UIMD

Unified Registry for
Inherited Metabolic Diseases

UNIFIED REGISTRY FOR INHERITED METABOLIC DISORDERS (U-IMD)

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INHERITED METABOLIC DISEASES (IMDS)

Each IMD is a rare condition with estimated individual prevalence ranging from 0.1 to 15 in 100,000 newborns but taken together patients affected by IMDs are numerous with at least one in 500 newborns. More than 1,650 (http://iembase.org/index.asp) inherited metabolic diseases (IMDs) have so far been identified. Depending on the underlying defect and its individual severity, the spectrum of clinical presentation of IMDs is wide, ranging from lethal neonatal metabolic crisis to progressive single or multiple organ dysfunction. Individuals affected by IMDs are confronted with significant and often severe health problems resulting in high morbidity, reduced life expectancy, and low quality of life.

EUROPEAN REFERENCE NETWORKS AND METABERN

European Reference Networks (ERN) were established by the European Commission to improve care for patients with 24 groups of rare disorders. MetabERN facilitates the access to the best available care and addresses the needs across the border of all patients affected by any rare inherited metabolic disease (IMDs) and their families. MetabERN is driven by the principle of patient-centred care for the provision of its services aiming at improving the quality of life of patients and families. MetabERN aims to connect the most specialised centres in the area of rare IMDs to promote prevention, accelerate diagnosis and improve standards of care across Europe for patients living with IMDs. MetabERN is entirely patient- and expert-led. Through the combination of patient experience and expert knowledge from across the EU, it captures the most innovative medical advances and tailors them to patient needs.

GOAL AND AIMS OF THE U-IMD PROJECT

The overall goal of the U-IMD project is to promote health for children, adolescents and adults affected with rare IMDs by promoting research on IMDs and the development of safe and efficacious new treatments by establishing the "Unified European Registry for Inherited Metabolic Disorders".

U-IMD is the first unified European registry that encompasses all IMDs from all disease subgroups of MetabERN, as there are:

- Amino acid-related disorders (AOA)
- Pyruvate metabolism, mitochondrial oxidative phosphorylation disorders, Krebs cycle defects, disorders of thiamine transport and metabolism (PM-MD)
- Carbohydrate, fatty acid oxidation and ketone bodies disorders (C-FAO)
- Lysosomal storage disorders (LSD)
- Peroxisomal disorders (PD)
- Congenital disorders of glycosylation and disorders of intracellular trafficking (CDG)
- Disorders of neuromodulators and other small molecules (NOMS)

SPECIFIC AIMS OF THE U-IMD PROJECT

The strategy of the U-IMD project is based on three major pillars:

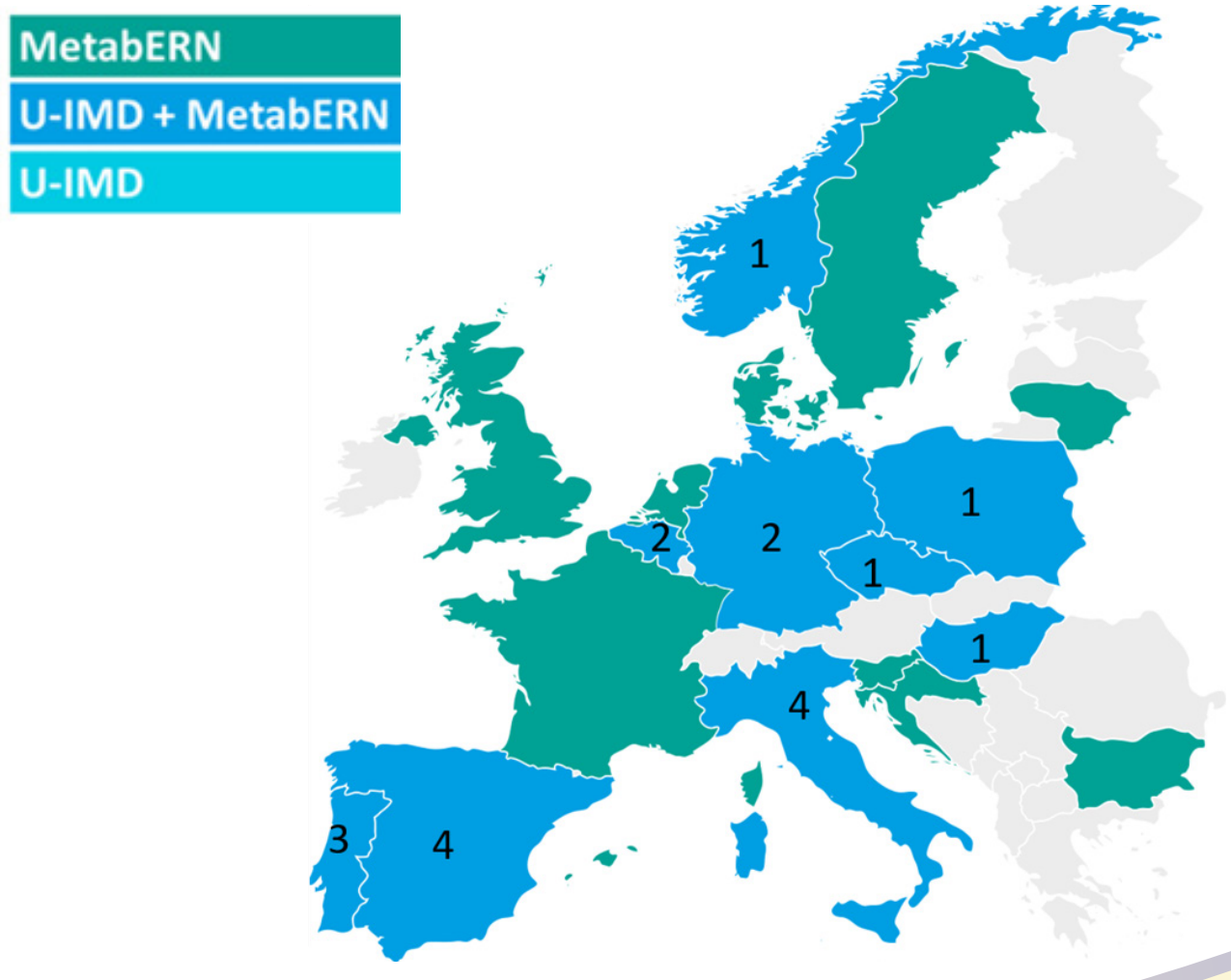
① the development of an innovative and semantically interoperable registry platform for all known IMDs as official patient registry of MetabERN. U-IMD has fully implemented the common data elements of the European Platform on Rare Disease Registration (EU RD Platform) and has integrated the tools of the European Rare Disease Registry Infrastructure (ERDRI).

② upgrading of existing IMD registries to reach interoperability among these registries, including U-IMD , using the patient registry of the International Working Group on Neurotransmitter Related Disorders (iNTD) as a pilot.

③ establishing a defined intersection of minimal core data elements with ERKReg, the patient registry of the European Rare Kidney Disease Reference Network (ERKNet), to foster collaboration for individuals with rare metabolic kidney disease.

U-IMD BENEFICIARIES AND PARTNERS

In addition to the U-IMD Beneficiaries15 further members (see map and table) of MetabERN joined the U-IMD project and started to enter data as of July 2021.



COUNTRY	HEALTH CARE PROVIDER
Belgium	**Bruxelles**
	Hôpital Universitaire des Enfants Reine Fabiola
	Antwerp
	University Hospital of Antwerp UZA
Czech Republic	**Prague (B)**
	General University Hospital in Prague
Germany	**Heidelberg (B)**
	University Hospital Heidelberg
	Magdeburg
	Otto-von-Guericke-University Med.Faculty, Central-German Network for rare diseases
Spain	**Barakaldo**
	Hospital Universitario Cruces
	Barcelona (B)
	Hospital Sant Joan De Déu
	Madrid
	Hospital Universitario 12 de Octubre
	Santiago de Compostela
	Hospital Clínico Universitario de Santiago
Hungary	**Szeged**
	University of Szeged, Faculty of Medicine
Italy	**Monza**
	Ufficio Sperimentazioni Cliniche Fondazione MBBM Onlus
	Rome (B)
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	Udine (B)
	University Hospital of Udine
	Verona
	Azienda Ospedaliera Università Integrata
Norway	**Oslo**
	Oslo University Hospital
Poland	**Krakow**
	Krakow University Hospital
Portugal	**Guimarães**
	Hospital da Senhora da Oliveira Guimarães
	Lisboa
	Centro Hospitalar Universitário Lisboa Norte (CHLN)
	Porto
	Centro Materno Infantil do Norte

B, beneficiary

U-IMD REGISTRY

DATA MODEL

U-IMD includes the complete set of Common Data Elements (CDEs) for Rare Diseases Registration as proposed by a working group coordinated by the Joint Research Centre (JRC) and works with the tools of the European Rare Disease Registry Infrastructure (ERDRI). As recommended by the CDEs, the registry employs as many as possible established controlled dictionaries for recording patient data, as there are:

The nosology of the Inborn Errors of Metabolism Knowledgebase (IEMbase) (also see Ferreira et al), the first overarching and most up-to-date and systematic nosology for IMDs. The nosology of the IEMbase is also mapped to the Orphanet coding system and the Online Mendelian Inheritance in Man coding system (OMIM), thus patient records in U-IMD are defined within all three coding standards.

The terms of the Human Phenotype Ontology for the description of the phenotype. (HPO)

The World Health Organization Anatomical, Therapeutical, Chemical (WHO ATC) classification system to record the treatment

The disease-specific sets of metabolic biomarkers developed by the IEMBase is used for the recording of biochemical markers. This set of biomarkers is additionally mapped to the coding system of the Human Metabolome Database (HMDB)

MODULAR DESIGN OF THE U-IMD REGISTRY*:

Module 1: Common Data Elements (CDE)
EU JRC Common Data Elements, case definition according to IEMBase nosology, mapped to ORPHA code and OMIM code, results from mutation analysis

Module 2: Clinical and cognitive phenotype
Human Phenotype Ontology (HPO), anthropometric data, Denver Developmental Screening test, Bayley Scales od Infant Development, Wechsler Intelligence Scales (WPPSI, WISC and WAIS).

Module 3: Pacient perspective
Pediatric Quality of Life Inventory (PedsQL), World Health Organisation Quality of Life (WHOQOL) questionnaire,
World Health Organisation Disability Assessment Schedule 2.0 (WHODAS 2.0).

Module 4: Treatment
Dietary treatment, transplantations, drug treatment coded according to the World Heatlh Organization Anatomical Therapeutic Chemical (WHO ATC) classification system.

Module 5: Biochemical markers (HMDB codes)
Disease specific selections of biochemical markers, coded according to the Human Metabolome Database (HMDB).

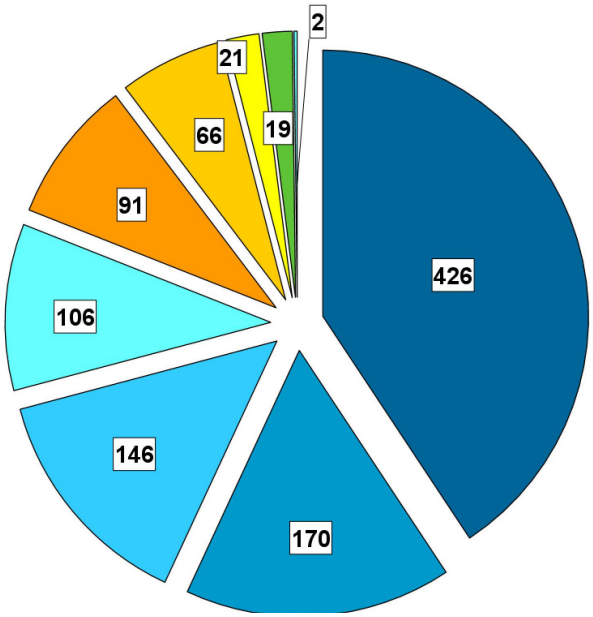
Module 6: ERKNet collaboration
U-IMD integrates the dataset developed by the registry od the European Reference Network for Rare Kidney Diseases (ERKNet), thus faciliating joined research projects between both Reference Networks

*Footnote *Details on the U-IMD data model can be found in a publication by Opladen et al*

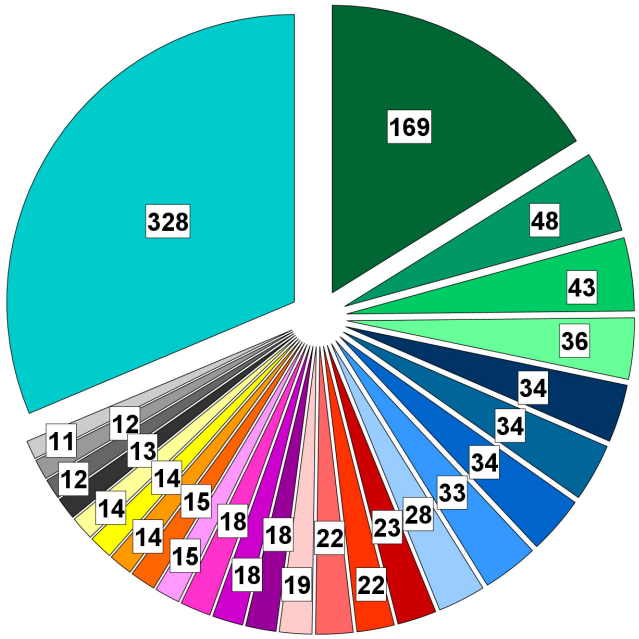
USE OF THE U-IMD REGISTRY

The new registry was approved and released in April 2019 at the annual MetabERN Board meeting. As of August 2021, over 2,000 individuals with confirmed diagnosis of an IMD have been enrolled. The spectrum of patients with individual disorders is shown below.

Details on the registry content can be found in publication by Opladen et al U-IMD: the first Unified European registry for inherited metabolic diseases - PubMed



- Disorders of Nitrogen-Containing Compaunds
- Disorders of Lipids
- Disorders of Carbohydrates
- Storage Disorders
- Disorders of Vitamins, Cofactors and Minerals
- Mitochondrial Disorders of Energy Metabolism
- Disorders of Peroxisomes and Oxalate
- Congenital Disorders of Glycosylation
- Disorders of Tetrapyroles



- Glucose-6-phosphatase deficiency
- Glutaryl-CoA dehydrogenase deficiency
- Fumarylacetoacetase deficiency
- Very long-chain acyl-CoA dehydrogenase deficiency
- Phosphomannomutase 2 deficiency
- Niemann-Pick disease type C1
- Argininosuccinate synthetase
- Phenylalanine hydroxylase deficiency
- Medium-chain acyl-CoA dehydroganase deficiency
- Ornithine transcarbamylase definiciency
- Methylmalonic aciduria and homocystinuria, clbC type
- Glycocerebrosidase deficiency
- Trifunctional protein α subunit deficiency
- Cystathionine β-synthase deficiency
- Galactose-1-phosphate uridylyltransferase deficiency
- 7-dehydrocholesterol reductase deficiency
- Hepatic phosphorylase kinase a2 subunit deficiency
- α-glucosidase deficiency
- Biotinidase deficiency
- Mitochondrial tRNA(Leu) 1 deficiency
- X-linked adrenoleukodystrophy
- Branched-chain ketoacid dehydrogenase E1α deficiency
- Mevalonate kinase deficiency
- Glycogen debranching enzyme deficiency
- α-iduronidase deficiency
- Other

The utility of U-IMD for the analysis of the natural disease course of ultra-rare diseases has been illustrated by Brennenstuhl et al [Phenotypic diversity, disease progression, and pathogenicity of MVK missense variants in mevalonic aciduria - PubMed]

INTEROPERABILITY OF U-IMD WITH OTHER REGISTRIES

The expertise gained from developing U-IMD is used to enhance other existing IMD registries like the EU-funded European Registry and Network for Intoxication type Metabolic Diseases (E-IMD; CHAFEA agreement no. 2010 12 01), the European Network and Registry for Homocystinurias and Methylation Defects (E-HOD; CHAFEA agreement no. 2012 12 02), and the registry of the International Working Group on Neurotransmitter Related Disorders (iNTD). The features developed for the new U-IMD registry were also implemented into the existing iNTD registry and will be implemented into the E-IMD and E-HOD registries for upgrading and sustaining patient registries that were established previously with EU co-funding (via HaDEA).

U-IMD also collaborates with other European Reference Networks (ERN), particularly with the European Rare Kidney Disease Reference Network (ERKNet): on individuals with metabolic nephropathies. The cooperation with ERKNet resulted in the inclusion of the full panel of disease progression parameters for rare metabolic kidney diseases. Therefore, individuals having an IMD with a high risk of developing renal disease manifestation and hence are eligible for both registries, are identically described in both the U-IMD and the ERKReg registries.

ETHICAL ISSUES AND DATA OWNERSHIP

The U-IMD registry is a web-based patient registry, pseudonymized data is remotely entered by experts, using password-protected user accounts and encrypted data transfer. U-IMD is implemented as an observational registry study, using a defined study protocol, subject to positive evaluation by the respective local ethics committee before any data entry is permitted. The U-IMD study protocol was produced ensuring study procedures according to GCP and GDPR. All beneficiaries obtained positive evaluations form their respective institutional ethics commissions. An English translation of the study protocol is available for distribution among further health care providers (HCPs) interested in joining the project. Patients are enrolled by providing written informed consent and retain the right to withdraw their consent at any time without any negative effects on their further medical care.. HCPs interested in joining U-IMD have to to sign the U-IMD Letter of Agreement (LofA), regulating rights and responsibilities within the U-IMD consortium.

Data ownership is retained by the individual HCPs at all times, with usage of the full dataset is governed by the U-IMD Consortium Agreement, granting members equal rights in initiating and deciding on mutual projects being subject to consensus within the consortium.

DISSEMINATION ACTIVITIES

A project website, accessible under: https://u-imd.org/ and a project leaflet were created. The leaflets were printed and distributed to all beneficiaries to support individual dissemination activities. Additionally, U-IMD is featured on the official MetabERN website.

U-IMD was presented at 30 different events targeting about 17,000 stakeholders from science, policy making and the general public, by oral and poster presentations as part of the respective official programmes. Most prominently U-IMD was represented with poster presentations at the SSIEM 2018 and 2019 and with oral presentations at the annual MetabERN Board meetings in 2018, 2019 and 2020. The beneficiaries also engaged in stakeholder liaison with special focus on other ERNs and registry projects within the field of IMDs, participating in the workshops and meetings organized by the JRC Ispra for all ERNs funded under HP-PJ-06-2016.

SUMMARY AND IMPLICATIONS OF U-IMD PROJECT

The main output is the newly established U-IMD registry (https://www.u-imd-registry.org/), allowing MetabERN to establish an own data source, facilitating unique research projects and collaborations with stakeholders including policy makers and industry. U-IMD further includes all disease progression parameters established by the registry of ERKNet, forming the foundation for collaborative projects targeting metabolic nephropathies which are target disease of both ERNs. The iNTD registry was upgraded for full interoperability of patient records with U-IMD, thus also integrating iNTD into the ERDRI concept and serving as a model for potential upgrades of further previously existing registries like the E-IMD registry and the E-HOD registry. Using data collected with the U-IMD, a first round of research projects on the level of MetabERN is agreed, with the aim of providing a better insight in the natural history of IMDs ultimately benefiting the health of affected patients.

The U-IMD consortium has started data collection in the registry together with members of MetabERN and additional interested European and international partners, establishing the data source for future natural history studies of IMDs not yet covered by registry structures of comparable scope. The U-IMD consortium is dedicated to an open multiple stakeholder approach, using its growing data source for collaborations with other scientific networks, policy makers and industry.

European Reference Network

MetabERN

European Reference Network for Hereditary Metabolic Disorders

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