UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

The supply of plasma-derived medicinal products in the future of Europe

28-29 April 2022 - Rome, Italy

CENTRO NAZIONALE SANGUE

PLASMA ITALIA

in collaboration with FIODS

The demand for PDMPs: concepts, methodologies, measurements

Giampiero Mazzaglia MD, PhD
Università degli studi di Milano-Bicocca

OUTLINE

- Definition and public health role of Plasma-derived Medicinal Products (PDMPs)
  - ➢The clinical value of PDMPs
  - ➢Consumption and Supply of PDMPs
- Key principles and criteria for estimating demand
  - ➢Models, prevalence & treatment monitoring (data sources)

PDMPs: DEFINITION

"Medicinal products based on blood constituents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin."

Guideline on plasma-derived medicinal products . EMA/CHMP/BWP/706271/2010

"PDMPs are critical in the prevention and treatment of major morbidities associated with a wide range of inherited and acquired medical conditions and diseases. **Human plasma, used as a source material to produce PDMPs, is recognized as a public good and of national interest.**"

Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma. Geneva: World Health Organization; 2021.

PDMPs: WHO ESSENTIAL MEDICINES

For blood products of human origin and plasma substitutes the ***WHO recognizes that achieving self-sufficiency***, *unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation,* ***and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population***.

World Health Organization Model List of Essential Medicines – 22nd List, 2021. Geneva: World Health Organization; 2021.

THE CLINICAL VALUE OF PDMPs:
Clinical indications

Albumin
Cirrhosis, hypovolemic& septic shock, burns, jaundice, kidney diseases

Immunoglobulins
Prevention and treatment of infections, prevention of hemolytic diseases of newborns

Polyvalent immunoglobulins
Immunological deficiencies, neurological, hematological and dermatological (auto) immune diseases

Coagulation factors

Factors VII, VIII, IX, X
Hemophilia A and B, von Willebrand disease, hepatic diseases

Antithrombin III
Congenital or acquired deficiency

Prothrombin complex concentrate
Bleeding

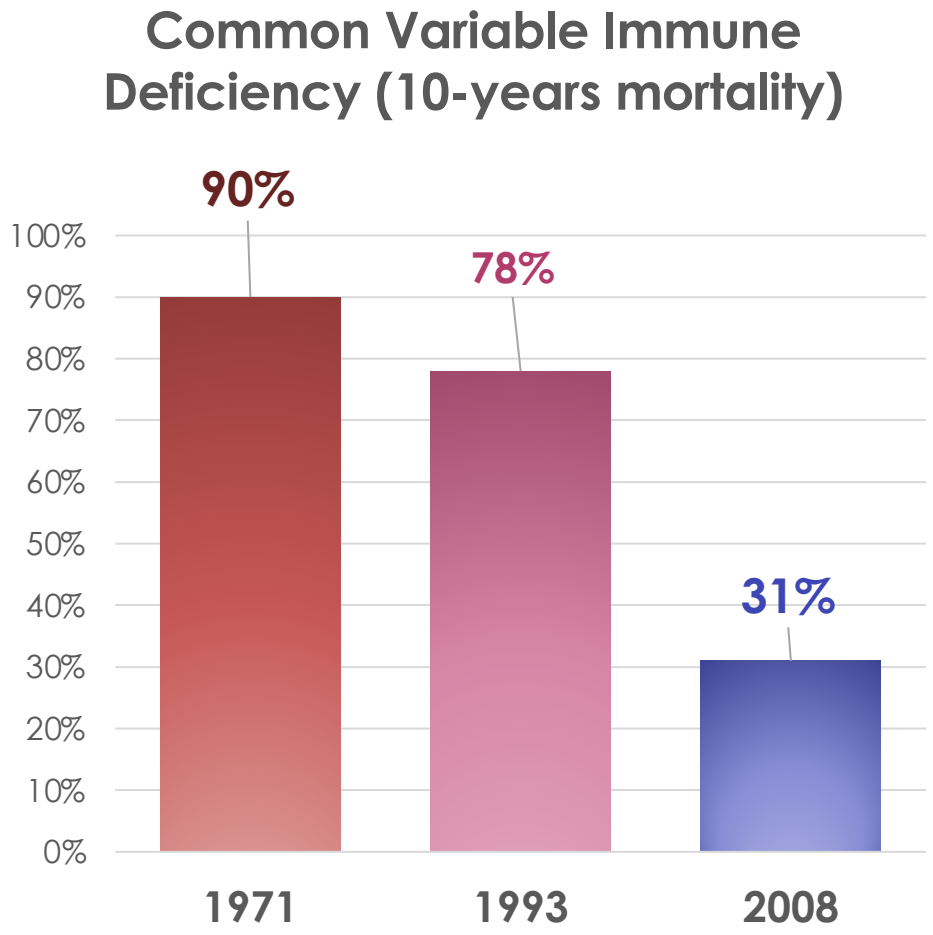
C1 esterase inhibitor
Hereditary angioedema

Alpha 1 protease inhibitor
Alpha 1 antitrypsin deficiency

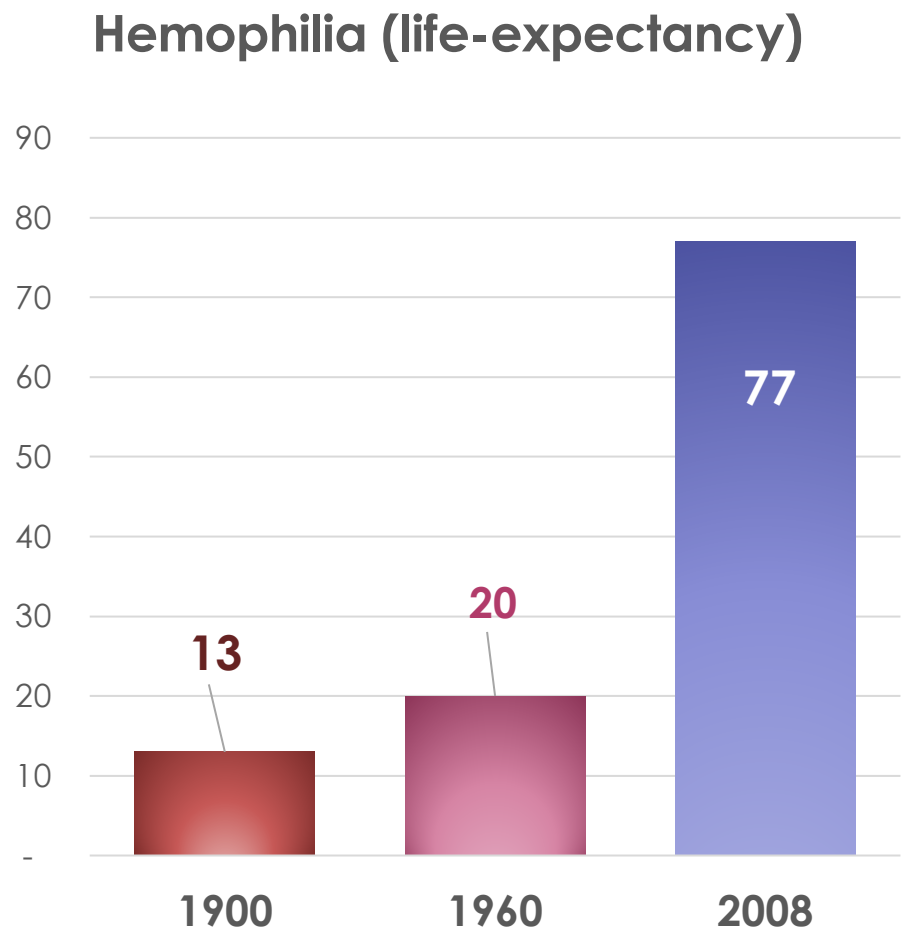
Fibrinogen
Congenital or acquired deficiency with risk of bleeding

Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma. Geneva: World Health Organization; 2021.

THE CLINICAL VALUE OF PDMPs:
Observed benefits

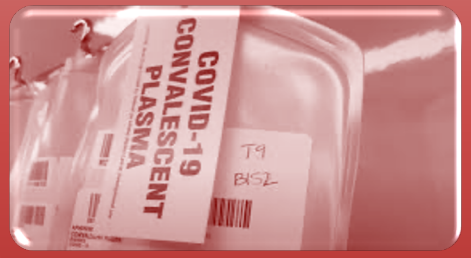


Blood. 2008; 112(2):277–286.



Haemophilia. 2016; 22(2) 676–683.

PLASMA COLLECTION & MANUFACTURING



Limited and complex resource: depending only on organized plasma collection. Collected in 100+ certified centers in the EU (2.5M L in 2019).

The **first litre** of plasma is fully utilised: all products are produced from the first litre.	As more plasma is fractionated, the product with the lowest demand is no longer produced.	As more plasma is fractionated, one-by-one, each plasma-derived therapy is no longer produced when demand is met.	Only one product remains, which is the one with the highest demand. When this demand is met, production stops and the **last litre** is used.
✓ Immunoglobulin	✓ Immunoglobulin	✓ Immunoglobulin	✓ Immunoglobulin
✓ Albumin	✓ Albumin	✓ Albumin	Albumin
✓ Factor VIII	✓ Factor VIII	Factor VIII	Factor VIII
✓ C1-inhibitor	C1-inhibitor	C1-inhibitor	C1-inhibitor

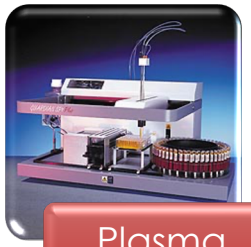
www.pptaglobal.org
Copenhagen Economics inspired by the Marketing Research Bureau (MRB)

LONG MANUFACTURING PROCESS

From donors to patients: 7 to 12 months

Plasma collection

Laboratory tests



Plasma pooling

Fractioning

Purification

Batch Release

Screening and testing of donors
Frozen storage

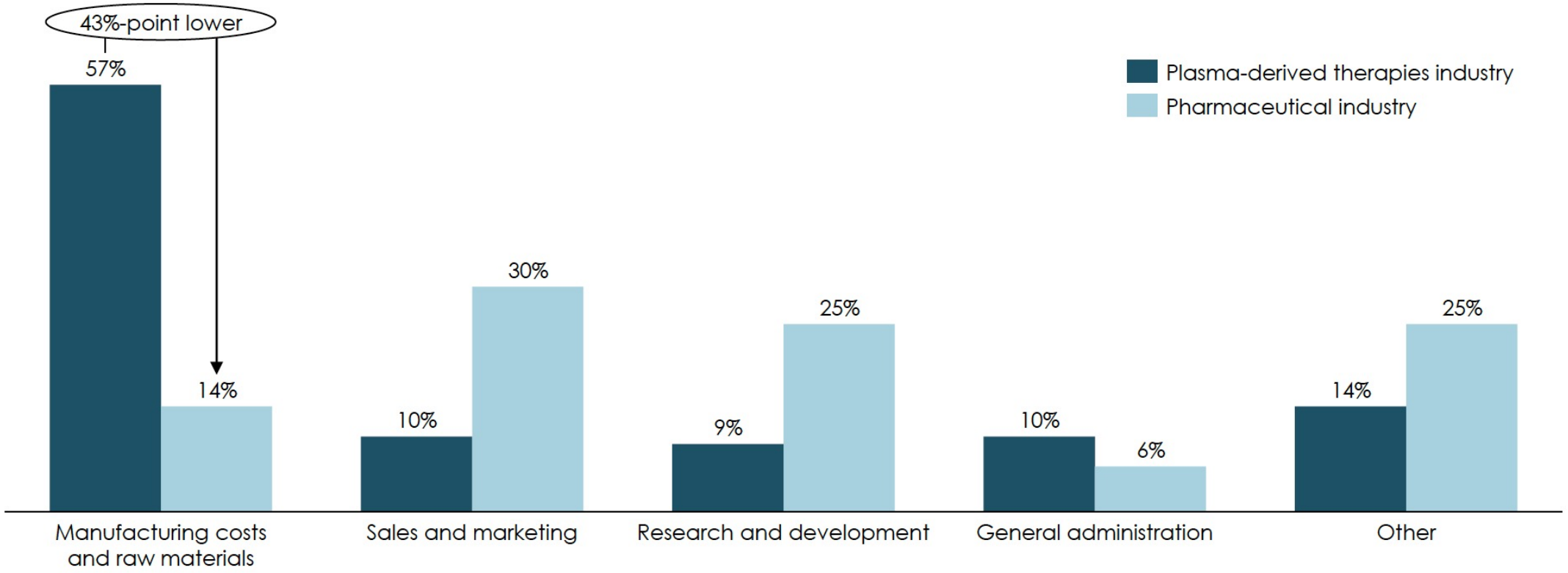
Manufacturing pool virus marker testing
Viral reduction treatment

Batch testing (quality, safety, efficacy)

EXPENSIVE MANUFACTURING PROCESS

Cost structure of producing plasma-derived therapies and traditional pharmaceutical products

Per cent of total costs



www.pptaglobal.org

Copenhagen Economics inspired by the Marketing Research Bureau (MRB)

THE CLINICAL VALUE OF PDMDs:
A growing number of clinical indications

1 million Europeans are affected by one of the 12 most common (groups of) rare diseases (*coagulation factors deficiencies, PID, HAE, CIPD, ITP, MMN, KD*) that can be treated with plasma-derived therapies

HOW IS PLASMA USED IN EVERYDAY MEDICINE?

In addition to helping those with rare, chronic diseases, plasma protein therapies are also used in everyday medicine, emergencies, and surgical medicine, as well as preventive medicine to treat the following:

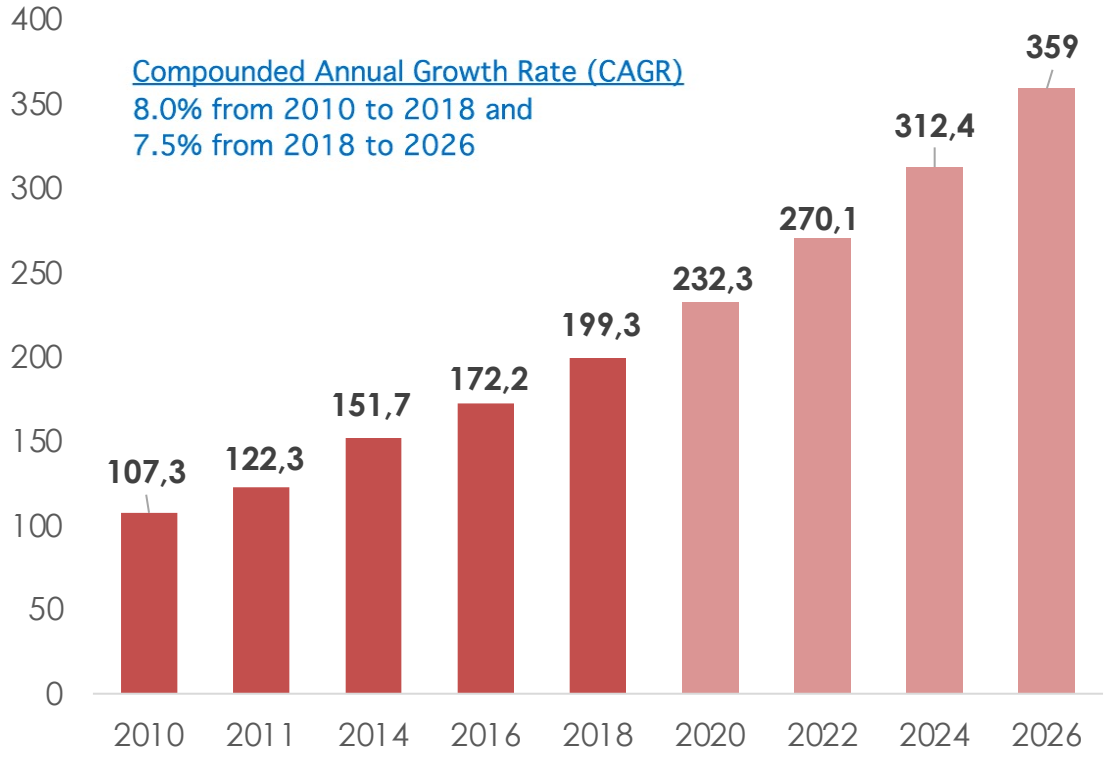
- ANIMAL BITES (ANTI-TETANUS IG)
- AUTO-IMMUNE DISEASES (IMMUNE GLOBULINS)
- BURNS (ALBUMIN)
- CARDIOPULMONARY ISSUES (ALBUMIN)
- HEPATITIS (ANTI-HBV IG)
- LIVER CONDITIONS (ALBUMIN)
- MAJOR SURGERY (ALBUMIN)
- ORGAN TRANSPLANTS (ANTI-CMV IG)
- PEDIATRIC HIV (IGIV)
- RH INCOMPATIBILITY (ANTI-RH IG)
- SHOCK (ALBUMIN)
- TRAUMA (ALBUMIN)

THE CLINICAL VALUE OF PDMPs:
An example of patients need for selected indications

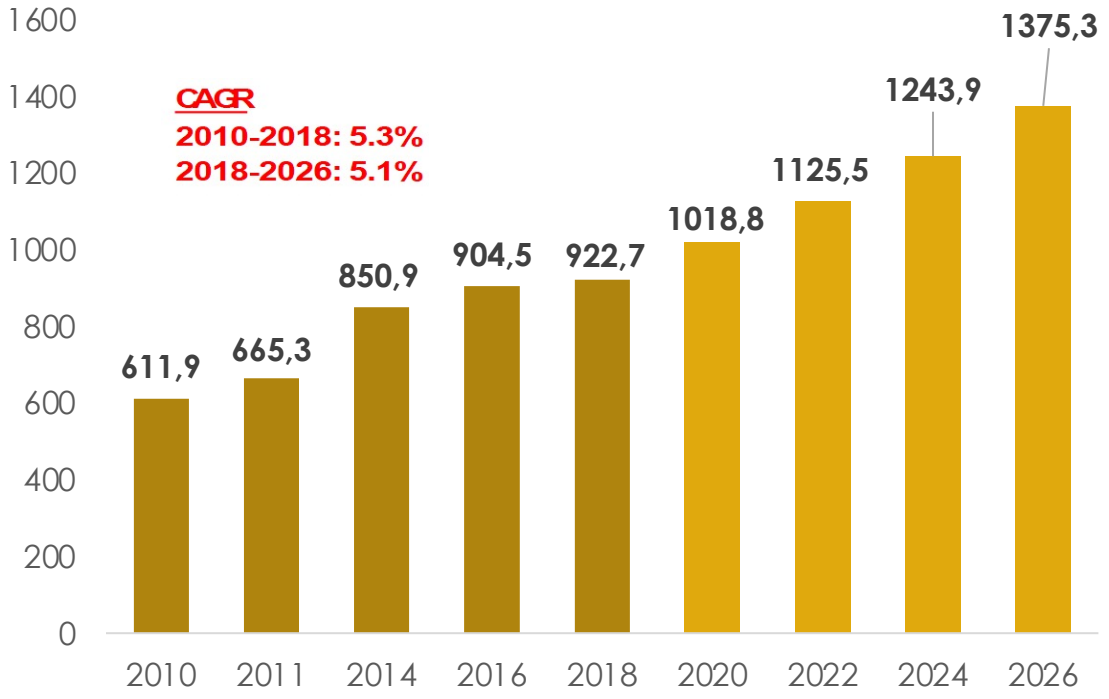
- Primary immunodeficiency diseases *(lack of therapeutic alternatives)*: 375,000
- Alpha-1 antitrypsin deficiency *(lack of therapeutic alternatives)*: *75,000*
- Chronic inflammatory demyelinating polyneuropathy *(poor therapeutic alternatives)*: 33,750
- Hemophilia *(available recombinant therapy)*: 150,000
- Hereditary angioedema *(available recombinant therapy)*: *15,000*

INCREASING PDMPs CONSUMPTION

Global IgG Demand (Metric tons)

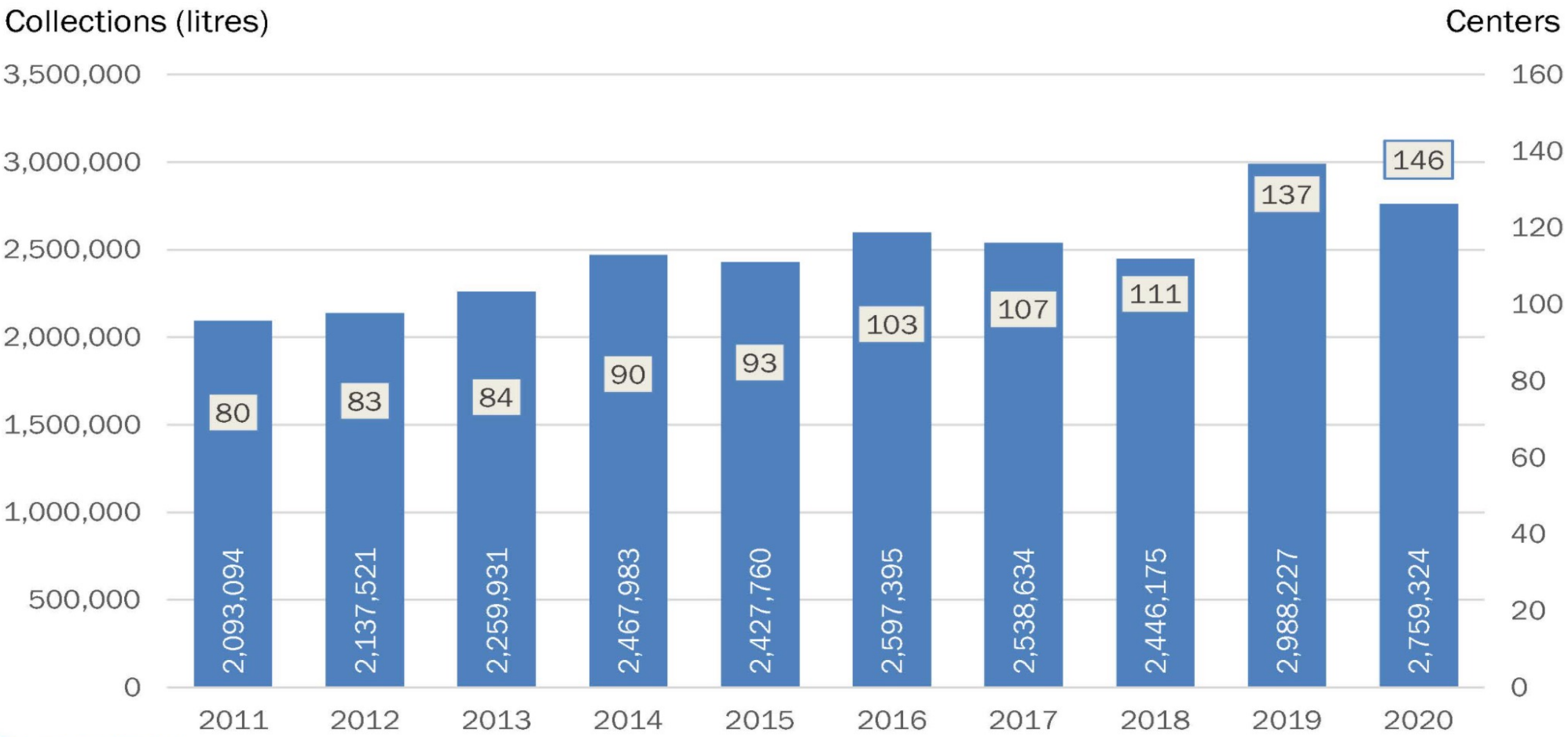


Global Albumin Consumption (Metric tons)

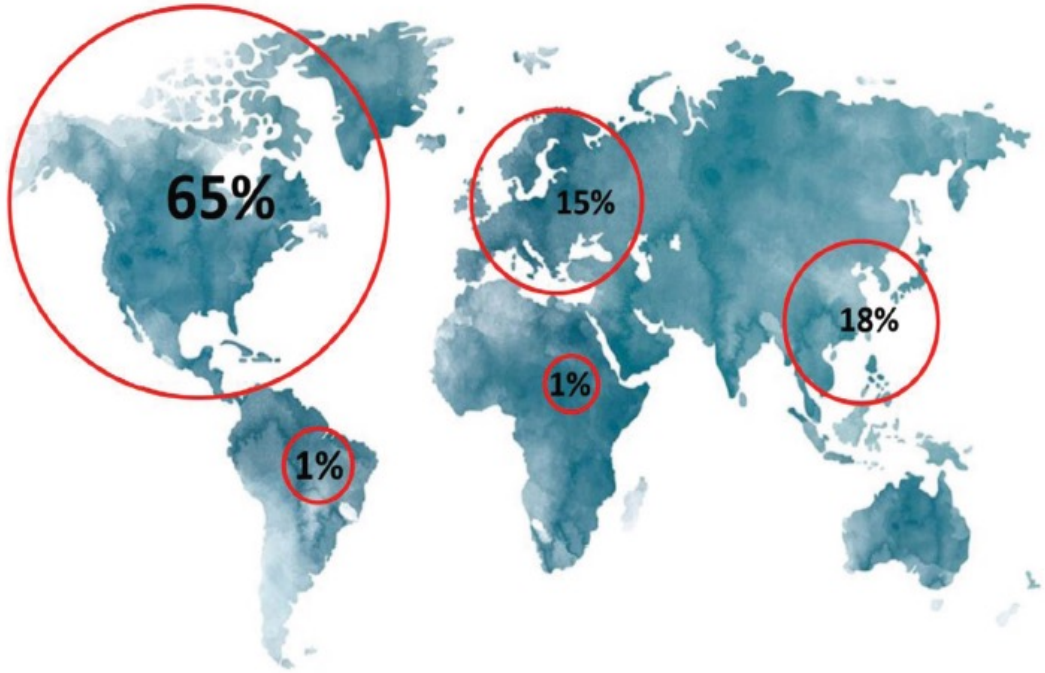


Source: Adapted from Marketing Research Bureau

INCREASING SUPPLY

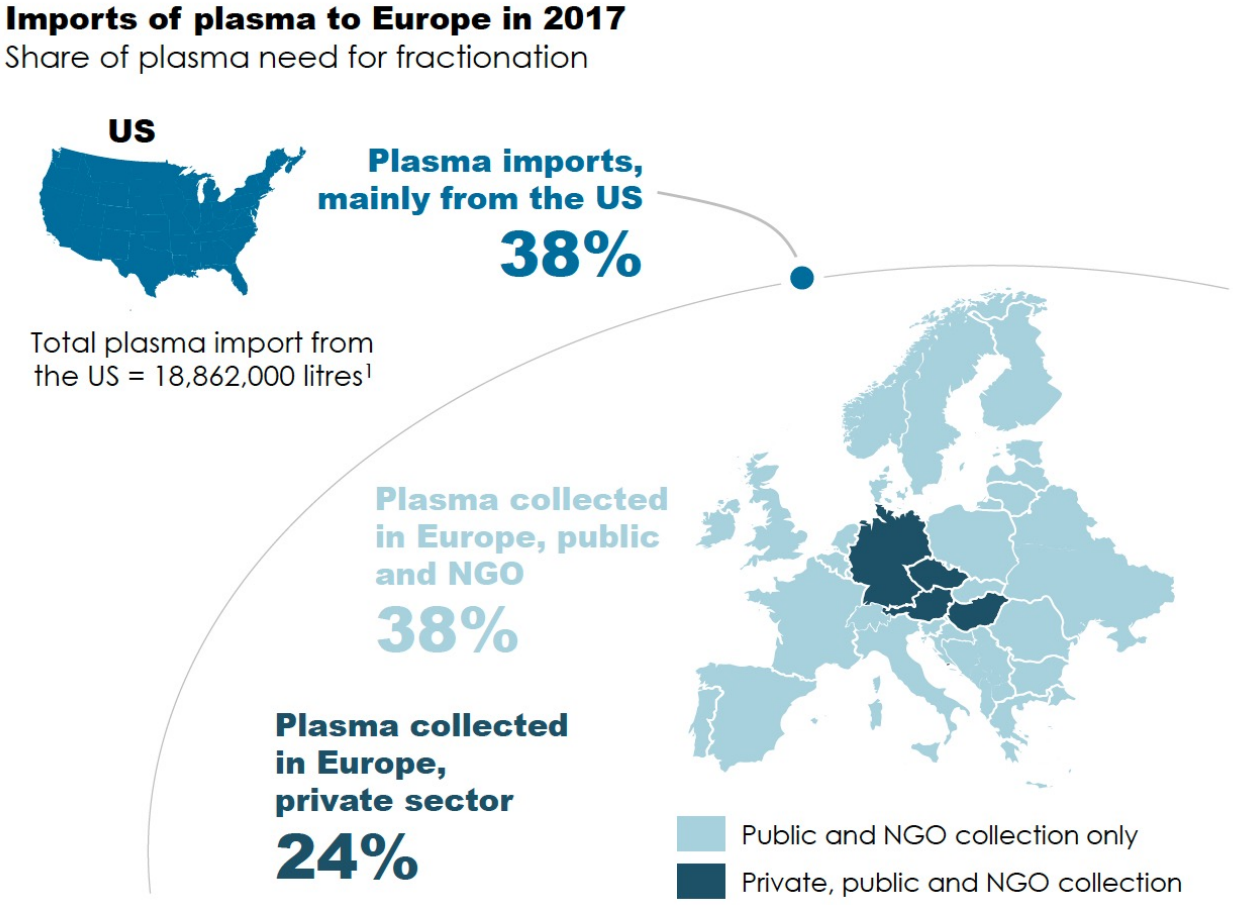


IS THAT ENOUGH?



The global distribution of plasma collection.

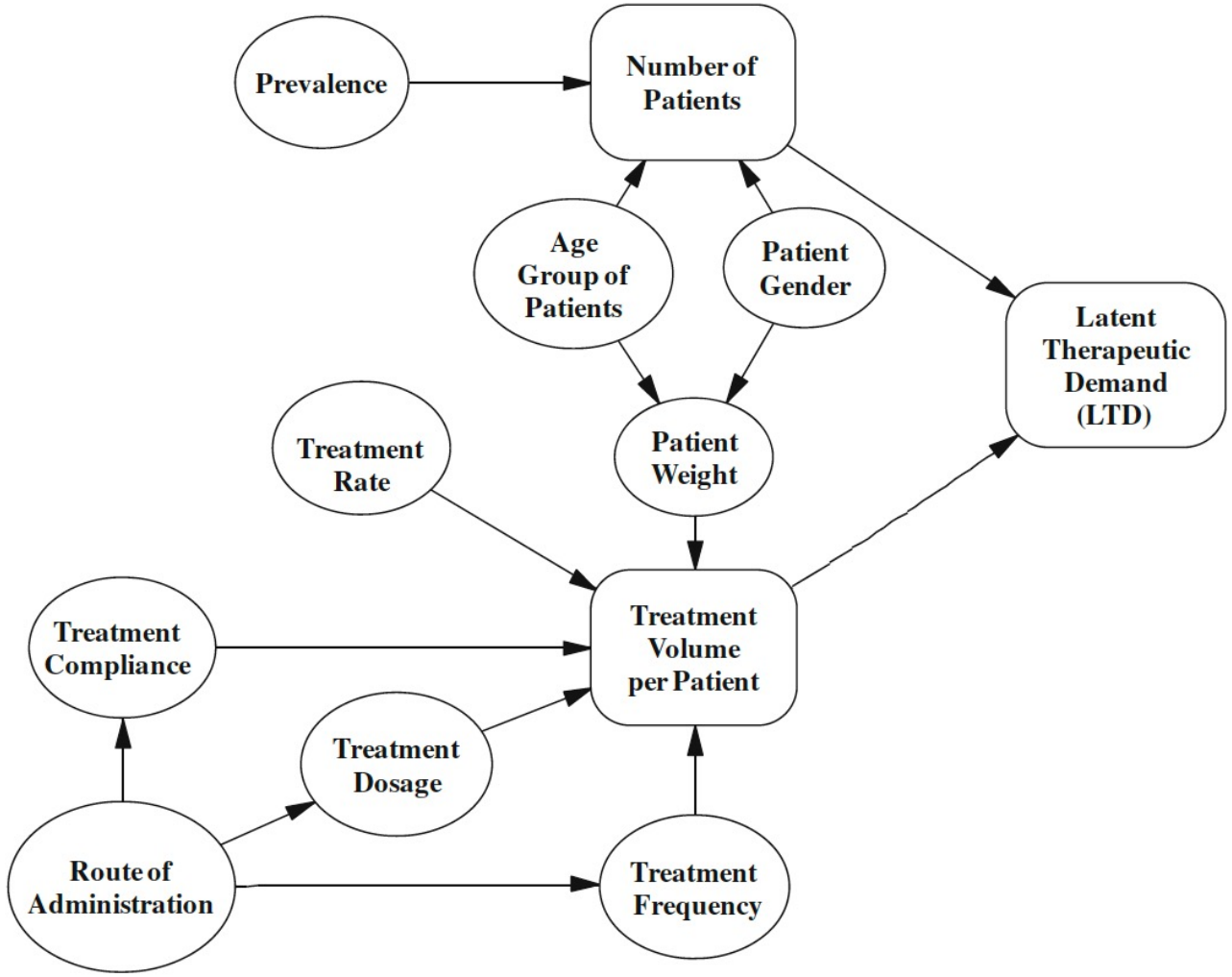
Curr Opin Allergy Clin Immunol. 2020 Dec;20(6):557-564.



Modeling Primary Immunodeficiency Disease Epidemiology and Its Treatment to Estimate Latent Therapeutic Demand for Immunoglobulin

- Underlying demand that represents how physicians would prescribe treatment and how patients would comply with the prescribed treatment if unlimited supplies were available (only EBG, no financial constrains)

Latent therapeutic demand

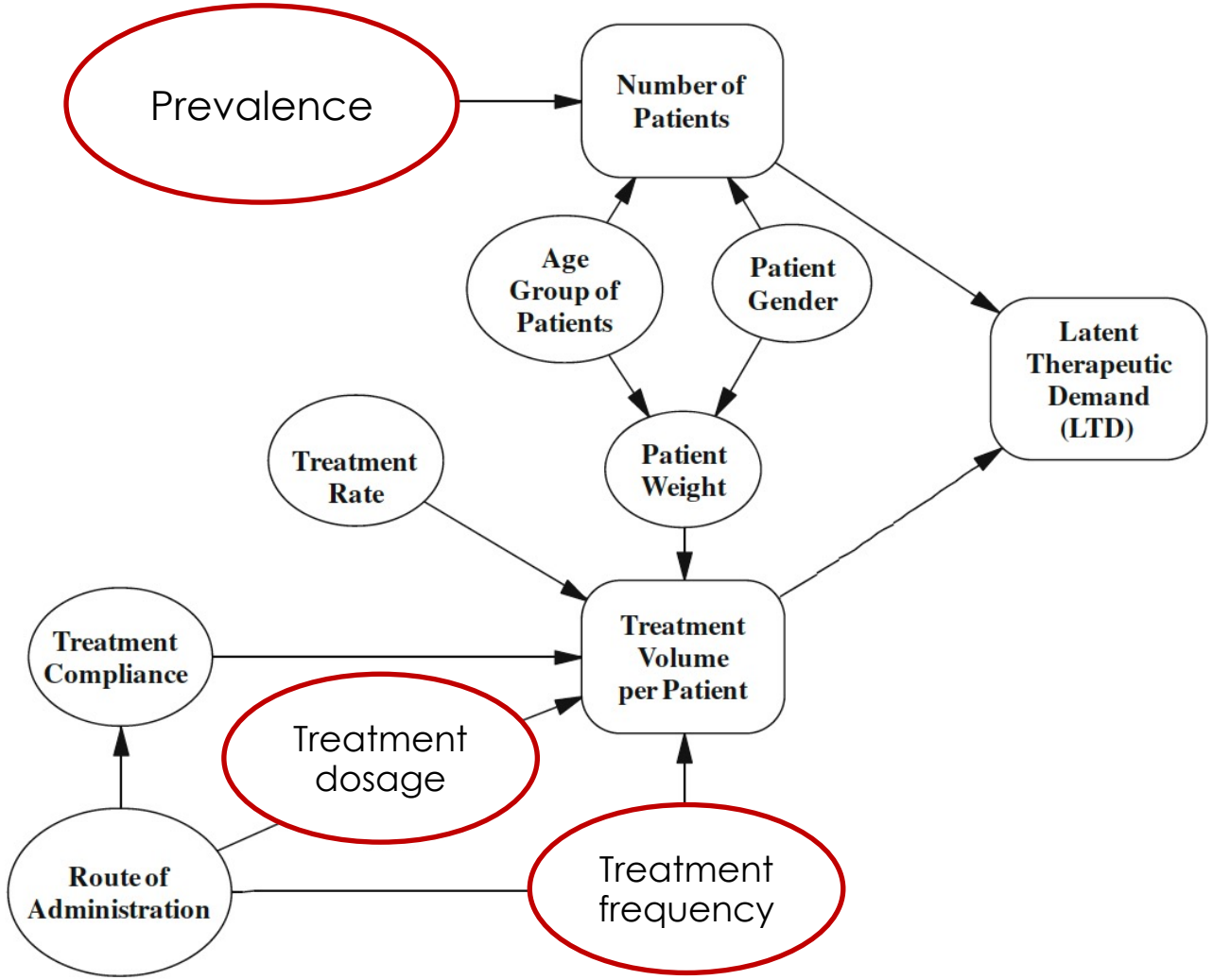


J Clin Immunol (2014) 34:233–244

Modeling Primary Immunodeficiency Disease Epidemiology and Its Treatment to Estimate Latent Therapeutic Demand for Immunoglobulin

- Underlying demand that represents how physicians would prescribe treatment and how patients would comply with the prescribed treatment if unlimited supplies were available (only EBG, no financial constrains)

Latent therapeutic demand

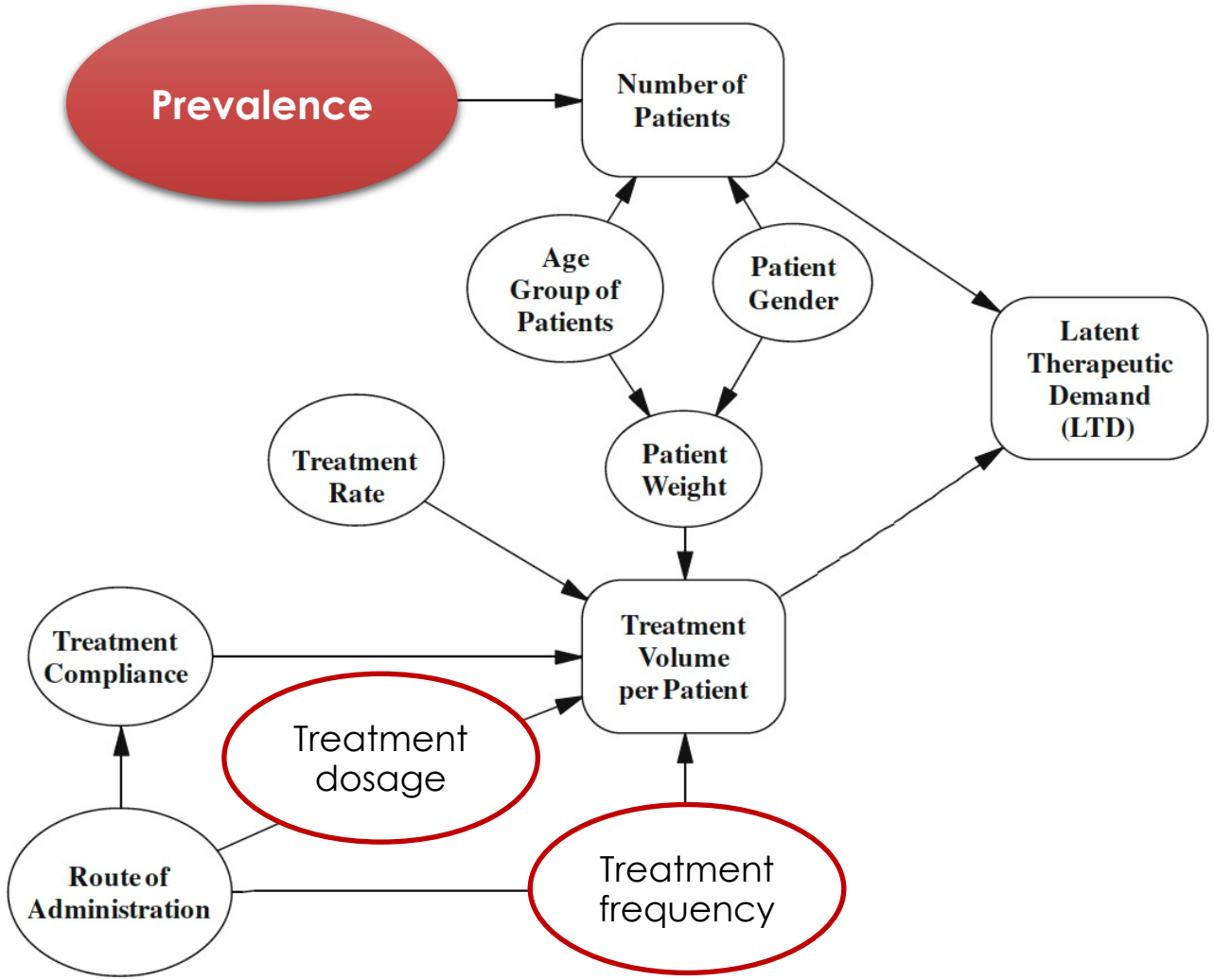


J Clin Immunol (2014) 34:233–244

Modeling Primary Immunodeficiency Disease Epidemiology and Its Treatment to Estimate Latent Therapeutic Demand for Immunoglobulin

- Underlying demand that represents how physicians would prescribe treatment and how patients would comply with the prescribed treatment if unlimited supplies were available (only EBG, no financial constrains)

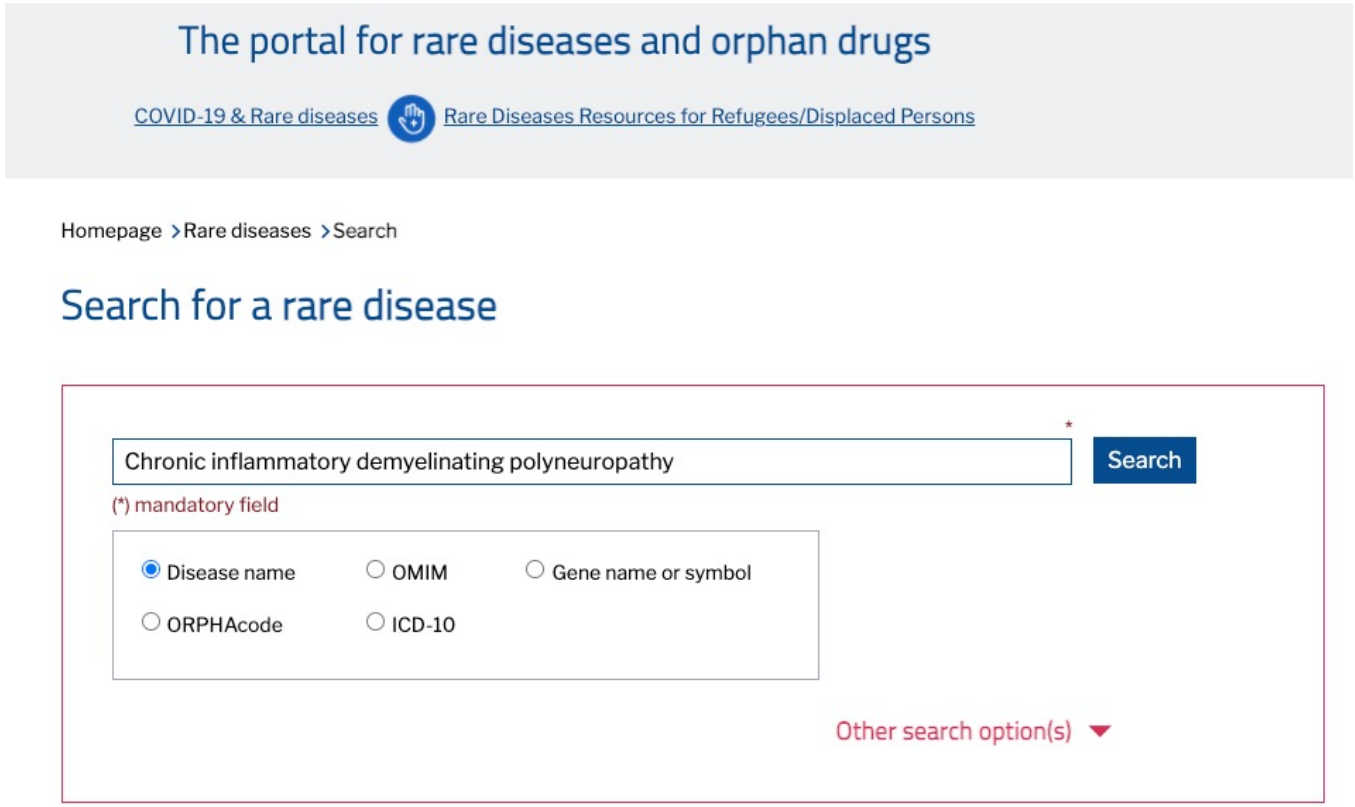
Latent therapeutic demand



J Clin Immunol (2014) 34:233–244

ESTIMATING PREVALENCE FOR PDMPs INDICATIONS

PDMPs indications, particularly those requiring immunoglobulins, are generally **rare diseases**



- Ongoing systematic literature survey of peer reviewed journals, specialized reports, registries, and international databases, with expert advice sought for epidemiological indicators not documented in the literature.

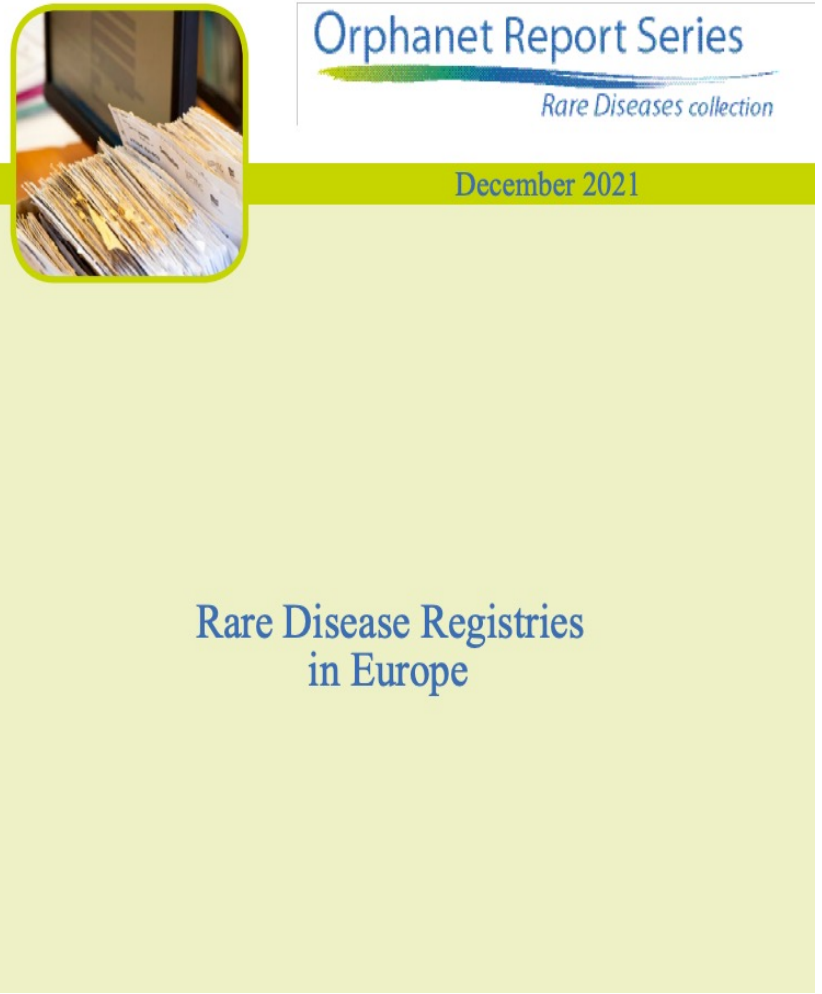
Orphanet portal for rare diseases

https://www.orpha.net/consor/cgi-bin/Disease_Search_Simple.php?lng=EN

ESTIMATING PREVALENCE FOR PDMPs INDICATIONS: *REGISTRIES*

"Organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular ***disease****, condition, or* ***exposure****"*

COVERAGE	NUMBER OF REGISTRIES*
European	97
International**	76
National	561
Regional	78
TOTAL	**812**

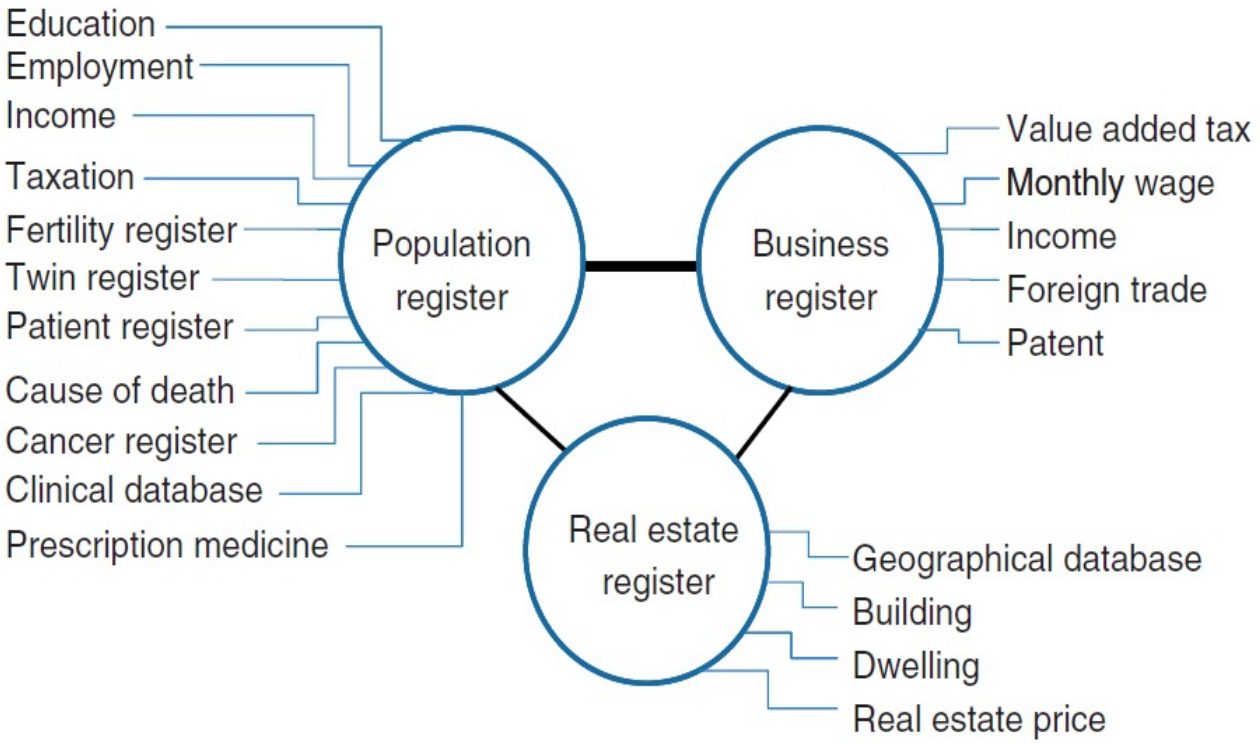


Gliklich RE, Dreyer NA: Registries for Evaluating Patient Registries: A User's Guide. 4TH edition, 2020
https://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf

ESTIMATING PREVALENCE FOR PDMPs INDICATIONS: *ELECTRONIC HEALTHCARE & CLAIMS DATABASES*

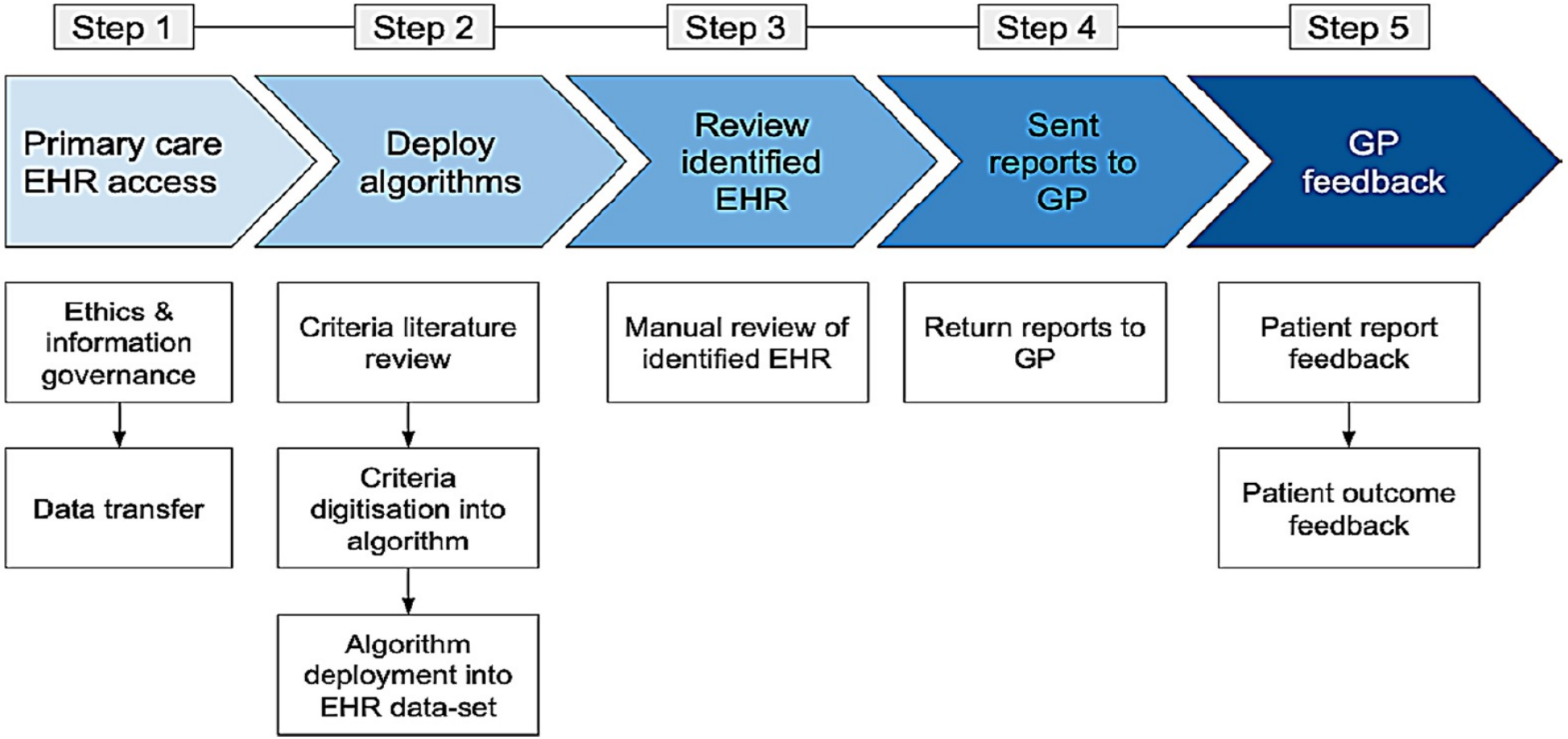
Routine-based systems collecting health-related information for managing patients care or for the payment and administration of health services

- Availability of data covering large populations, thus enabling the **study of rare exposures and outcomes**;
- Theoretical completeness of the information from a source population, thus **reducing the risk of selection bias**
- Routine collection, independent from any research hypothesis, which **reduce differential recall & non-response bias**
- Long-term follow-up (**time & cost reduction**)



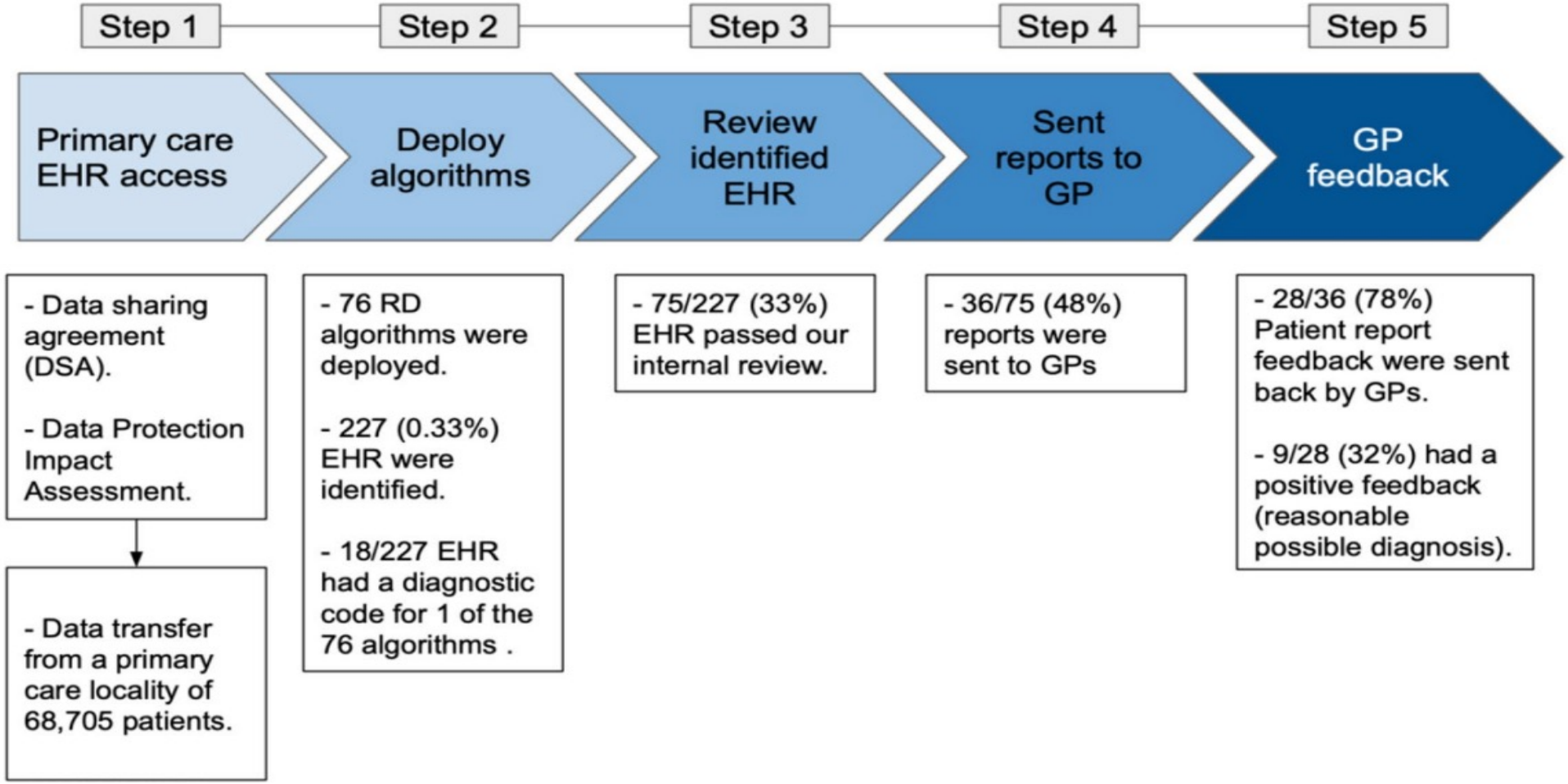
Baron JA, et al. Ann Epidemiol 2000; 10: 200-204

Is it possible to implement a rare disease case-finding tool in primary care? A UK-based pilot study



Buendia et al. Orphanet Journal of Rare Diseases (2022) 17:54

Is it possible to implement a rare disease case-finding tool in primary care? A UK-based pilot study



Buendia et al. Orphanet Journal of Rare Diseases (2022) 17:54

REAL WORLD DATA FOR PDMPs INDICATIONS:
STRENGHTS AND WEAKNESSES

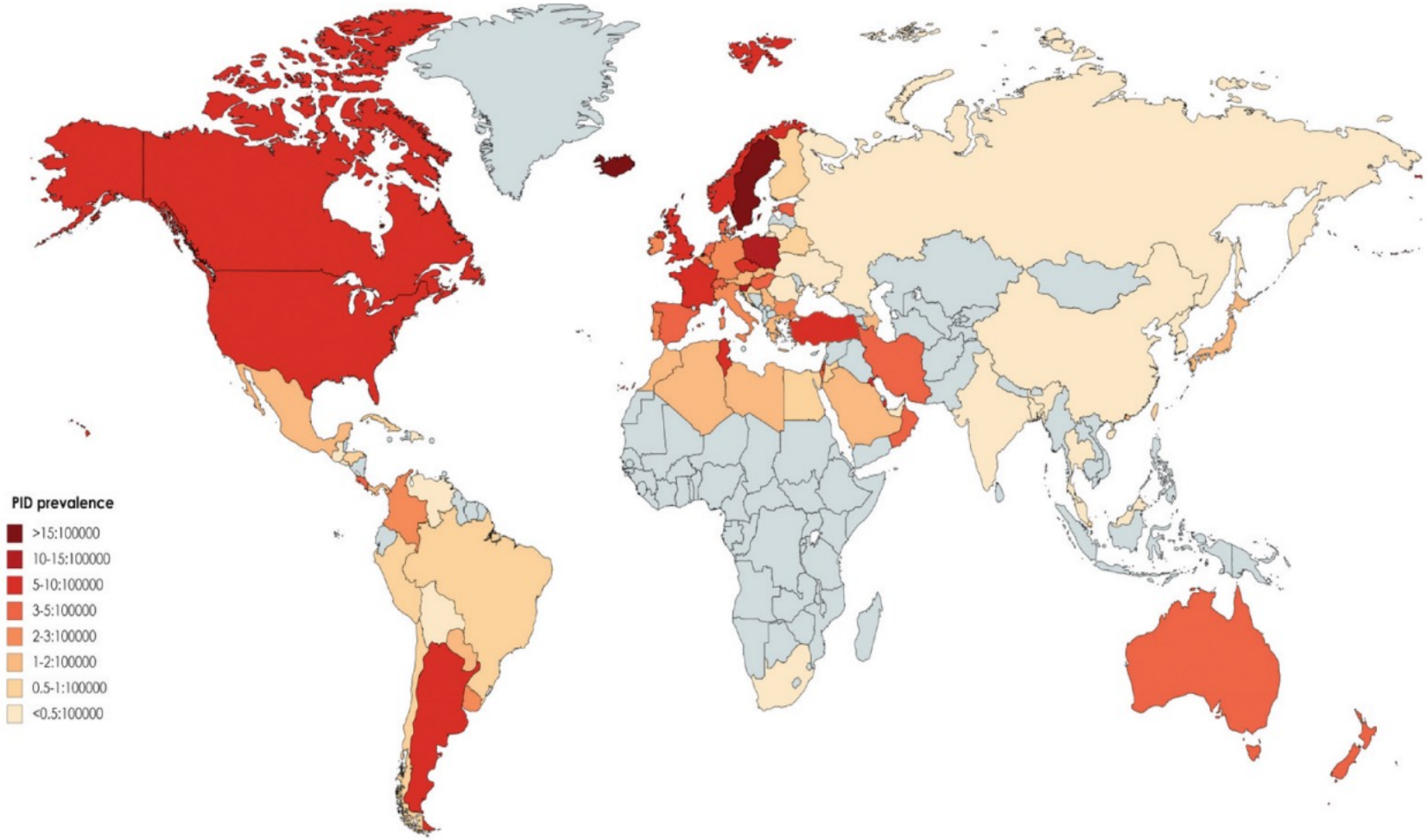
			EHRs		Registers		
		Claims databases	GPs	FPs	National/regional	Disease-specific	Drug registers
Orphan drug utilization							
Indication for orphan drug use		+	+	++	+++	+*	NK
Primary care	Out-patient prescribing covered by the NHS	NA	+++	+++	+*	+*	
	Out-patient drug dispensing covered by the NHS	+++	NA	NA	NA	+*	
	Out-patient drug dispensing not covered by the NHS	NA	+++	+++	NA	+*	
	Out-patient drug dispensing not covered by the NHS	NA	NA	NA	NA	+*	
Specialist setting	Out-patient drug dispensing covered by the NHS	+++	++	++	NA	+*	
	Out-patient drug prescribing not covered by the NHS	NA	+	+	NA	+*	
In-patient drug prescribing/dispensing		NA	NA	NA	NA	+*	
Patient drug history		+++	+++	+++	+*	+*	
Diagnosis and treatment of rare diseases							
Diagnosis		+++	+++	+++	+++	+*	NK
Onset date		NA	++	++	++	+*	
Severity		NA	NA	NA	NA	+*	
Drug safety							
Acute conditions		+++	++	++	+*	+*	NK
Chronic conditions		++	+++	+++	+*	+*	
Date of death		+++	+++	NA	+++	+*	
Cause of death		NA	+	+++	NA	NA	
Patient medical history and healthcare service utilization							
Hospitalization		+++	NA	NA	NA	NA	NK
Emergency department admission		+++	+	+	NA	NA	
Laboratory procedures, diagnostic tests, imaging		+++	+	NA	NA	NA	

Abbreviations: EHRs: electronic health records; FPs: family pediatricians; GPs: general practitioners; NA – not available. NHS – national health service. NK: not known. *Availability strongly related to the drug which the register is created to study. **Legend**: +: minimal information collected; ++: moderate amount of information collected consistently; +++: large amount of information collected consistently and accurately. This evaluation was the result of a round-table consensus among the co-authors of the present paper, based on their experience the respective data sources.

Expert Opinion on Drug Safety, 18:6, 497-509

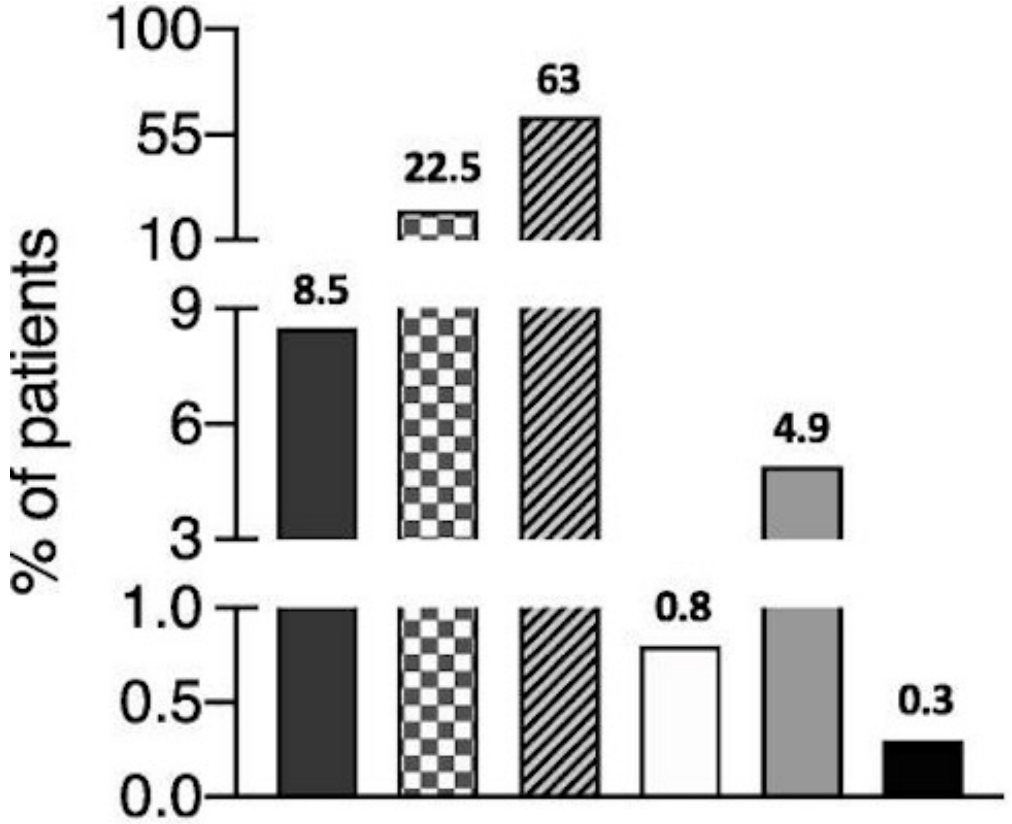
PREVALENCE OF PID

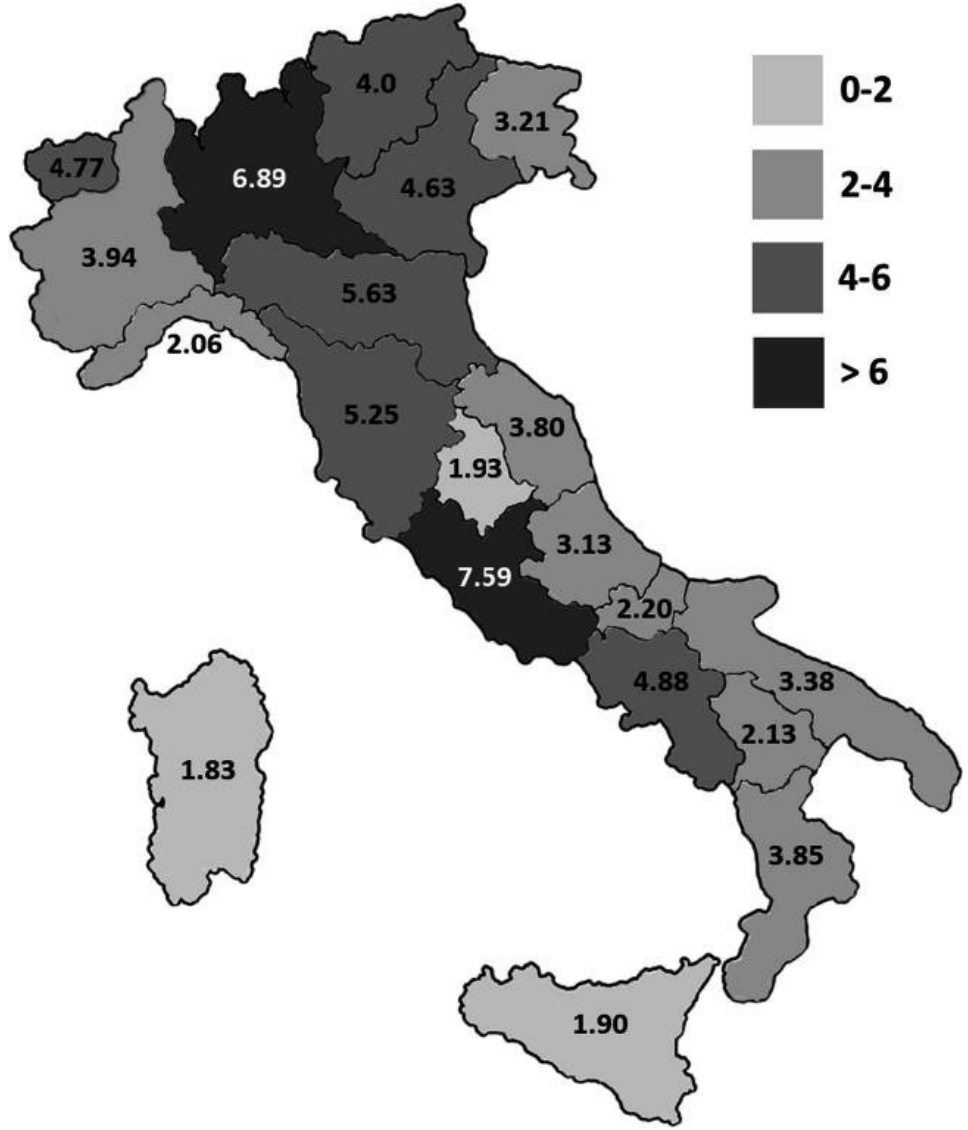
«….achieving the basic requirement for the global PID burden estimation and registration of undiagnosed patients will require more reinforcement of the progress, involving both improved diagnostic facilities and neonatal screening.»



EXPERT REVIEW OF CLINICAL IMMUNOLOGY 2020, VOL. 16, NO. 7, 717–732

PREVALENCE OF PID

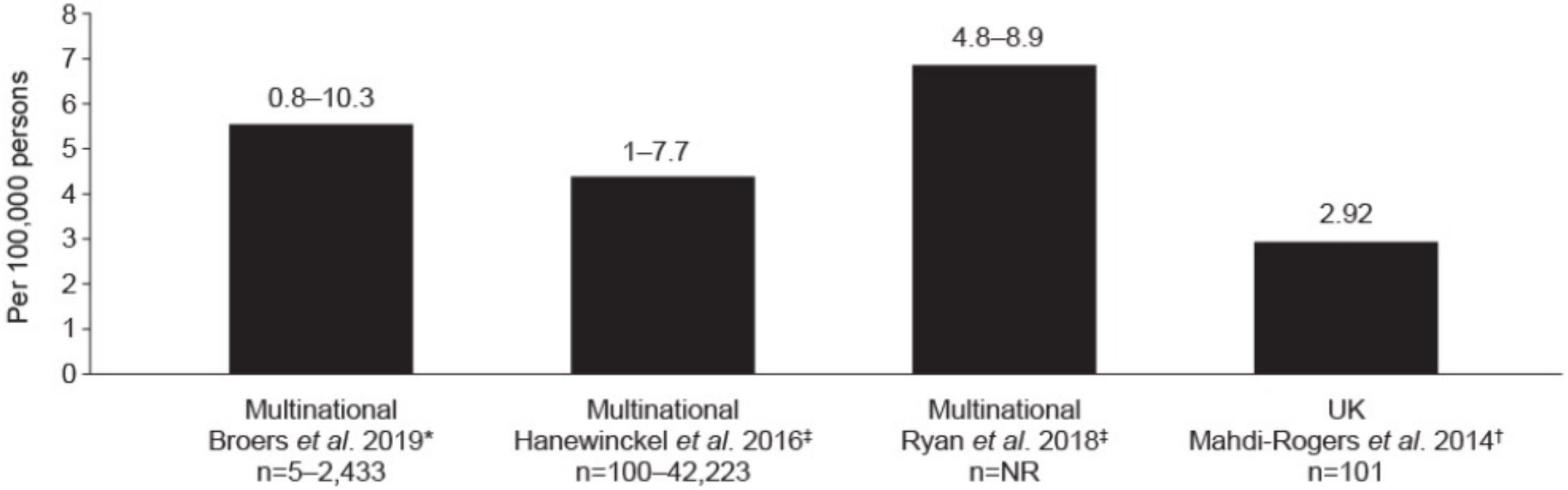




Lougaris_The Italian Registry PID IPINET_J Clin Immunol_2020

PREVALENCE OF CIDP

"The limited number of publications available on epidemiology, humanistic burden, and economic burden impairs the current assessment of the burden of disease."

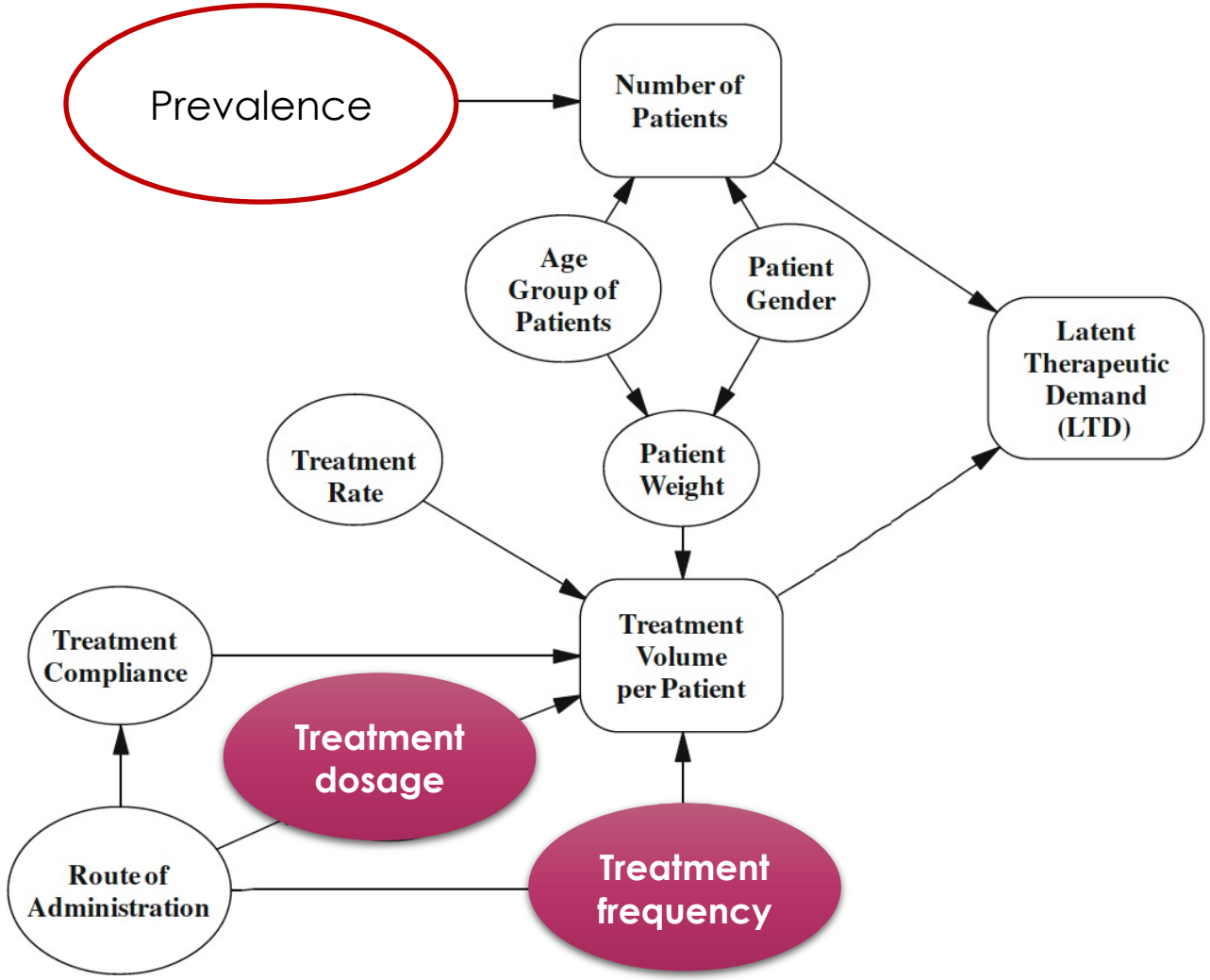


Querol_Systematic Rev Burden CIDP_J Neurol_2020

Modeling Primary Immunodeficiency Disease Epidemiology and Its Treatment to Estimate Latent Therapeutic Demand for Immunoglobulin

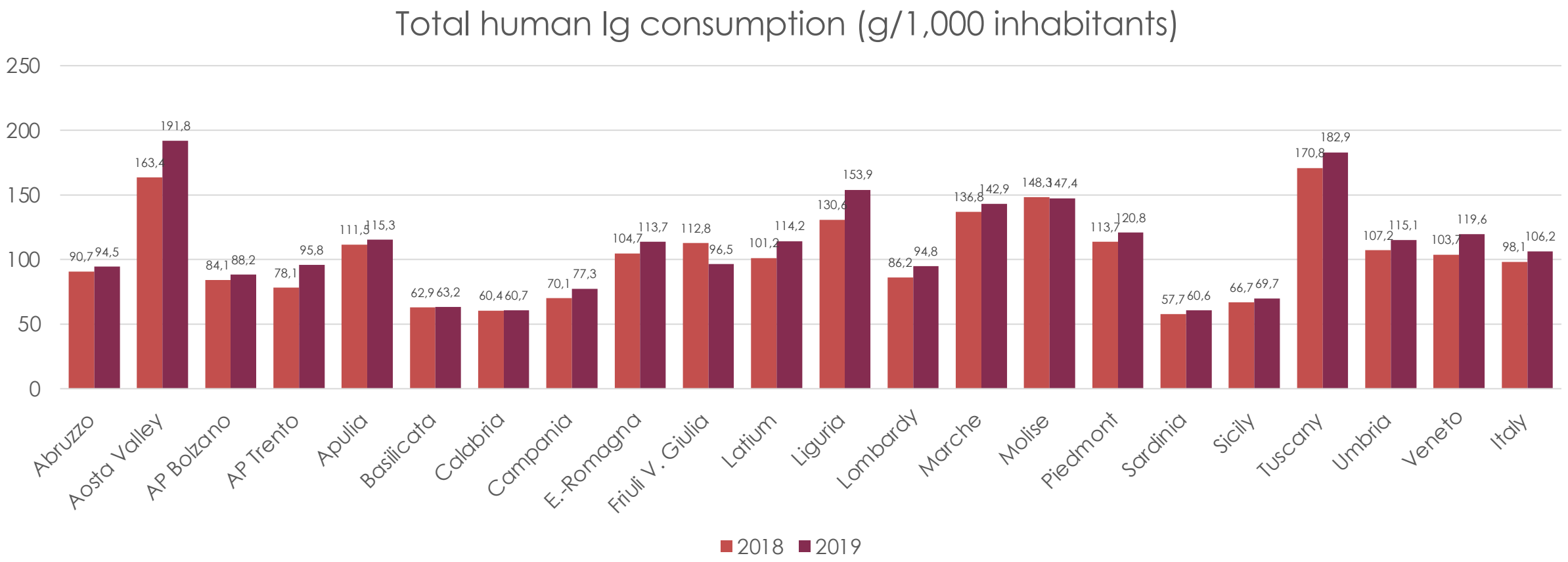
- Underlying demand that represents how physicians would prescribe treatment and how patients would comply with the prescribed treatment if unlimited supplies were available (only EBG, no financial constrains)

Latent therapeutic demand



J Clin Immunol (2014) 34:233–244

MONITORING PDMPs TREATMENT (ITALY)



Candura F, et al. Demand for plasma-derived medicinal products in Italy. 2019. Roma: Istituto Superiore di Sanità; 2021. (Rapporti ISTISAN 21/13 EN).

MONITORING PDMPs TREATMENT (EU)

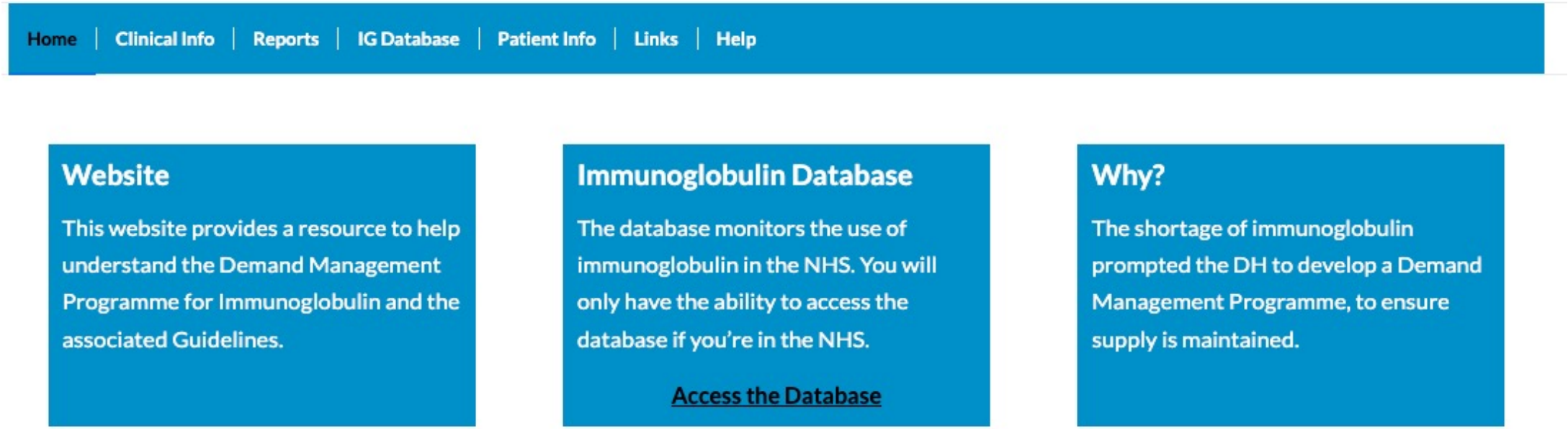
	DK	FR	GERMANY	ITALY	SPAIN
Data provider	The Danish Medicines Agency	Caisse Nationale d'Assurance Maladie des Travailleurs Salariés	Wissenschaftliches Institut der AOK (Research Institut of the AOK)	Italian Medicines Agency. OSMED	Department of Pharmacy and Health Products
Setting	Out/Inpatient	Outpatient	Outpatient	Out/Inpatient	Outpatient
Population coverage	100	87	85	100	100
ATC/DDD	Yes	Yes	ATC	Yes	Yes
OTC	Yes	No	No	Yes	No
Patients level (demographics, socioeconomic)	Yes	Yes	Yes	Demographics	No

Ferrer P, et al. Int J Public Health. 2014 Oct;59(5):877-87.

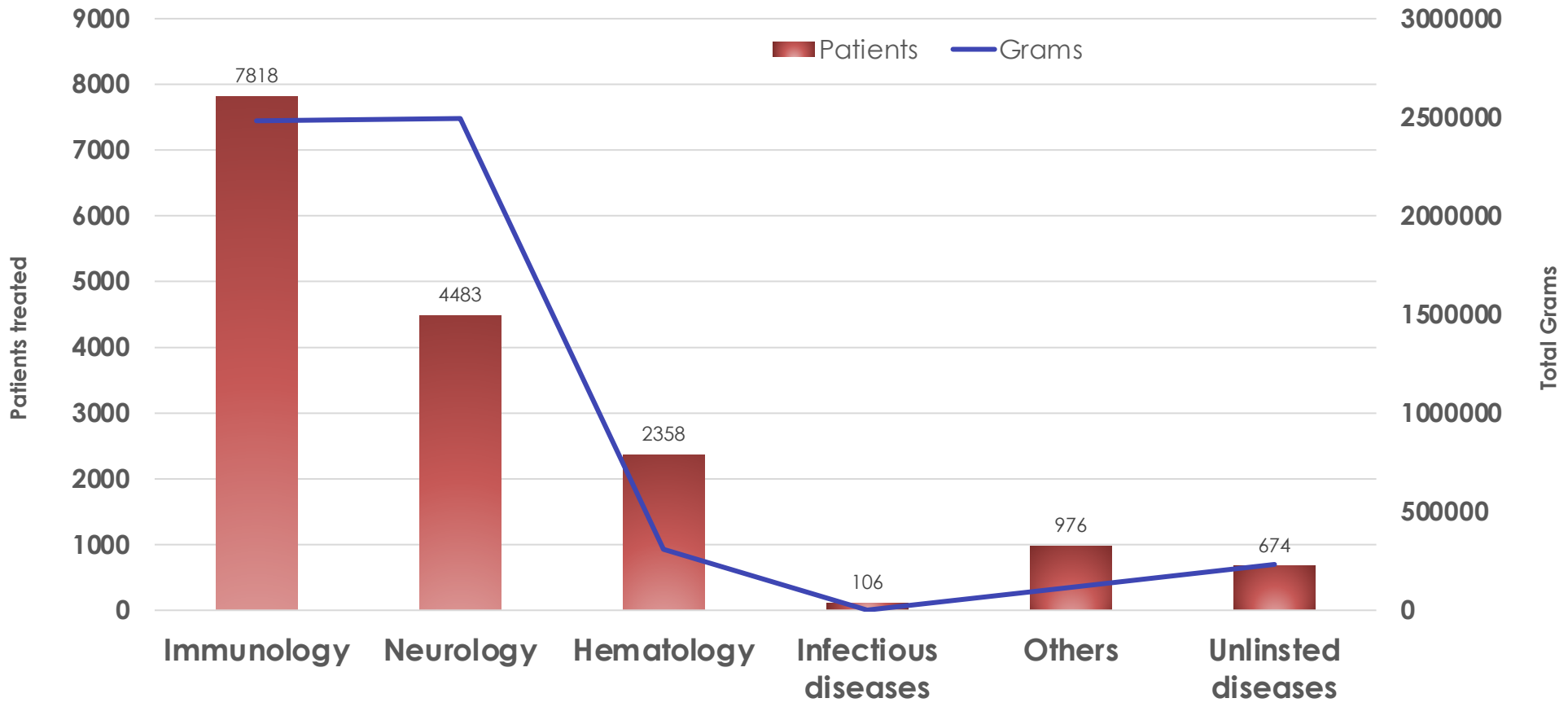
MONITORING PDMPs TREATMENT (UK)

To complement the Clinical Guidelines and Demand Management Plan, support long-term planning, and provide data on the use of immunoglobulin in rare disorders

NHS England



MONITORING PDMPs TREATMENT (UK)



https://igd.mdsas.com/reports/

MONITORING PDMPs TREATMENT (UK)

Table 1.2 Neurology - volume of recorded immunoglobulin and patients on Ig therapy 2019/20

Condition	Patients	Grams
Chronic inflammatory demyelinating polyradiculoneuropathy	1,592	1,258,566
Multifocal motor neuropathy	669	629,302
Myasthenia gravis	733	197,828
Inflammatory myopathies	380	173,501
Guillain–Barré syndrome	958	145,250
Stiff person syndrome	103	59,014
Paraprotein-associated demyelinating neuropathy (IgM)	38	25,106
Rasmussens Encephalitis	10	5,345
Total	**4,483**	**2,493,812**

https://igd.mdsas.com/reports/

CONCLUSIONS

- The increased plasma consumption requires a systematic and structured system for estimating demands
- Prevalence of diseases estimation (in particular RD) rely on ongoing data collection which may help to achieve the objective (although recognizing the limitations)
- Need for more powerful systems to estimate PDMPs use; consumption important but linkage to patient level information will permit more efficient estimates of future demands.