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REVIEW

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Centralization of the management of gestational trophoblastic disease in Europe: from local centers to European Reference Networks

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Abstract

Gestational trophoblastic disease (GTD) encompasses a group of rare disorders ranging from pre-malignant to malignant conditions. Today, the management of GTD in Europe has evolved into a centralized approach which is crucial for the best outcomes. To investigate the centralized approach, we conducted a literature search on the PubMed/MEDLINE database and others such as SCOPUS, Google Scholar, Cochrane Library, January 2025. Additionally, we searched the official websites of European countries and the EU for information about European Reference Networks (ERNs) and national centers for GTD. We identified three phases in the centralization process of GTD management in Europe. The initial phase involved local hospitals and the development of the concept of centralized and specialized treatment for GTD. In the second phase, national centers for GTD were established. Finally, the creation of ERNs brought these national centers together. ERNs use advanced and multi-level tools of health communication. As conclusion, the current approach to managing GTD in Europe emphasizes the centralization of treatment and follow-up, with national centers and ERNs serving as the core components of this strategy. This approach may be an example of the best management of GTD for the world.

Keywords

Rare diseases; Centralization of management; Gestational trophoblastic disease; European Reference Networks; Health communication

1. Introduction

Gestational trophoblastic disease (GTD) consists of a group of disorders including the pre-malignant conditions of complete hydatidiform moles (CHMs), partial hydatidiform moles (PHMs) as well as malignant invasive moles, choriocarcinoma, and the very rare placental site trophoblastic tumor/epithelioid trophoblastic tumor [1]. All types of GTD are considered as a rare disease due to its incidence. The most common forms of GTD, which are CHM and PHM, affect approximately 1 to 2 in 1000 pregnancies in most Western countries [1]. The malignant variants of the disease are collectively termed gestational trophoblastic neoplasia (GTN). In GTD, human chorionic gonadotrophin is produced by trophoblastic tissues and acts as a biomarker for diagnosis, evaluation of treatment response, early relapse detection, and confirmation of cure. After diagnosing GTD, it is essential to stage the disease and determine the International Federation of Gynecology and Obstetrics/World Health Organization prognostic risk score to initiate chemotherapy regimen. Because approximately 75% of GTN cases occur after the development of hydatidiform moles, follow-up of hydatidiform moles is crucial. GTN has high cure rates if treated in experienced centers [2].

Rare diseases (RD) are chronic, severe, and often life-threatening or disabling conditions with a low prevalence. In the European Union (EU), a disease is defined as rare when it affects no more than 1 in 2000 individuals. Over 6000 distinct RDs have been identified in the EU, around 80% of which are genetic in origin, with approximately 70% manifesting during childhood. RDs represent a major public health concern, affecting over 35 million people across the EU [3]. Beyond the large number of people affected, rare diseases present major challenges in diagnosing and treatment, including limited knowledge and training, delayed or missed diagnoses, insufficient understanding of disease mechanisms, lack of effective therapies, and restricted access to treatment and care. A centralized approach that unites patients with highly experienced specialists is regarded as the most effective strategy for addressing RDs. To support this model, national centers have been established across Europe. Nevertheless, in many instances, no single country possesses adequate resources to manage all RDs effectively. To overcome these limitations, the EU established the European Reference Networks (ERNs) to promote collaboration among national centers. ERNs are distinctive, e-health-based, patient-centered virtual networks that integrate expertise, knowledge, and resources to improve the

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diagnosis and treatment RDs. The first 24 ERNs were launched in 2017, comprising more than 900 specialized healthcare units from over 300 hospitals in 26 Member States (Table 1) [3]. Among them, EURopean Rare Adult solid CANcer network (EURACAN) focuses rare adult solid tumors and is organized into 10 domains, one of which covers GTD (Table 2).

2. Methodology

We conducted a literature search on the PubMed/MEDLINE database and others such as SCOPUS, Google Scholar, Cochrane Library, January 2025, using the following search terms: GTD, GTN, current management of GTD, follow-up in GTD, centralized treatment in GTD, RDs, ERNs, and national and international referral centers for the management of GTN. Additionally, we searched the official websites of European countries and the EU for information about ERNs and national centers for GTD.

3. Centralization

Today, the management of GTD in Europe has evolved into a centralized approach. This process began with local hospitals dedicated to the treatment of GTD and the development of the centralization concept, ultimately leading to the establishment of national centers and ERNs. According to EURACAN, approximately 21,000 women of childbearing age in the EU develop GTD each year. The centralization of management is expected to reduce morbidity and mortality in these women [4].

The idea of centralizing treatment began with the increasing awareness of RDs. This growing awareness accelerated research and clinical trials on RDs, highlighting the need to bring patients from different locations together. Centralized research and trials, in which new treatment options and drugs were tested, demonstrated that bringing and evaluating patients together resulted in longer survival rates [5]. These positive outcomes were a significant step in developing the concept of centralization.

Numerous studies from the 1970s to the present have demonstrated the importance of centralizing GTD cases. According to a report by Brewer *et al*. [6], both morbidity and mortality rates for patients with GTD were nine times lower at a center with experienced physicians in managing GTD than for patients treated by "occasional" physicians. Similarly, Golfier *et al*. [7] evaluated epidemiological data from the French Trophoblastic Disease Reference Center, particularly

TABLE 1. 24 European Reference Networks on rare diseases.

Abbreviations of the networks	Names of the networks
BOND	European Reference Network on Rare Bone Disorders
CRANIO	European Reference Network on Rare craniofacial anomalies and ENT disorders
Endo-ERN	European Reference Network on Rare Endocrine Conditions
EpiCARE	European Reference Network on Rare and Complex Epilepsies
ERKNet	European Reference Network for Rare Kidney Diseases
ERN-RND	European Reference Network on Rare Neurological Diseases
ERNICA	European Reference Network on Rare inherited and congenital anomalies
ERN-LUNG	European Reference Network on Rare Respiratory Diseases
ERN-Skin	European Reference Network on Rare and Undiagnosed Skin Disorders
EURACAN	European Reference Network on Rare Adult Cancers (solid tumors)
EuroBloodNet	European Reference Network on Rare Hematological Diseases
EURO-NMD	European Reference Network for Rare Neuromuscular Diseases
ERN-EYE	European Reference Network on Rare Eye Diseases
ERN GENTURIS	European Reference Network on GENetic TUmour RIsk Syndromes
GUARD-HEART	Gateway to Uncommon and Rare Diseases of the HEART
ITHACA	Rare Congenital Malformations and Rare Intellectual Disability
MetabERN	European Reference Network for Rare Hereditary Metabolic Disorders
PaedCan-ERN	European Reference Network for Paediatric Cancer (haemato-oncology)
RARE-LIVER	European Reference Network on Rare Hepatological Diseases
ReCONNET	Rare Connective Tissue and Musculoskeletal Diseases Network
RITA Rare	Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases Network
TRANSCHILD	European Reference Network on Transplantation in Children
VASCern	European Reference Network on Rare Multisystemic Vascular Diseases
EUROGEN	European Reference Network on urogenital diseases and conditions

Resource: Networks, https://ec.europa.eu/health/ern/networks_en, accessed 10 January 2025.

TABLE 2. Ten EURACAN domains.

Ten EURACAN domains
Rare cancer of the connective tissue (sarcomas)
Rare cancer of the female genital organs and placenta
Rare cancer of the male genital organs, and of the urinary tract
Rare cancer of the neuroendocrine system
Rare cancer of the digestive tract
Rare cancer of the endocrine organs
Rare cancer of the head and neck
Rare cancer of the thorax
Rare cancer of the skin and eye melanoma
Rare cancer of the brain and spinal cord

Resource: https://euracan.eu/, accessed 10 January 2025.

analyzing GTN rates following molar pregnancies registered between 1999 and 2004. They concluded that creating reference centers for trophoblastic disease improves patient treatment [7]. Kohorn [8] investigated factors influencing outcomes for patients with GTD globally. Physicians known to treat GTD were sent a questionnaire, and 32 responses from 17 countries were received, totaling 26,153 patients. The results indicated that patients treated by physicians experienced in GTD management had better outcomes and survival rates [8]. Freitas *et al*. [9] reviewed the medical records of women with GTN treated at 10 Brazilian GTN Reference Centers from 1960 to 2017. They found that the risk of mortality from both low- and high-risk GTN can be reduced by reference centers [9]. In a recent report, Golfier and Seckl [2] concluded that setting up expert centers and national frameworks for GTD management is associated with achieving optimal disease outcomes. Another report by Seckl and Ghorani [10] emphasized that improving outcomes depends on establishing dedicated centers with appropriate patient pathways, in line with new international guidelines created in Europe as a result of multiple consensus-building meetings.

Making a correct histologic diagnosis is crucial in GTD to ensure the appropriate subsequent treatment after the initial treatment. Several studies have shown that an experienced pathologist is essential for accurate diagnosis. According to Hancock *et al*. [11], histologic diagnosis correction was necessary in 5% of patients with CHM and 32% of those initially diagnosed with PHM. Among these revised diagnoses, 15% (25 of 170) of CHMs and 4% (4 of 96) of PHMs developed trophoblastic neoplasia [11]. Similarly, Golfier *et al*. [7] reviewed epidemiological data from the French Trophoblastic Disease Reference Center between 1999 and 2004. They showed that of the 329 patients referred as singleton molar, nonmolar, or unspecified pregnancies, the referent pathologist at the center had an overall agreement rate of 75% (247 of 329) with the referring center. When the initial diagnosis was CHM, the agreement rate was 95%, but for PHM, the agreement rate was 68% (75 of 110), with approximately 1 in 3 disagreements (13 of 35) reclassified as nonmolar pregnancies [7]. Schoenen *et al*. [12] examined the value of centralized pathology review by expert pathologists and its potential impact on clinical management in a prospective multicenter study based on the Belgian Gestational Trophoblastic Diseases Registry. They analyzed 1119 cases from 2012 to 2020, with referral pathologists reviewing all initial histological diagnoses. The study revealed a 35% discordance rate between expert and non-expert pathologists, with almost 95% of CHMs but only 61% of PHMs confirmed by expert pathologists. Another significant finding was that the diagnosis of GTN was altered in 42% of cases, indicating that systematic centralized pathological review of GTD modified the diagnosis in one-third of cases. Their results also showed that a change in diagnosis would impact clinical management in 98% of patients [12]. A pathologist can gain valuable experience by evaluating numerous cases, which is possible if all cases are referred to a center. According to a study by Fehlmann *et al*. [13], approximately 150 cases are expected to be diagnosed in Switzerland every year. On average, a Swiss pathologist may see one case per year, gynecologists one case every 5 years, and medical oncologists only one case every 16 years [13]. However, if a single pathologist, gynecologist, and oncologist at a center see all these cases, they can gain substantial experience.

A centralized approach is needed to achieve a sufficient patient count for research and trials that test new guidelines and identify treatments to improve outcomes. Centralization also addresses the limited access patients have to clinical research studies, including those trialing novel agents. A centralized approach allows an increasing number of patients to enroll in clinical trials each year. Regarding GTN, two groups of patients experience worse outcomes due to the development of multidrug-resistant disease: those with risk factors including liver with or without brain metastases, defined as ultra-high-risk (usually with an International Federation of Gynecology and Obstetrics score of $\geq$13), and those with the epithelioid trophoblastic tumor and placental site trophoblastic tumor subtypes. There are a limited number of immunotherapy trials for these groups [14]. We believe that a centralized approach is crucial to enroll more patients in clinical trials, thereby identifying new therapeutic agents for these high-risk groups.

4. Phases in the management of gestational trophoblastic disease in Europe

We identified three main phases in the management of GTD in Europe (Fig. 1). Initially, there were no national or international referral centers, and patients with GTD were treated entirely in local hospitals. Over time, regional centers began to develop, accepting complex cases referred by local hospitals. These regional centers eventually evolved into national centers, bringing together the best experts and resources to develop new treatment, diagnosis, and follow-up options. In addition to providing optimal treatment to patients, these national centers educated new experts and conducted numerous research programs. After approximately 20 years of effort, the EU established 24 ERNs for RDs, including rare genetic disorders and rare cancers (Table 1). One of these 24 ERNs is EURACAN, which focuses on adult solid cancers. EURACAN has 10 domains, one of which is "Domain 2: Rare Cancer of the Female Genital Organs and Placenta" (Table 2).

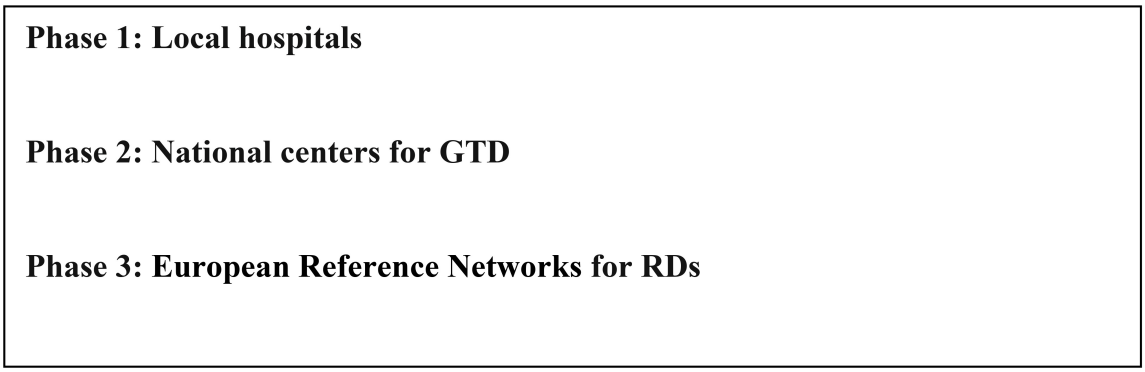

FIGURE 1. Three phases in the management of GTD in Europe. GTD: Gestational trophoblastic disease; RDs: Rare diseases.

4.1 Phase 1: local hospitals

Initially, local hospitals were responsible for the diagnosis and treatment of GTD. The initial treatment of GTD began with the evacuation of a molar pregnancy, which was followed by monitoring of the human chorionic gonadotrophin concentration to detect any transition to GTN. At this stage, all treatment options were administered at local hospitals because of the absence of specialized referral centers focused on GTD. Over time, certain hospitals and clinics gained more experience and began to serve as referral centers for GTD. These regional centers eventually evolved into national centers, which brought together the best experts and resources. With the establishment of national centers, the role of local hospitals became limited to the evacuation and diagnosis of molar pregnancies and initial patient follow-up.

4.2 Phase 2: national centers for gestational trophoblastic disease

The rarity of GTD and the need for multidisciplinary management, involving experts in pathology, molecular biology, imaging, nuclear medicine, surgery, radiotherapy, and medical oncology, led to the establishment of national centers. These centers manage the treatment and diagnosis of high-risk and ultra-high-risk patients and evaluate complex cases, while also performing various other functions. These include conducting clinical and epidemiological research, educating doctors and patients, supporting local centers, preparing guidelines, and setting standards for healthcare and treatment centers.

The first national centers for GTD in Europe were established in the United Kingdom in 1973 at Charing Cross Hospital in London and Weston Park Hospital in Sheffield [13]. According to the official site of Charing Cross, the center has treated more than 3500 patients with various forms of GTD, making it the largest center for this disease worldwide [15]. Serving a population exceeding 22 million across Northern England and North Wales, the Sheffield center registers roughly 600 women each year after a diagnosis of molar pregnancy [16].

Today, there are approximately 100 national centers in Europe where patients with GTD can receive treatment, with approximately 15 of these being specific centers dedicated to GTD [17]. The European Organization for Treatment of Trophoblastic Diseases (EOTTD) is an international organization aimed at strengthening diagnostic process, treatment, follow-up, and research in GTD by consolidating the expertise of clinicians and researchers in the field. According to the EOTTD, there are currently 22 national centers for GTD in Europe, located in Amsterdam, Aarhus, Belgrade, Bern, Bratislava, Budapest, Cork, Dundee, Geneva, Leuven, Liege, London, Lyon, Milano, Madrid, Nijmegen, Oslo, Prague, Porto, Sheffield, Stockholm, and Warsaw [18].

4.3 Phase 3: European Reference Networks for rare diseases and EURACAN for gestational trophoblastic diseases

ERNs are virtual, cross-border networks that bring together healthcare professionals and patient representatives from across Europe. Although national centers marked a significant improvement in managing RDs, they often proved insufficient on their own. To address these limitations, the EU established ERNs in 2017, following approximately 20 years of effort [19]. The EU had a longstanding commitment to advancing policies and initiatives on RDs, recognizing that RDs affect more than 35 million people in the EU and that the lack of harmonization between national health systems left patients with RDs particularly vulnerable [20]. However, according to the EU founding treaties, health is not a common policy area; this means the EU cannot make binding decisions on health issues that member states must implement [21]. The governance, funding, organization, and provision of healthcare continue to fall under the responsibility of each EU Member States. Despite this, the EU adopted a directive on cross-border health issues and patient rights that does not contradict the founding treaties. The "Directive 2011/24/EU on the application of patients' rights in cross-border healthcare", adopted on 19 January 2011, was aimed at easing access to cross-border care and clarifying the legal regulations surrounding patient mobility [22]. The directive further set up ERNs to foster cross-border collaboration in complex specialist care and lessen the financial burden of treatments.

At their launched in 2017, the ERNs already included over 900 specialized healthcare units operating within more than 300 hospitals across 26 Member States (Table 1). ERNs consolidate expertise and resources by convening the foremost

specialists across Europe, thereby providing patients with dependable information and evidence-based treatment options [19]. Eligibility for ERN membership requires meeting the following criteria: a minimum of 10 healthcare providers originating from at least 8 different Member States; each endorsed by their national authorities; and all must demonstrate common expertise in a defined clinical field, treatment, or disease [3].

The ERN system is underpinned by three essential e-health tools:

ERN Collaborative Platform: By connecting all networks, the platform supports cross-ERN collaboration for cases that benefit from combined expertise of multiple networks.

ERN Clinical Patient Management System: This multi-country system allows for the sharing of clinical data, including medical imagery. With patient consent, a patient's clinical data can be shared following a consultation process to support joint diagnostic and treatment decisions. These data may also be stored for future research purposes.

ERN Public Website: This site hosts clinical guidelines, patient information, and a range of other network-produced resources for healthcare professionals and the public.

Among the 24 ERNs, EURACAN focuses on rare adult solid cancers [23]. EURACAN brings together 75 specialized cancer centers and groups all rare adult solid cancers into 10 domains (Table 2). "Domain 2: Rare Gynecological Cancers" includes a group of different tumor types that can be divided into three categories: GTD, rare ovarian tumors, and other rare gynecological cancers. The mission of EURACAN, as stated on its official site, is to advance diagnosis, clinical management, knowledge generation, research, and communication people with rare adult solid cancers [4].

There are three ways for patients to be referred to EURACAN:

Healthcare professional referral: A healthcare professional can make an appointment for the patient at a nearby EURACAN expert center.

Expert consultation: A healthcare professional can contact EURACAN experts on the patient's behalf to seek a second opinion and receive advice from EURACAN specialists.

Self-referral: Patients can also self-refer to ask for a second opinion at any stage of their treatment.

5. Limitations

First, the review was restricted to English-language publications, potentially overlooking relevant studies published in other European languages. Second, because our focus centered on treatment centralization, we selected literature related to this theme and could not fully assess outcomes from non-centralized settings. Lastly, the study was limited to Europe, and no global comparisons were performed.

6. Conclusion

Today, it is widely accepted in Europe that the treatment of GTD should be centralized to achieve the best outcomes. The challenges in managing GTD, stemming from its rarity, can be effectively addressed only through a centralized approach. Although there may be some minor variations, it is crucial that after the initial diagnosis and treatment of GTD, follow-up care, treatment of high-risk patients, and management of patients with resistance to initial chemotherapy be conducted in highly specialized national centers. For more complex cases, support from EURACAN can be sought in Europe.

AVAILABILITY OF DATA AND MATERIALS

This narrative review is based on previously published studies that are fully referenced within the manuscript. No new datasets were generated or analysed. All data supporting the findings of this article are available from the cited literature.

AUTHOR CONTRIBUTIONS

İG—planning and design of the study, searching literature and writing the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study is a narrative review of previously published literature and did not involve human participants or animals. Therefore, ethical approval and informed consent were not required.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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