the DAs. In 2017, no common classification codes were used. Currently, the continuous monitoring program is based on the ICD-10 and Orphanet codes (Supplementary material). For example, in some applications, "spina bifida" was classified as DA 1.2, whereas it was classified as DA 1.4 in the monitoring system. Another contributing factor for the discrepancies was the application process itself. During the first application, HCPs could apply for multiple DAs and were asked to supply patient numbers as they felt appropriate to indicate their expertise. This resulted in applications where not every DA applied for

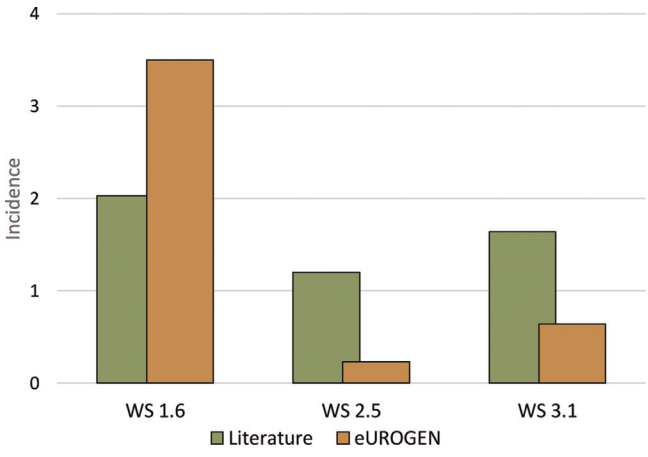


Fig. 7 – Examples of incidences found in the literature and from eUROGEN data. Incidence ratios are shown per 10 000 live births (DA 1.6) and per 100 000 (DA 2.5 and DA 3.1). DA = disease area; WS = workstream.

had patient numbers. This was later corrected by the continuous monitoring system. In the application round in 2019, applicant HCPs were required to meet specific criteria set by the ERNs to determine whether the applicant had the required levels of expertise. These criteria included minimum numbers of patients and volumes of surgical procedures. Although these criteria are difficult to establish and are based on ERN eUROGEN member consensus, they aim to further define the standards of care and increase quality within ERN eUROGEN.

Recently, an overview of rare diseases and their identification codes was validated by ERN eUROGEN and Orphanet [7]. This validation greatly improves standard registration. However, some DAs covered by ERN eUROGEN still lack an Orphanet code. Even where a disease was clearly defined by an Orphanet or ICD-10 code, discussion about classifications persisted. The term "posterior hypospadias" can broadly be interpreted and was used according to each clinician's expert opinion, illustrated by the higher incidence of posterior hypospadias than would be expected from the literature (Supplementary material). These findings underline the need for further expansion of clear definitions.

4.3. Thresholds for members

Besides coding impediments, difficulties with transition from paper to electronic patient files might contribute to discrepancies. Although most current members use electronic patient files, some HCPs work with paper files. These are prone to errors due to manual counting, whereas electronic files have other challenges, for example, the need for correct coding. In addition, extraction of patient numbers differs across HCPs because some clinical teams must personally extract numbers, whereas others have data specialists. To further improve data quality, extraction method monitoring and the option of local funding to improve data extraction need to be investigated.

4.4. Future actions

As a result of these findings, future actions will include re-evaluation of the members and current practices to maintain levels of expertise. ERN eUROGEN is building a patient registry to analyse and compare early clinical outcomes of care. This will function as a foundation for future research, aimed at providing new insights and optimal care studies on rare diseases.

In January 2021, the UK HCPs were discontinued from ERN eUROGEN due to the Brexit deal, resulting in the loss of six full HCP members and one country [17]. However, the applicants from the 2019 call are under assessment and are expected to expand ERN eUROGEN substantially. This will also make it possible to compare disease incidences in Europe with those in countries outside of Europe. Some conditions are more prevalent in other parts of the world, and exchange of knowledge will further improve both care and evidence for guidelines. Furthermore, to expand the coverage, new DAs will be added in 2021. In addition, knowledge sharing is expanding with more frequent webinars, development of clinical guidelines, and the start of the EU-mobility programme facilitating expertise exchange between HCPs. With these future actions, ERN eUROGEN aims to expand the network and increase the quality of care for our patients.

5. Conclusions

ERN eUROGEN aims to improve knowledge exchange and expertise sharing, to optimise care pathways and innovate cure potential for all rare urorectogenital diseases and complex conditions in the EU. The data show that ERN eUROGEN's HCPs and expert multidisciplinary teams are treating an increasing number of patients and performing an increasing number of complex surgical procedures. Despite having a well-structured continuous monitoring system, challenges persist regarding extraction of patient numbers and procedures, and validation of these data. Improvements are needed in patient registration. Furthermore, geographical expansion of the network is needed to provide equal care for all patients suffering from rare urorectogenital diseases and complex conditions in Europe.

Author contributions: Wout F.J. Feitz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Oomen, Leijte, Feitz.
Acquisition of data: Shilhan, Battye, Members of ERN eUROGEN.
Analysis and interpretation of data: Oomen, Leijte.
Drafting of the manuscript: Oomen, Leijte.
Critical revision of the manuscript for important intellectual content: Shilhan, Battye, Members of ERN eUROGEN, Feitz.
Statistical analysis: Oomen, Leijte.
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Administrative, technical, or material support: Shilhan.
Supervision: Feitz.
Other: None.

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Loes Oomen: Data curation, Formal analysis, Methodology, Validation, Visualization, Writing - original draft, Writing -

review & editing. **Erik Leijte:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Darren E. Shilhan:** Conceptualization, Data curation, Project administration, Resources, Writing - review & editing. **Michelle Battye:** Conceptualization, Funding acquisition, Project administration, Writing - review & editing. **Members of ERN eUROGEN:** Resources, Writing - review & editing. **Wout F.J. Feitz:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing - original draft, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2021.02.043.

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