

# Is rare cancer care organized at national health system level? Multiple case study in six EU countries

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**Background:** As a system of European Reference Networks (ERNs) emerges, the differences in quality of care for patients with rare cancers may increase at national level. We aimed to elucidate the processes and healthcare planning principles through which the reference centres (RCs) for rare cancers are embedded in national health systems. **Methods:** We used a multiple case-study design based on the experiences of Czechia, Finland, France, Italy, Lithuania and Spain. Using sarcoma as an example of rare cancer, 52 semi-structured interviews were conducted during on-site visits, including a multidisciplinary group of professionals, Ministry of Health professionals, patient representatives and European policymakers. **Results:** The comparative analysis showed substantial heterogeneity in the processes for formalizing RCs' status and in their levels of integration in the different health systems, but two models (centre-based and the network-based) can be envisaged at national level. RCs for rare cancers were legally established only in France and Spain. Expert clinicians cooperate in a structured way, using network mechanisms, in France and Italy, and these countries, plus Finland and Lithuania, had a referral system to facilitate patients' access from non-expert centres to RCs. Seven key healthcare planning principles in instituting RCs at the national level were identified. **Conclusions:** The conditions governing patient access to treatment centres—whether RCs or not—are decided at the national level. It is advisable to progressively align the European and national levels so that the RCs that participate in the ERNs also play a significant role at the national level.

## Introduction

'The whole is more than the sum of its parts' could be the motto of the 24 European Reference Networks (ERNs) for rare diseases, 4 of which focus on rare cancers.<sup>1</sup> This type of European cooperation, organized around national expert centres and endorsed by national authorities, opens the door to discussing cases, defining clinical standards and referring patients for clinical trials. ERNs also aim to overcome shared problems in health care for rare cancers, including difficulties in diagnosis, a lack of effective treatments, scarce research opportunities and barriers to accessing expert centres.<sup>2,3</sup>

For the purposes of this article, 'expert centres' are defined as all treatment centres that are formally or informally recognized as specialized centres providing the highest quality of care for a certain disease or group of diseases. These centres are termed 'reference centres' (RCs) if their status is formally accredited and/or embedded within a referral system for patients who need highly specialized care.

While requirements for accessing ERNs are standard for all European Union (EU) member states, the conditions governing patients' access to national expert centres depend on the organization of healthcare systems (e.g. degree of centralization). Because ERNs should be embedded in national health systems, the country-based

level can be envisaged as a key context for fully leveraging ERNs. As stated by one country representative from the Board of Member States, 'ERNs must not become freestanding islands of excellence operating in isolation. . . [they have to ensure] good links to hospital and primary care services and benefit communities in their locality'.<sup>4</sup> The more RCs for rare cancers and their cooperation are developed at the European level, the greater the probability for increased gaps in quality of care when other centres (and not only RCs) treat these patients at the national level. Because of this, we focussed on the national organization of health services that provide care for patients with rare cancers (24% of the total cancer cases diagnosed annually in the EU-28<sup>5</sup>), i.e. the context of four ERNs.

This study took place in the framework of Work Package 10 of the EU Joint Action on Rare Cancers (JARC), proposed by the European Commission.<sup>6,7</sup> Using sarcoma as an example, we tried to elucidate how RCs are positioned and embedded in national health systems in Czechia, Finland, France, Italy, Lithuania and Spain.

## Methods

### Study design

We adopted a multiple case-study design to analyze six countries that established expert centres or RCs for rare cancers. The case-study approach facilitates the understanding of complex phenomena by identifying and detangling the roles played by contextual variables.<sup>8,9</sup> While national experiences were our units of analysis, we focussed on one rare tumour (sarcoma) in order to standardize the context and enable a comparative analysis. Sarcoma is a good example of rare cancers. Many patients spend months or years trying to find a diagnosis.<sup>10</sup> The different subtypes require expert multidisciplinary teams (MDTs) for treatment planning, and variability in clinical practice is an important problem. Different studies show that only 40–50% of sarcoma patients are treated according to the clinical guidelines, even in places with dedicated care networks.<sup>11,12</sup> At the same time, sarcoma represents 1% of all cancers in Europe<sup>5</sup> (i.e. it is not very rare), and services are fairly well organized, with national academic groups and patient organizations, which allows for exploration.

The case study applied mixed methods (qualitative study plus case-site observation). Criteria for selecting countries included variety (with cases from different European regions) and feasibility of the field study (i.e. stakeholders from these countries were involved in the JARC Joint Action). The qualitative study consisted of 52 one-on-one semi-structured interviews (average duration: 49 min) conducted by one co-author (J.P.) during six on-site visits to different European countries from February to July 2018 (table 1). Interviews were audio-taped and transcribed. We extracted key information from the transcriptions and anonymized responses to protect confidentiality. Prior to the field work, the health authorities of participating countries—gatekeepers for accessing the study setting and respondents—received a study protocol and 'how-to' guide for the research (Supplementary material). The interview script (Supplementary material) was finalized following a pilot interview with an expert clinician in sarcoma (external to the study) and had the consensus of all co-authors (J.P., A.T., P.G.C. and J.M.B.). On starting the interview, participants received an information sheet specifying the objectives and the importance of the research (Supplementary material) and signed informed consent and a confidentiality agreement.

### Sample strategy

We used a purposive sampling strategy, selecting informants following the criterion of discourse representativeness.<sup>13</sup> The inclusion criteria were: informants working at two sarcoma RCs at national level; members of the ERN for rare adult solid cancers; and mature national experiences, with a relatively homogeneous disease-based community of physicians, clinical researchers and patients.

**Table 1** National RCs on rare cancers and stakeholders included in the study

Country	Centre	No. informants
Czechia	Professionals:	
	Masaryk Memorial Cancer Institute (Brno)	3
	University Hospital Motol (Prague)	3
	Patients' representatives	1
	Health authorities	1
France	Professionals:	
	Hôpital Ambroise Paré (Paris)	1
	Institut the Cancérologie Gustave Roussy (Paris)	1
	Institut Bergonié (Bordeaux)	1
	Patients' representatives	1
	Health authorities	1
Finland	Professionals:	
	Helsinki University Hospital (Helsinki)	3
	Turku University Hospital (Turku)	3
	Patients' representatives	1
	Health authorities	3
Italy	Professionals:	
	Fondazione IRCCS Istituto Nazionale di Tumori (Milano)	3
	Health authorities	1
Lithuania	Professionals:	
	Hospital of Lithuanian University of Health Sciences (Kaunas)	12
	University Hospital Santaros Klinikos (Vilnius)	7
	Patients' representatives	1
	Health authorities	1
Spain	Professionals:	
	University Hospital Sant Pau (Barcelona)	1
	Catalan Institute of Oncology (Hospitalet de Llobregat)	1
	Health authorities	2

### Data analysis

Data were examined inductively. In identifying the thematic areas related to national RCs (J.P., A.T. and J.M.B.), we differentiated the core issues (e.g. legal status) from the specific health system embedding (e.g. role of health authorities) and compared policy issues separately. Relevant quotations from the interviews are used anonymously (Supplementary material). Following the content identification, we performed a thematic analysis (J.P. and A.T.),<sup>13,14</sup> grouping data into codes and categories to allow a narrative description. We used the Atlas.ti 6.2 to collect and organize data.<sup>15</sup> All co-authors shared four assumptions, constituting the study rationale (table 2).

## Results

The sample for each selected country involved a multidisciplinary group of professionals dealing with sarcoma, including medical oncologists ( $n=10$ ), radiation oncologists ( $n=4$ ), surgeons ( $n=8$ ), pathologists ( $n=5$ ), radiologists ( $n=2$ ), geneticists ( $n=2$ ), nurses ( $n=3$ ), patients' representatives ( $n=7$ ), national health authorities ( $n=9$ ); and European policymakers involved in the launch of the ERNs ( $n=2$ ). The analysis of how RCs for rare cancers are embedded in the health care systems was organized into four domains that correspond to two cross-cutting issues (1 and 4) and two scenarios (2 and 3).

### 1. Differential aspects affecting the positioning of RCs for rare cancers within health systems

Three aspects (legal status, designation process and funding) were relevant when assessing the positioning of RCs within the different health systems. First, legal establishment (i.e. ministerial decree, government ordinance or any legally binding act) afforded RCs a singular status in relation to other centres; this was the case in France

**Table 2** Rationale for developing the study

1. Diagnosis is of the utmost importance in sarcoma, which has over 100 pathological subtypes. Differential diagnosis is crucial so that patients do not spend months or years trying to find a diagnosis, compromising appropriate treatments and prognosis. There is a need to link many medical treatments to clinical trials.
2. Non-expert professionals have to systematically ask for advice for every patient at any major treatment decision to make.
3. Reference centres may not be 'experts' in all subtypes of sarcoma or able to provide a very specific procedure (e.g. bone sarcoma surgery). As clinical expertise is not distributed homogeneously among reference centres, cooperation between them is essential.
4. Centralizing care for patients with rare cancers in expert centres is a necessary condition to guarantee high health care quality.

and Spain (table 3). In contrast, in Lithuania and Czechia many clinicians and policymakers were concerned that the lack of specific legal status could lead to the duplication of specialized services.

Secondly, there was substantial variation in the processes for designating expert centres as RCs for rare cancers. While in Spain or France the health authorities accredit RCs based on a formal set of standards (e.g. patient volume), in Finland and Czechia, they are informally identified because they are university centres and/or have highly specialized services (although rare cancer treatment is centralized by law in Finland in its five university hospitals). Furthermore, there is an obvious difference depending on whether the responsibility for selecting and controlling RCs is held solely by health authorities (e.g. Spain) or jointly with a scientific group for sarcoma (e.g. France). In the former case, the authorities are both guarantors and managers of the RC system; in the latter, they exercise indirect control and entrust the functions of management and selection of centres to the French Sarcoma Group. The greater visibility of RCs may be enough to accelerate referrals, and accreditation processes may also involve greater workloads, so a final relevant aspect at the RC level is whether they receive specific funding. This only happens in France (table 3).

## 2. Cooperation between RCs

Only in France and Italy is the concept of expert centre associated, by default, with a system of expert centres working together. The RCs in these countries are embedded in a formal clinical network with a framework for clinical communication and a ranking of centres based on their clinical expertise. Both national experiences had as a background a consolidated sarcoma academic group that, in accordance with health policy objectives, institutionally evolved towards a healthcare network system. In France, there are 28 regional expert centres on sarcoma, 3 of which (in Lyon, Bordeaux and Paris) are also national referral centres (the others are officially appointed as competent centres). Among other responsibilities, the three national RCs define the common clinical protocol for the network.

The absence of formal mechanisms in countries, such as Spain, Lithuania, Czechia and Finland does not imply a lack of professional collaboration, which instead is mainly based on personal relationships and/or their willingness to share difficult cases (referring patients or exchanging images or pathological samples) or cases that require a very specific technique or access to a trial that may not be available in a given centre. In these countries, sarcoma academic groups (including the transnational Scandinavian Sarcoma group, concerning Finland) are of the utmost importance for national experts, since there is no other formal platform to transfer clinical knowledge.

## 3. Collaboration and access to RCs from non-expert centres

In France and Lithuania, there are formal care instruments to ensure patient access to RCs from non-expert centres. For example, in France, after the pathological double-reading (recommendation followed in 80% of sarcoma patients, according to informants), guidelines advise discussing and/or referring the case to the regional expert tumour committee in order to guarantee the maximum care quality or to administer an innovative treatment. The discussion between expert and non-expert centres is based on virtual tumour boards, which provide medical advice and a proposed treatment plan. For its part, Lithuania has created referral pathways, known as 'green corridors', to refer patients with complex pathologies like sarcoma to RCs from Kaunas and Vilna.

Spain and Czechia have no specific mechanisms for referring patients to RCs. The selection of RC is determined by a mix of factors, including geographic proximity, patients' choice and particularly referring clinicians' perceptions of the quality of care in RCs. The cases of Italy and Finland are halfway between the formal referral and the non-referral pathway. In Italy, an informal network enabling clinical exchanges between expert and non-expert centres (including a shared database) existed until the creation of the new 'institutional' network, although this is still not active; in the professional network, referral mostly depended on professionals' relationships. To mitigate the high patient migration from southern to northern Italy, the accreditation system aims to select both hubs (expert centres) and spokes (centres capable of delivering high-quality medical treatment in partnership with the hubs). In Finland, legislation restricts the delivery of rare cancer care to the five university hospitals, with even further specialization between them (i.e. very rare cancers can be treated in only one or two sites).

Conceptualizing RCs on a spectrum between two variables (i.e. the role of health authorities and scientific groups as well as the positioning of RCs within health systems), we grouped the countries on the basis of ideal models for organizing rare cancer care (figure 1). In the network model (followed by France and Italy), RCs act as central nodes within a stable system of inter-hospital relationships and include an explicit objective to achieve equitable access to high-quality care. In contrast, according to the centre-based model (Czechia, Spain, Finland and Lithuania), patients' freedom to choose an RC is directly or indirectly prioritized, with varying levels of involvement from the health authorities in ensuring a stable supply of RCs.

## 4. Healthcare planning principles in establishing national RCs

The comparative analysis of the cases revealed several key healthcare planning principles (a–g) applied when positioning the RC at a national level.

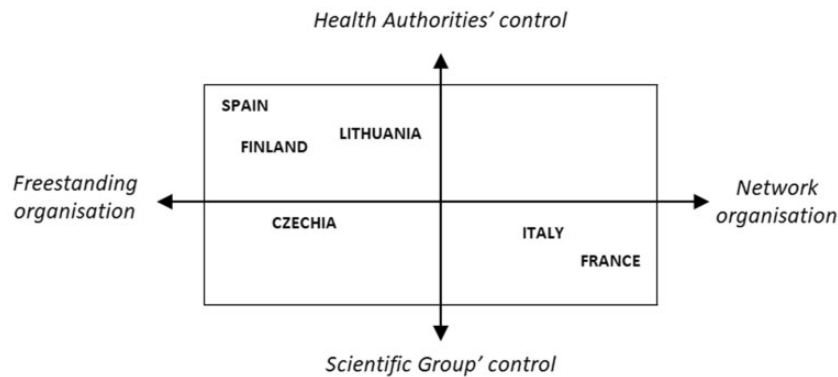
- a. The formalization of RC status within the health system is a precondition for health authorities' control
 

Health authorities can assume opposite positions regarding the type of control they exercise, acting as guarantors of a system led by expert professionals (e.g. France), or alternatively as gatekeepers that accredit the centres themselves (e.g. Spain). In both situations, RCs have received—and can therefore lose—formal designation as such. External control of the centres can only be exercised if the RCs are recognized as legitimate actors in the health systems.
- b. Since rare cancer patients are rare, centralization of care should not be
 

The identification of RCs is associated with—but not contingent on—the idea that all patients can benefit from their care. The dispersion in the provision of sarcoma treatments in non-expert

**Table 3** RCs for rare cancers: legal status, designation and funding at national level

	Czechia	Finland	France	Italy	Lithuania	Spain
Legal status						
Specific			✓			✓
In transition				✓	✓	
Non-specific	✓	✓				
France: RCs were established in the network framework, within which they had to operate (French Cancer Plan, 2009–13). Under the coordination of the French Sarcoma Group (GSF-GETO), the NETSARC network was formed for soft tissue and visceral sarcomas ( <i>n</i> = 28), the ResOs network for bone sarcoma and rare bone tumours and the RRePS network for pathological review.						
Italy: The National Network of Rare Tumours (RNRT) was endorsed to identify and accredit RCs, behaving as hubs, along with other centres acting as spokes, but the network is not active yet (State-Regions Agreement, 2017).						
Lithuania: The legal denomination of ‘competent centres’ was changed to ‘national reference centres’ (National Plan on Rare Diseases, 2015), but this was challenged in court because it limited the constitutional right of patients to be treated in any healthcare centre.						
Spain: The establishment of a system of ‘Centres, Services and Units of Reference (CSUR)’ for specific diseases or procedures includes sarcoma (Royal-Decree, 1302/2006). Five sarcoma CSURs in adults were accredited.						
Designation process						
Full accreditation system						✓
Formal designation			✓	✓	✓	
Non-formal designation	✓	✓				
Czechia: The ‘reference centre’ label is associated with being a university hospital, having highly specialized services and a high patient volume.						
Finland: The Centralization Act (582/2017) restricted the delivery of treatments for rare diseases (including rare cancers) to the five university hospitals.						
France: The selection of RCs requires reaching consensus at the network level, a tacit process based on criteria like patient volume or scientific activity. The Institut National Du Cancer (INCA) certified the networks in 2014.						
Italy: Health authorities—through the AGENAS agency, in charge of the functional coordination of the RNRT—are in charge of designating and accrediting RCs. A system of expert centres, however, is not fully established yet.						
Lithuania: The official title of ‘reference centre’ was implemented in explicit alignment with the eligibility criteria for ERN candidate centres in order to avoid the existence of a dual accreditation system. Following the suspension mentioned above, the criteria used were those of the National Plan on Rare Diseases (2015).						
Spain: A fully formal designation process exists. The Ministry of Health selects candidates using an accreditation system (renewed every 5 years) based on the fulfilment of care standards and external auditing, including an on-site visit.						
Funding						
Specific funding			✓			
Non-specific funding	✓	✓		✓	✓	✓
France: Health authorities allocate specific funding that is administered by RCs included in the different networks.						



**Figure 1** System of national RCs for rare cancers: strategic analysis of countries

centres, not to mention the accidental interventions that typically occur in superficial soft tissue sarcomas, is considered excessive in almost all the countries included in the study. Lack of diagnosis and centralization of treatment procedures in RCs compromise the quality of care that patients receive.

- c. Do not say networking when you mean centralization  
The debate on what should be centralized—patients (through referrals) or decisions (patients receive care in non-expert centres according to a treatment plan proposed by the RC)—is common in all countries; even the French network organization has not managed to avoid this dilemma. All informants agreed that centralization of care is preferable when treatment performance is challenging, not just the treatment decision. One informant stressed, ‘[T]he idea is not to collaborate just for the sake of collaboration’, while another commented, ‘It’s good to coordinate with other centres in the management of an acute complication,

but the latter might have been less likely to happen in the first place in an expert centre’.

- d. A centralized referral system facilitating patients’ transition to RCs is needed to avoid differences in access between patients  
Patients’ prognosis and access to a wide range of treatments depends on their early referral to a RC (or virtual consultation), but sometimes specific referral criteria and systems are absent, even for reviewing pathological samples, so not all patients have the same opportunities for diagnosis and treatment, nor do they benefit from access to clinical trials or information on the disease in general, including from local and international patient associations.
- e. The designation of RCs should encompass the subpathological level  
The condition of ‘expert’ or ‘reference’ centre implies a leading role for highly specialized MDTs. However, since professional

specialization often extends to the level of disease subgroups, the identification of experts in soft tissue, bone or spinal sarcomas can lead to highly specialized MDTs (e.g. a bone sarcoma tumour board). Nevertheless, health systems do not identify the RCs as 'experts' at such a specific level, a fact that several informants criticized. Expert units are well-known by clinicians and patient organizations, and access to the most expert teams at the sarcoma subgroup level should be facilitated by default. Of course, not all rare cancers have distinct subgroups.

- f. Clinical guidance should be agreed by RCs and established at a health system level

Ideally, RCs within a single health system should work according to the same clinical practice guidelines or protocols. In France or Czechia (for bone sarcoma), RCs agreed on a common source of evidence, which enabled clinicians to talk in common language and be evaluated against the same clinical standards. In general, experts agree on the importance of having the same guidelines at national level although they did not have a clear preference about which specific guidelines should be used.

- g. Professionals should be formally entitled to participate in steering the rare cancer care system

Some academic groups for sarcoma assume critical roles in accrediting RCs or co-defining the organization of healthcare services and outcomes evaluation with health authorities. Formally engaging rare cancer experts can help align diagnostic and treatment planning with expert recommendations rather than with hospitals' bureaucratic processes. For instance, in the case of Ewing's sarcoma, there is a national tumour board implemented by the French Sarcoma Group that convenes once a month to discuss the most difficult cases.

## Discussion

The comparative analysis of the six countries showed that the status of RCs, the ties between them, and a political framework that favours the referral of cases to RCs are essential to allow all rare cancer patients to benefit from the highest standards of care. Legal status for RCs marks their place in the health system, which is critical considering the challenge of making professionals more sensitive to the specificities of these tumours.<sup>16</sup> The formalization of their status, the articulation of a designation process and even specific financing, based on designs as different as those used in France and Spain, are preconditions for the development of strategies that involve the entire health system. At the same time, considering the need to cooperate between expert teams, it is striking that only two of the six countries—France and Italy—have established formal collaboration mechanisms, and just four countries—France, Finland, Italy and Lithuania—have tried to put in place a centralized referral system from non-expert centres to RCs. This last aspect, related to the objective of achieving equitable access to high-quality care, entails the inherent need for establishing a specific policy framework that overcomes an approach to RCs based exclusively on their own activities.

In that line, we found two healthcare strategies—the 'centre-based' and 'network-based' models—to position and embed RCs within the health system. Although they are not solely the result of rational choices but also context-dependent aspects, these strategies provide an architecture for the two decisive factors that shape the role of RCs in health systems: first, a solid and consolidated academic group's professional networks, and second, health authorities that understand that rare cancers require a specific area of intervention. France is paradigmatic, since the interplay of these factors empowers expert professionals to dynamically coordinate and manage the service offer, while authorities control and support these decisions institutionally. In that country, experience has shown that around 30% of the histology diagnoses were modified after systematic central review.<sup>17</sup>

In fact, different studies have shown better survival in sarcoma patients managed by expert centres.<sup>18–21</sup> Thus, it is imperative that the countries following the centre-based model, where there are no collaboration mechanisms between expert and non-expert centres, facilitate patients' access to RCs. Lithuania, with 3 million inhabitants and two RCs, implemented a system to capture the patients who need their services. This decision addresses the fact that the diagnostic process is often chaotic, with fragmented care continuity and jumps between care levels and hospitals.

Clearly, the creation of ERNs provides a window of opportunity to improve rare cancer care in Europe, as is the definition of a European agenda of priorities for 2030<sup>22</sup> or the development of a list made up of 12 families of rare cancers.<sup>2</sup> The prospect of assessing this situation is clearly linked to implementation of Europe's Beating Cancer Plan and to the establishment of the European Health Data Space in terms of interoperability between health information systems and cancer registries. However, our study shows that the conditions governing patient access to treatment centres—whether RCs or not—are decided at the national level. The European and national levels should be progressively aligned so that RCs participating in the ERNs fulfil a significant role also at the national level. The room for improvement in the national organization shown in this study is evident. A review of European cancer plans shows marked differences between countries in terms of priorities and planning criteria in the area of rare cancers.<sup>23</sup> Future research avenues on potential differences in health outcomes between patients treated at RCs and non-RCs might be explored.

This study's strengths are based on the breadth and multidisciplinary representation of the sample, which included healthcare professionals, patients and planners. Selection bias was avoided through use of a gatekeeper external to RCs and clear sampling criteria. To avoid social desirability bias, where participants misrepresent their improvement efforts to provide desirable answers,<sup>24</sup> we instructed respondents to share both positive and negative experiences. Regarding limitations, we mainly focussed on sarcoma, precluding the description of all experiences that might exist in rare cancer care organization and limiting the potential generalizability of our findings and recommendations. Another limitation was that healthcare professionals from non-expert centres were not interviewed. One country did not provide the number of informants required (table 1). Finally, the interview data are from mid-2018, although according to co-authors, no relevant changes have occurred since then.

In brief, the comparative analysis of the six cases shows that the status of the centres, the ties between them, and a political framework that favours the referral of cases to RCs are essential to their effective operation. The case of sarcoma highlights the importance of looking beyond a single centre's results, from a perspective underpinned by the recognition that rare cancers require expert, coordinated care. Regardless of the healthcare context and the chosen model of care, ensuring the centralization of patients in externally evaluated RCs, the implementation of a centralized referral pathway and full cooperation and networking between RC experts at a sub-pathological level are key factors for avoiding the persistent inequities in access to care. These factors separate at one end of the spectrum the patients with access to an RC that is actively involved in the ERN from others who are treated in regional hospitals with an uncertain level of expertise.

## Supplementary data

Supplementary data are available at *EURPUB* online.

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## Disclaimer

The European Commission is not responsible for the content of this report. The sole responsibility for the report lies with the authors, and the Consumers, Health, Agriculture and Food Executive Agency is not responsible for any use that may be made of the information contained herein.

*Conflicts of interest:* None declared.

## Data availability

The data underlying this article cannot be shared publicly due to confidentiality reasons (i.e. content generated in the framework of one-on-one interviews).

### Key points

- Legal status, process of designation and funding are differential aspects affecting the positioning of reference centres for rare cancers within health systems.
- Only in France and Italy is the concept of expert centre associated with a system of expert centres working together.
- Finland, France, Italy and Lithuania had a referral system to facilitate patients' access from non-expert centres to reference centres.
- Two models of reference centres' integration in national health systems, namely, the centre-based and the network-based, were found.
- From the health policy standpoint, it is of vital importance to integrate Reference Centres at the health system level in order to improve rare cancer patients' access to high-quality care.

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