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# EUROPEAN REFERENCE NETWORKS: TOWARDS EQUITY IN RARE DISEASES

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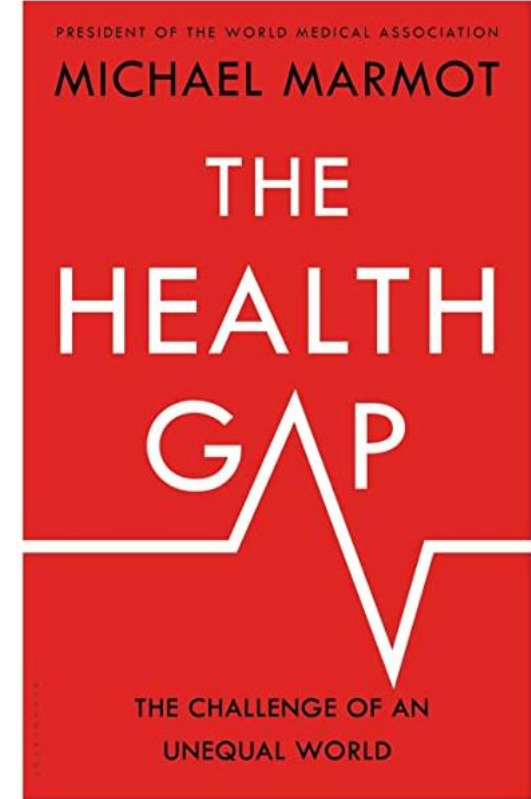


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**Health inequities** are **avoidable** and **unjust** differences in exposure and vulnerability to health risk factors, health-care outcomes and the social and economic consequences of these outcomes.

**Equity in health** means that everyone should have a fair chance to achieve their full health potential and that nobody should be disadvantaged in reaching it.

**The determinants of health** are factors which influence health status and determine health differentials or health inequalities. They are many and varied and include **biological/ genetic, environmental, behavioural, socioeconomic, environmental, healthcare, and political determinants.**



# Rare cancers are not so rare: The rare cancer burden in Europe

Gemma Gatta <sup>a,\*</sup>, Jan Maarten van der Zwan <sup>b</sup>, Paolo G. Casali <sup>c</sup>, Sabine Siesling <sup>b</sup>, Angelo Paolo Dei Tos <sup>d</sup>, Ian Kunkler <sup>e</sup>, Renée Otter <sup>b</sup>, Lisa Licitra <sup>f</sup>, Sandra Mallone <sup>g</sup>, Andrea Tavilla <sup>g</sup>, Annalisa Trama <sup>a</sup>, Riccardo Capocaccia <sup>g</sup>, The RARECARE working group

DEFINITION: cancers with an incidence of **less than 6 per 100 000** persons per year.

- > 500 000 new cases / year in the EU, ~**24%** of all cases.

- Considerably **worse outcomes**:

5-year survival: rare cancers - 47%, common cancers - 65% [Ray-Coquard I et al, 2017].

1999-2007, improvement of survival: rare cancers – by 3%, common cancers – by 5.5% [RareCareNet].

**Main factors:**

- ✓ Biological disease factors,
- ✓ limited availability of timely and accurate **diagnosis**,
- ✓ lack of effective, innovative **therapies** and drugs,
- ✓ Lack of **clinical practice guidelines** [Gatta G et al, 2017].

## **“POST CODE LOTTERY” IN RARE CANCERS: GEOGRAFIC INEQUITIES**

G. Gatta, A. Trama, R. Capocaccia, RARECARENet Working Group (2019). Epidemiology of rare cancers and inequalities in oncologic outcomes:

**5-year survival, 41 rare cancers:**

- IT, DE, BE: **55%;**
- BG, LT, SK: **40%.**

Laura Botta, Gemma Gatta, Annalisa Trama, ... RARECAREnet working group (2020). Incidence and survival of rare cancers in the US and Europe:

**5-year survival, 196 rare cancers:**

- US: **54%;**
- Europa: **48%.**

**Fewer diagnoses – worse outcomes.**

# Geographic inequities in orphan drug access: EU13 vs. EU15



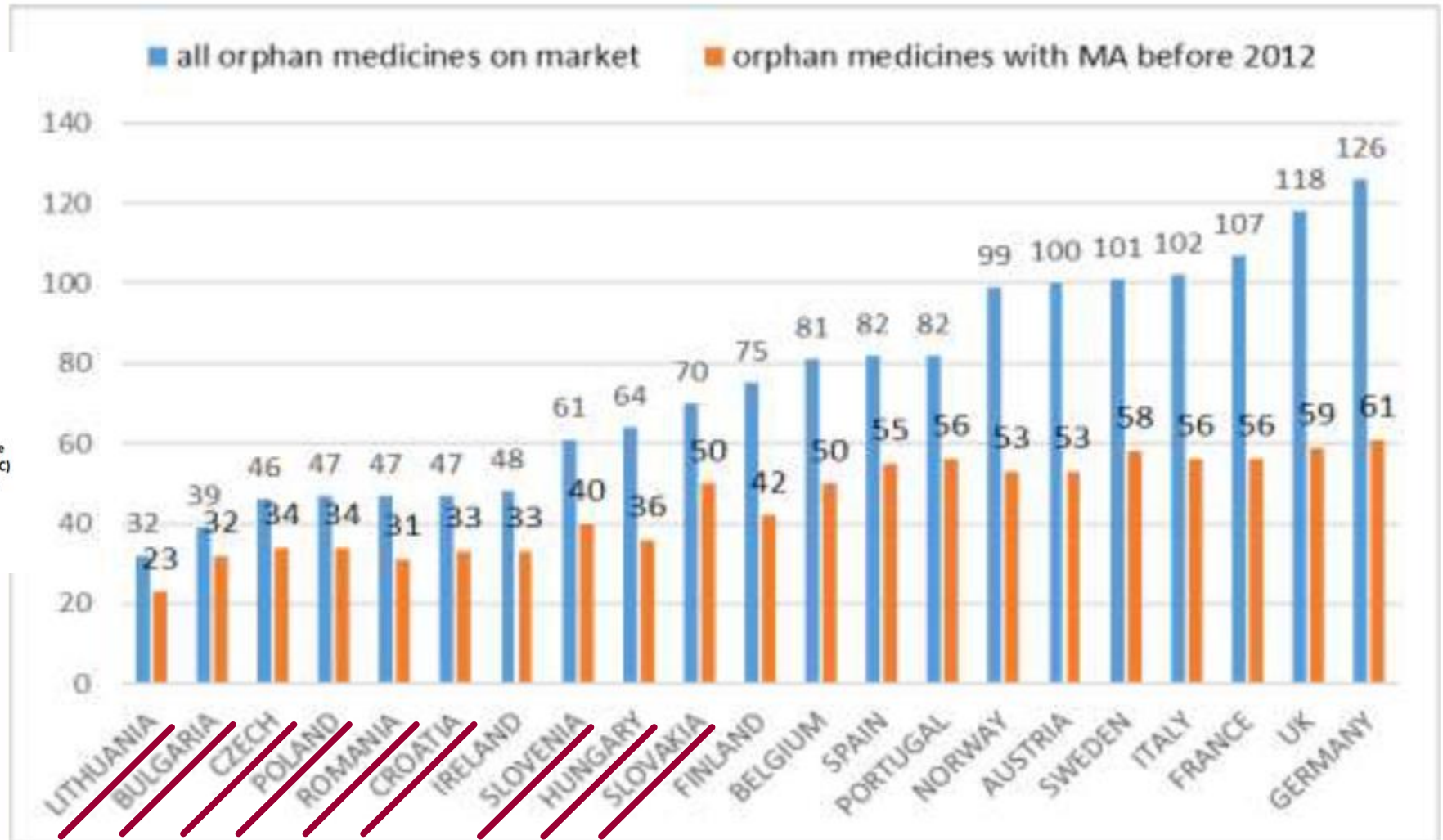
Brussels, 11.8.2020  
SWD(2020) 163 final  
PART 1/6

COMMISSION STAFF WORKING DOCUMENT  
EVALUATION

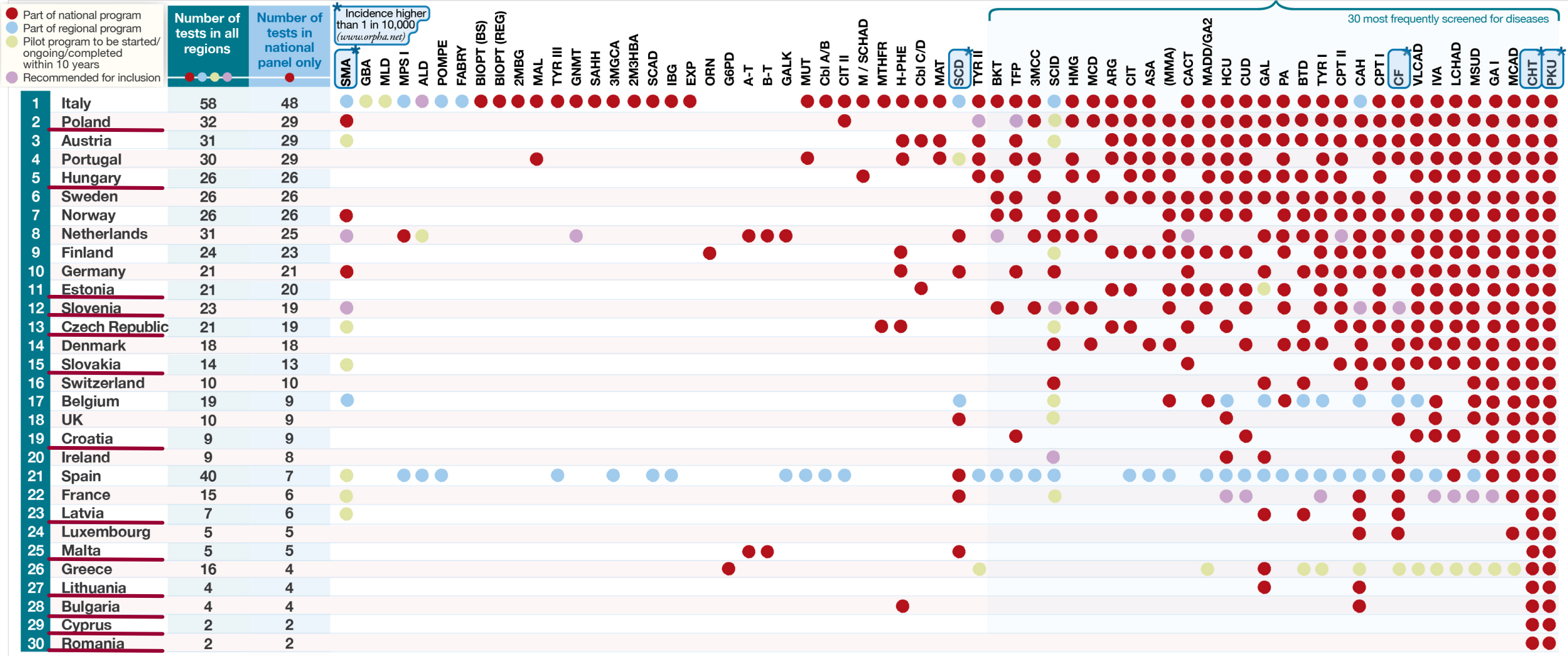
Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

{SEC(2020) 291 final} - {SWD(2020) 164 final}

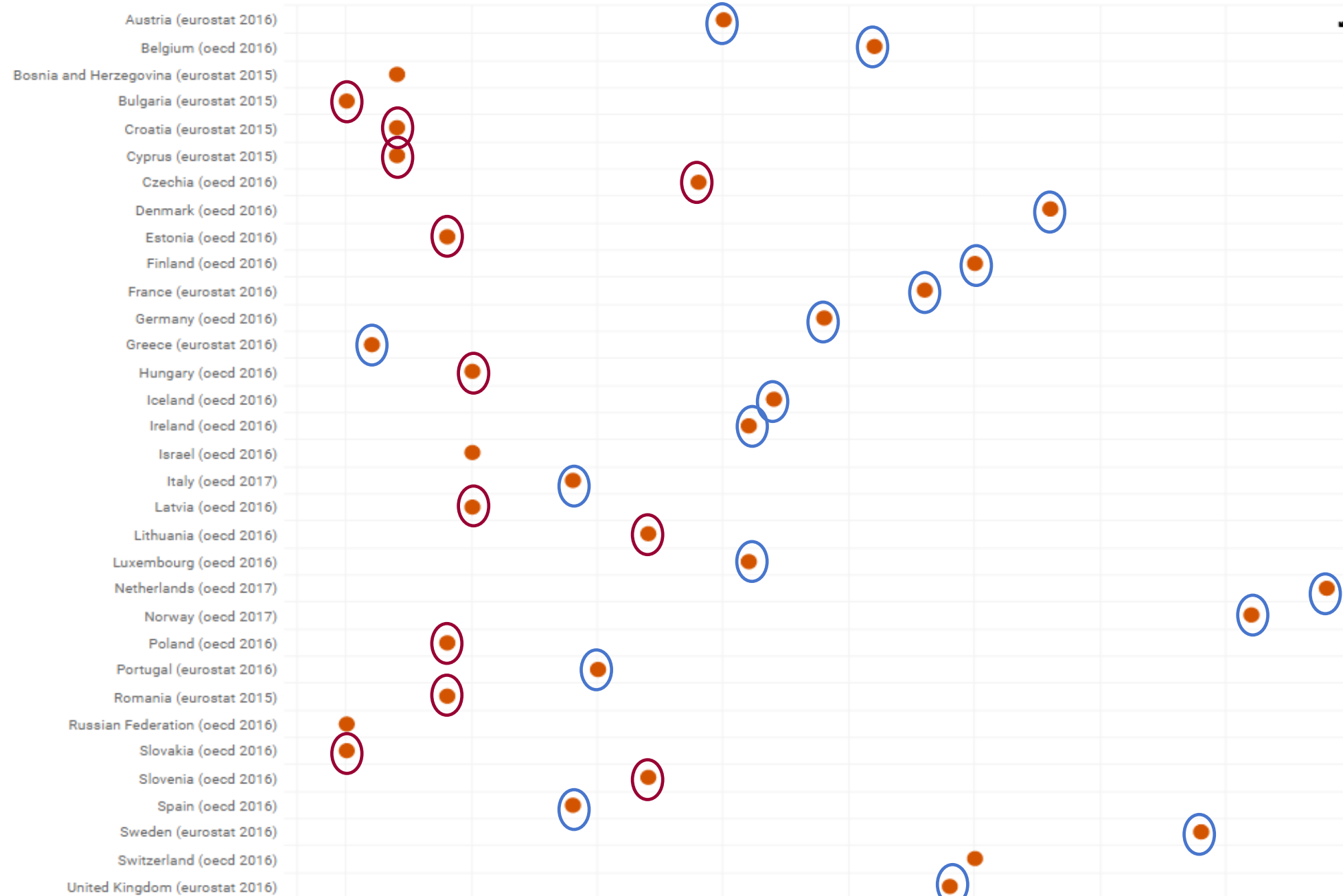
**Figure 7:<sup>131</sup> Number of orphan medicines for which sales were observed in 2016 (IQVIA) by Member State**



# Geographic inequities in neonatal screening: EU13 vs. EU15

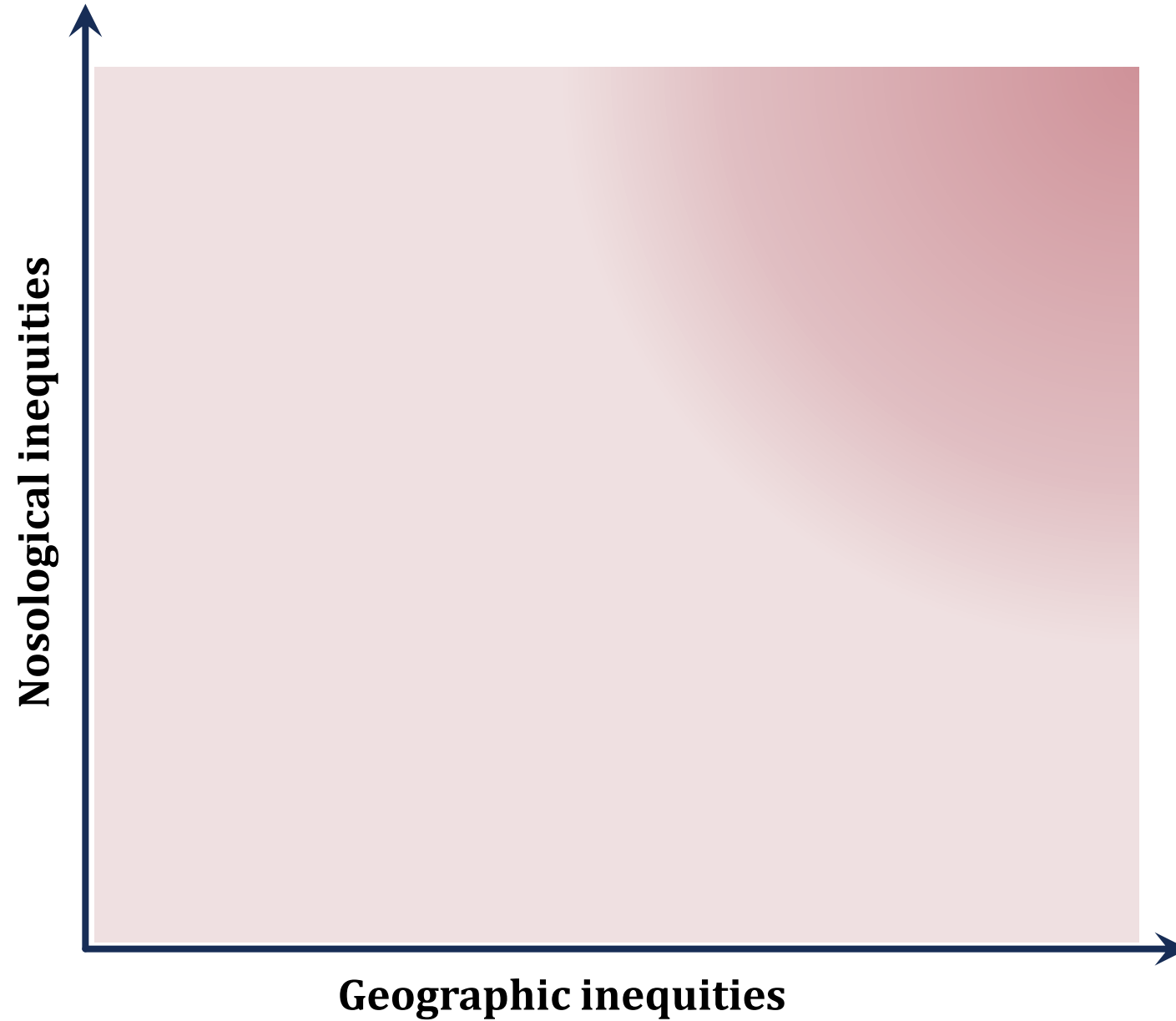


# Total expenditure on long-term care as a percentage of GDP: EU13 vs. EU15



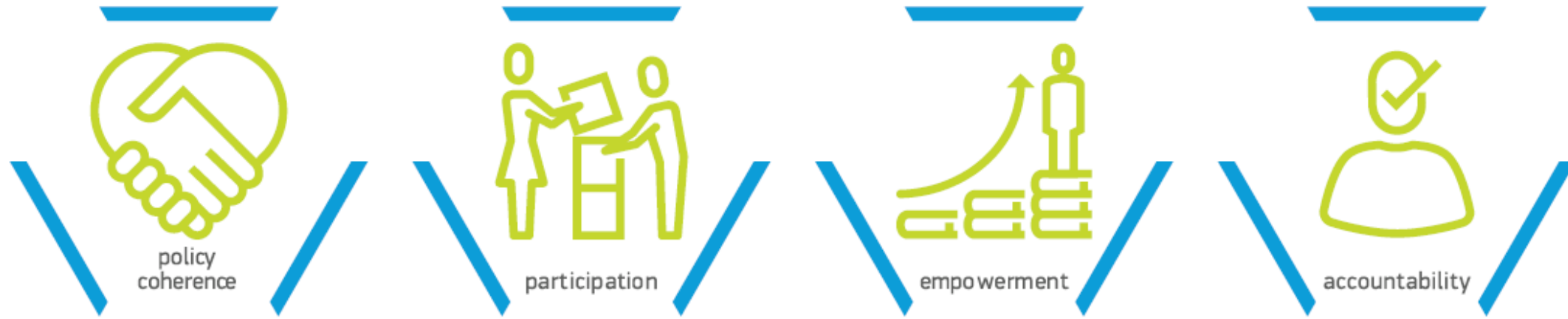
WHO HESRi Health Equity Data  
[https://worldhealthorg.shinyapps.uropean\\_health\\_equity\\_dataset/](https://worldhealthorg.shinyapps.uropean_health_equity_dataset/)

# Health inequities in rare diseases: **double blow for some countries**





## Four drivers of health equity: WHO framework



Each of these social and institutional factors drive health equity on their own, but are **dynamic and interact** with each other.

Determinants of health in rare diseases: **biological/ genetic**, environmental, behavioural, socioeconomic, environmental, **healthcare, political determinants**.



# DIRECTIVE 2011/24/EU on the application of patients' rights in cross-border healthcare

## *Article 12*

### *European reference networks*

1. The Commission shall support Member States in the development of European reference networks between healthcare providers and centres of expertise in the Member States, in particular in the area of rare diseases. The networks shall be based on **voluntary** participation by its members, which shall participate and contribute to the networks' activities **in accordance with the legislation of the Member State** where the members are established and shall at all times be open to new healthcare providers which might wish to join them, provided that such healthcare providers fulfil all the required conditions and criteria referred to in paragraph 4.
6. Measures adopted pursuant to this Article **shall not harmonise any laws or regulations** of the Member States and shall **fully respect the responsibilities of the Member States** for the organisation and delivery of health services and medical care.



European  
Reference  
Networks

**24** European Reference Networks

**>1600** Centers of Expertise across the EU

**1 – 1.5 mln.** RD patients/ year

**INNOVATION triangle:**

**Highly-specialized  
healthcare**

**Research, clinical trials**

**Education, training,  
capacity building**

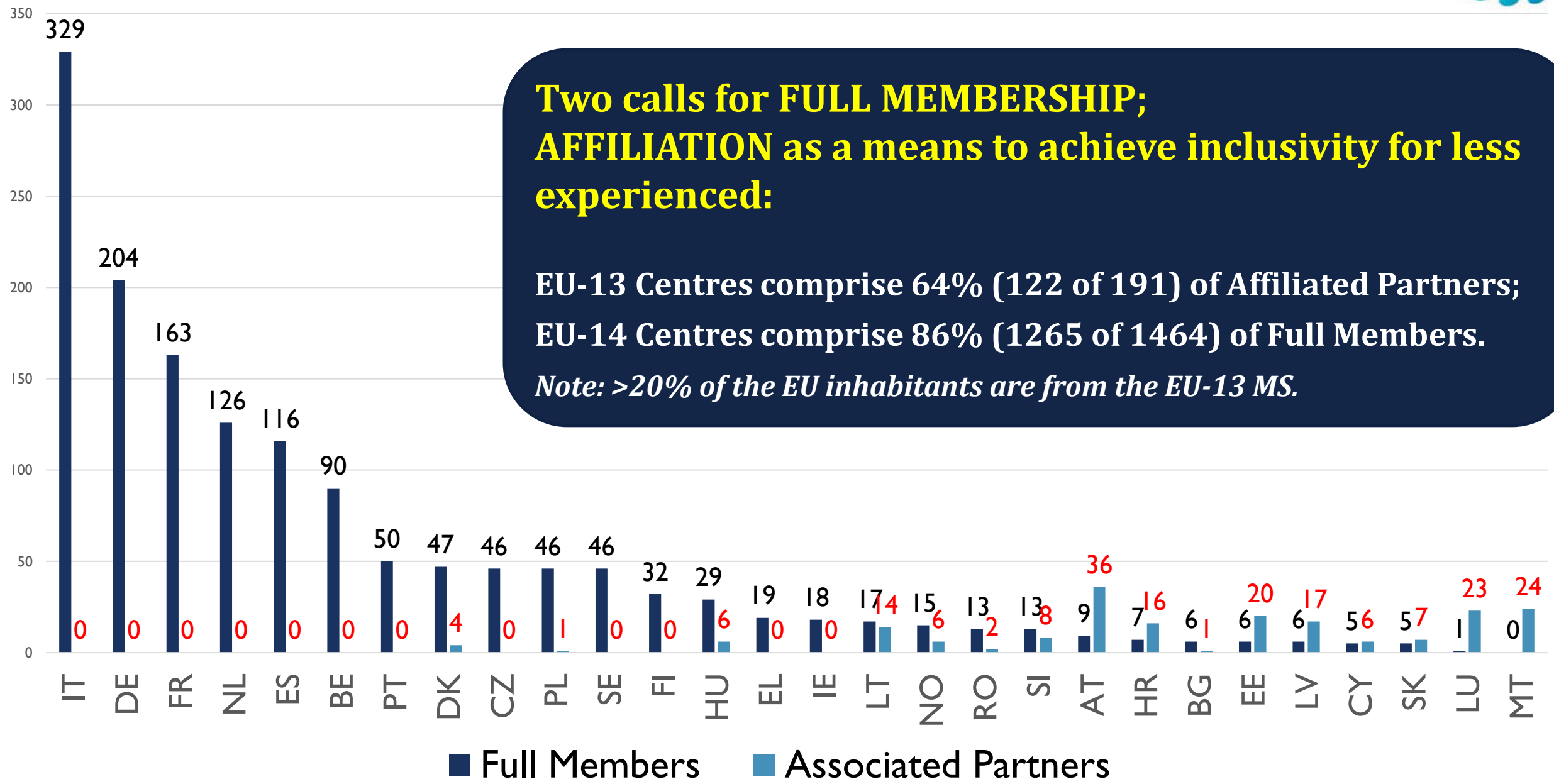
**Home to EVERY RD  
Accessibility  
Quality assurance**

**TACKLING INEQUITIES**

**ECONOMIES OF SPEED,  
SCALE AND SCOPE for MS**

Rare disease area	ERN
Pediatric cancer	PeadCan ERN
Rare haematological diseases	EuroBloodNet
Inherited metabolic diseases	MetabERN
Congenital malformations and rare intellectual disabilities	ITHACA
Rare neurological diseases	ERN-RND
Rare kidney diseases	ERKNet
Rare urogenital diseases	eUROGEN
Transplantation in children	TRANPLANTCHILD
Rare endocrine diseases	ENDO-ERN
Rare eye diseases	ERN-EYE
Rare skin diseases	ERN Skin
Rare adult cancers	EURACAN
Rare liver diseases	RARE-LIVER
Rare neuromuscular diseases	EURO-NMD
Rare multisystemic vascular diseases	VASCERN
Genetic tumour risk syndromes	GENTURIS
Craniofacial anomalies and ear, nose and throat diseases	ERN CRANIO
Congenital anomalies	ERNICA
Rare heart diseases	GUARD-HEART
Rare immunodeficiencies, autoinflammatory and autoimmune diseases	ERN RITA
Rare respiratory diseases	ERN LUNG
Rare epilepsies	EpiCARE
Rare bone diseases	ERN BOND
Rare connective tissue and musculoskeletal diseases	ReCONNET

# GEOGRAPHIC INCLUSIVITY of ERNs: All ERN Centres (> 1600)



# GEOGRAPHICAL INCLUSIVITY of ERNs: Full Members/ million of inhabitants



**LT and SI:**  
**Success story? Regional leadership?**

## Hospitals with the largest number of ERN Full Members (> 10 Full Members)

NL: Erasmus MC: University Medical Center Rotterdam – 24;  
 FI: Helsinki University Hospital – 21;  
 IT: AO di Padova – 21;  
 DK: Rigshospitalet - 20;  
 IT: IRCCS Ospedale Pediatrico Bambino Gesù, Roma – 20;  
 BE: UZ Gent – 20;  
 SE: Karolinska University Hospital – 20;  
 BE: UZ Leuven – 19;  
 ES: Hospital de Sant Joan de Déu – 19;  
 DK: Aarhus University Hospital – 18;  
 ES: Hospital Universitari Vall d' Hebron – 18;  
 NL: Radboud University Medical Center Nijmegen – 18;  
 NL: University Medical Center Utrecht – 18;  
 IT: Fondazione Policlinico Universitario A. Gemelli – Roma – 16;  
 BE: Cliniques universitaires Saint-Luc – 15;  
**CZ: University Hospital Motol – 15;**  
 DE: Charité Universitätsmedizin Berlin – 15;  
 FR: APHP, Hôpital Necker Enfants Malades – 15;  
 IT: Fondazione IRCCS CA'Granda Ospedale Maggiore Policlinico – 15;

NL: Academic Medical Centre of Amsterdam – 15;  
 NL: University Medical Centre Groningen – 15;  
 NL: Leiden University Medical Center – 14;  
 SE: Sahlgrenska University Hospital – 14;  
 BE: Antwerp University Hospital – 13;  
 DE: Universitätsklinikum Hamburg-Eppendorf – 13;  
 NO: Oslo University Hospital - 13;  
**LT: Vilnius University Hospital Santaros Klinikos - 12;**  
 DE: Universitätsklinikum Freiburg – 11;  
 FI: Hospital District of Helsinki and Uusimaa – 11;  
 IT: AOU Senese – 11;  
 IT: IRCCS Istituto Giannina Gaslini, Genova – 11;  
**SI: University Medical Center Ljubljana - 11;**  
 ES: Hospital Clinic de Barcelona – 10;  
 ES: Hospital Universitario La Paz – 10;  
 IT: AOU Federico II di Napoli – 10;  
 IT: AOU Meyer di Firenze – 10;  
 PT: Centro Hospitalar Universitario do Porto – 10.

## Hospitals with the largest number of ERN Full Members and Affiliated Partners (> 10 FM and AP)\*

LU: Centre Hospitalier du Luxembourg – 24 (1);  
**MT: Mater Dei Hospital – 24 (0);**  
 DK: Rigshospitalet - 22 (20);  
**EE: Tartu University Hospital - 21 (5);**  
 DK: Aarhus University Hospital – 20 (18);  
**SI: University Medical Center Ljubljana - 19 (11);**  
**LT: Vilnius University Hospital Santaros Klinikos - 18 (12);**

**HU: Semmelweis University - 16 (10);**  
 NO: Oslo University Hospital - 16 (13);  
 AT: Medical University of Vienna/ Vienna General Hospital - 14 (2);  
**HR: University Hospital Center Zagreb - 14 (6);**  
**LV: Children`s Clinical University Hospital, Riga - 14 (5);**  
**LT: Hospital of Lithuanian University of Health Sciences Kauno Klinikos - 13 (5);**  
 AT: Medical University Innsbruck – 12 (2).

# GEOGRAPHICAL INCLUSIVITY of ERNs: All ERN Centres/ million of inhabitants



**We still have some "whitish" spots on the EU map**

# ERN Board of Member States: **MANDATES**

## COMMISSION IMPLEMENTING DECISION 2014/287/EU

### Article 6: Board of Member States

Member States are invited to set up a Board of Member States which **shall decide whether or not to approve the proposals for Networks, their membership and the termination of a Network.**

## COMMISSION IMPLEMENTING DECISION (EU) 2019/1269

(2) To increase the efficiency of the European Reference Networks, the Board of Member States should become the **forum for exchanging information and expertise** in order to steer the development of the ERNs, provide guidance to the Networks and to the Member States and advise the Commission on matters related to the establishment of the Networks.





# Integration of ERNs into national systems



## Areas for intervention (ERN BoMS Statement 2019)

- Legal framework
- Care pathways
- Referral to ERNs systems
- Support to ERNs from MS
- Awareness raising/ education

Centralization/collaboration

## National governance

National networks

Integrated care  
Patient-centredness

Tackling wasteful spending

Quality assurance

Data management

Support to national HCP

Patient pathways and CPMS

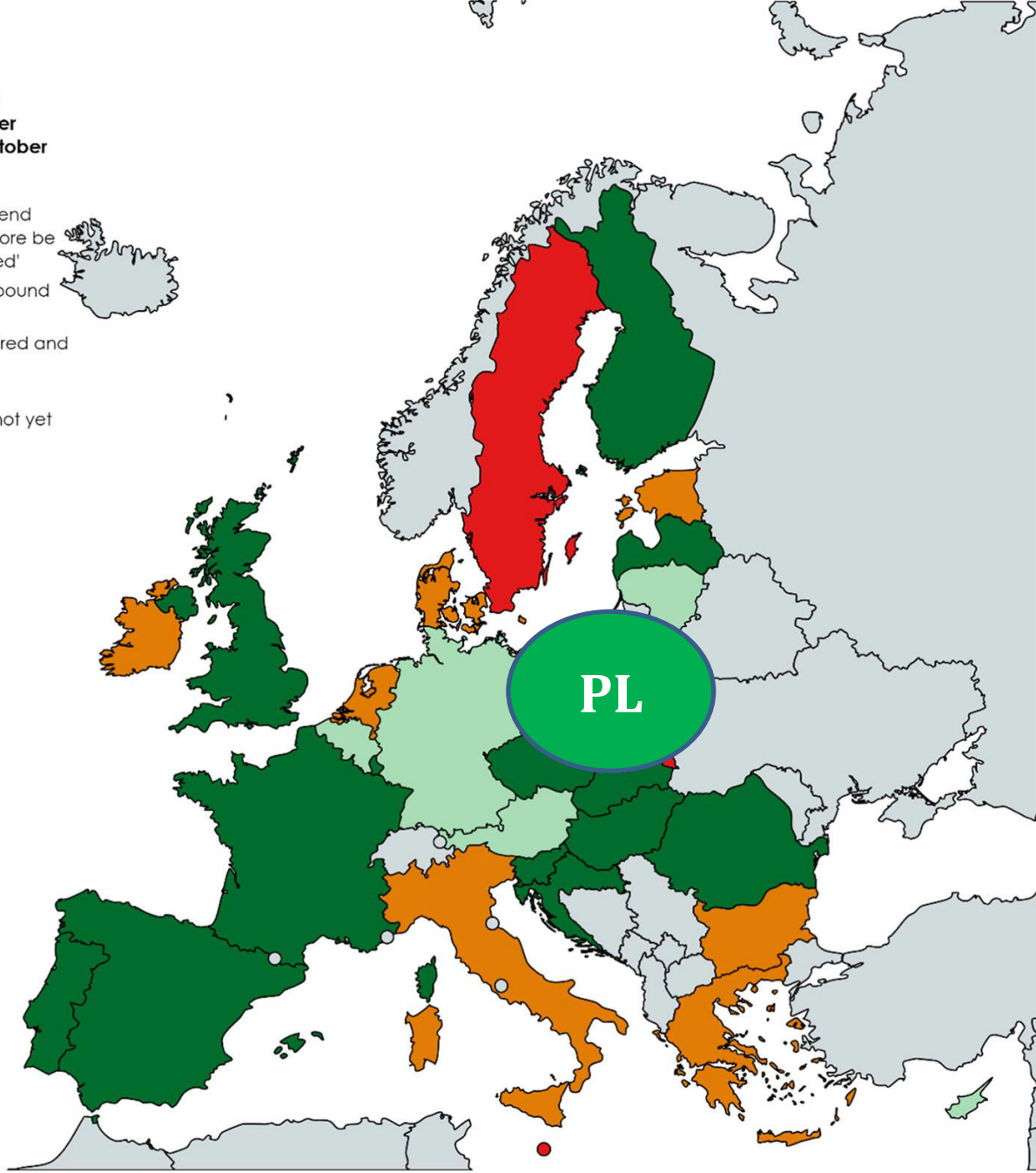
Undiagnosed disease programmes

**JOINT ACTION ON ERN INTEGRATION**

*What is the use of enormous amounts of expertise if they remain confined to the individual centres participating in the network? These centres must be able to reach all patients in their territories – and in other Member States, if no national reference centre has been established – in order to really make a difference to the care of these patients. Thus, ERNs are effective only in so far as they are inclusive, proactively reaching out to the populations they serve.* Expert Panel on Effective Ways of Investing in Health (EXPH): Opinion on Application of the ERN model in European cross-border healthcare cooperation outside the rare diseases area, 2018.

Status Quo of NP/NS in EU Member States and Former Member States AS OF October 2020

- NP/NS with no specific end date, which can therefore be considered 'open-ended'
- NP/NS which are time-bound and still 'in date'
- NP/NS which have expired and are not yet formally renewed/replaced
- Countries which have not yet adopted a NP/NS



**2022: 28/30 EU/EEA countries (26 EU + NO and CH) have NP/NS**

**Rare disease National plans/strategies:**

- Common goals, values and principles
- Coherent, integrated, sustainable solutions
- National collaboration
- Responsibility and commitment

**Many NP/NS – predecessors of ERNs!!**

**Huge differences in**

- NP/NS **quality**
- NP/NS **implementation**

# Accountability – the weakest point in ERNs and RD



Driving forward health equity – the role of accountability, policy coherence, social participation and empowerment. Copenhagen: WHO Regional Office for Europe; 2019.

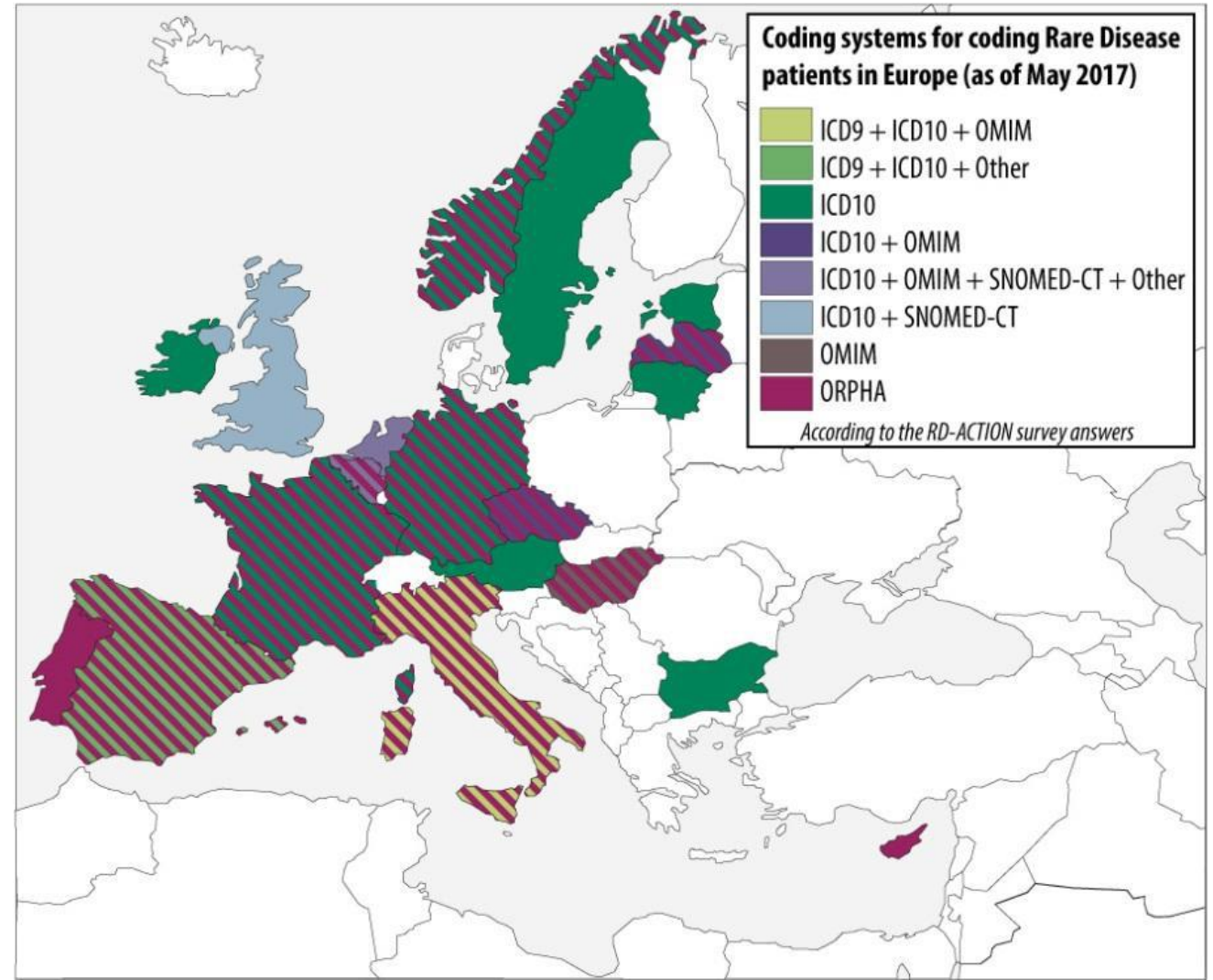
# RARE DISEASE CODIFICATION, TRACKING, MONITORING

- ICD10: **559** specific codes matching Orphanet rare disease entities (including groups of diseases)
- SNOMED CT: T0 mapping (08/2015): **38%** of ORPHA entities in SNOMED CT.
- ICD11: **3718**/ 6164 rare disorders (2015).
- ORPHA codes: nearly **7000**.

NO TRACKING =  
NO INDICATORS =  
NO MONITORING/  
BENCHMARKING =

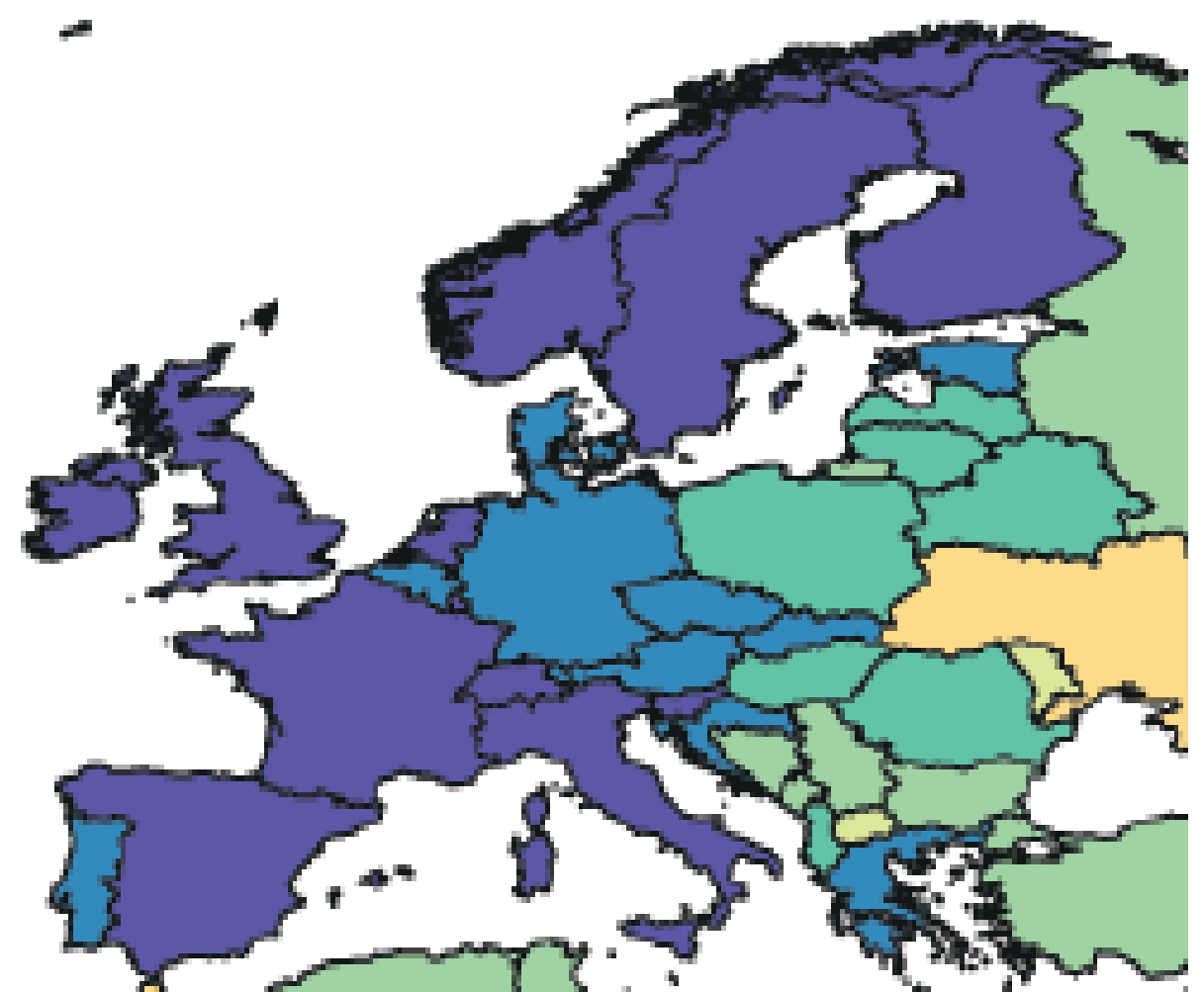
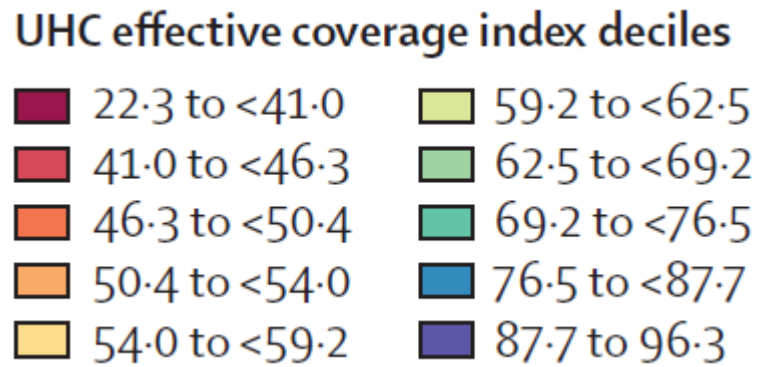
**NO VISIBILITY –  
NO PROBLEM!!!**

**No measures to compare  
inequities across and in the MS.**



# GLOBAL MEASUREMENTS OF HEALTH INEQUITIES: RARE DISEASES ARE LEFT BEHIND!

Map of the UHC effective coverage index, by decile, in 2019.



GBD 2019 Universal Health Coverage Collaborators\*. Measuring universal health coverage based on an index of effective coverage of health services in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019.



European  
Reference  
Networks

Working for patients with  
rare, low-prevalence and  
complex diseases

**Share. Care. Cure.**



**European, national and global  
collaboration in rare diseases**

*Thanks for your attention*