We have identified a network of 12 EU molecular diagnostic laboratories that can offer testing to any EU family. These laboratories are able to offer genetic testing for Wolfram (8), Alström (6), Bardet-Biedl (3), Wolcott-Rallison (1) and Thiamine-Responsive Megaloblastic Anemia (2) syndromes.

We have also compiled a comprehensive mutation database including over 680 unique DNA variants in the different genes known to be associated with these conditions. This has been compiled using the Leiden Open Variation database (LOVD) software and can be viewed at: https://lov.euro-wabb.org.

EURO-WABB REGISTRY: We agreed a common dataset of clinical, investigation and molecular diagnostic data to distinguish between the syndromes and provide a searchable database for researchers. We also incorporated data fields for other rare diabetes syndromes. We wrote an ethics submission template for national approvals, which includes consent to link national and international registries. The core dataset includes 44 data fields which define and separate the syndromes; the extended dataset comprises 370 fields of detailed phenotyping information. The core dataset has been designed to be completed in 15 minutes. The registry data is standardised using ESPE and WHO ICD-10 coding systems where possible. The full datasets can be accessed at www.euro-wabb.org.

DATA COLLECTION: We designed a web-based registry (NesC, University of Glasgow) with built-in security for data confidentiality, anonymised data collection, and facility for patients to self-register. Clinical partners (e.g. physicians) can, with the consent of their patients, upload anonymised information on phenotype and genotype, but still control access and retain ownership of their own data. Research partners submit proposals to a scientific advisory committee to access the anonymised data. There is no access to patients except through their participating physicians.

DISCUSSION: This EU Registry will improve patient services, health professional awareness, and allow recruitment into clinical trials. The common core dataset for European Union states can be shared between national rare disease registries as they are developed; and will allow linkage with other international disease registries. The registry data will be used to increase the understanding of the natural history of WABB diseases, to serve as an evidence base for clinical management, and to aid the identification of opportunities for intervention to stop or delay the progress of the disease processes. The detailed clinical characterisation will allow inclusion of patients into studies of novel treatment interventions, including targeted interventions in small scale open label studies; and enrolment into multi-national clinical trials. The registry will also support wider access to genetic testing, provide information for affected families and health professionals; and encourage international collaborations for patient benefit. It is hoped that this will lead to an improved quality of life for WABB patients achieved through earlier diagnosis, prompt identification and management of complications and increased healthy life years.

EURO-WABB PROJECT: EURO-WABB is a 3 year project with funding from the EU Health Programme Framework. The aim of the project is to support efficient diagnosis, treatment and research for Wolfram, Alström and Bardet-Biedl (WABB) syndromes and other rarer diabetes syndromes (Wolcott-Rallison syndrome, and Thiamine-responsive megaloblastic anaemia) in Europe and beyond, through the development of a EURO-WABB European Registry of patients.

RARE DIABETES SYNDROMES: WABB syndromes are all rare (less than 1:300,000) autosomal recessive disorders. They are chronic, progressive, multi-system disorders and are often misdiagnosed or diagnosed late. Affordable access to molecular genetic testing is limited in Europe and treatable complications are often missed. There are no orphan drug treatments available, and no access to well characterized cohorts of patients to undertake research. The syndromes exhibit clinical overlap; all can cause blindness, deafness, and diabetes mellitus or impaired glucose tolerance. Wolfram syndrome is an endo- reticulum stress disorder characterized by young onset diabetes and bilateral optic atrophy. It is also known as DIDMOAD syndrome, for the other disease features including diabetes insipidus, diabetes mellitus, optic atrophy, and deafness. Alström syndrome is a ciliopathy disease characterized by infancy onset obesity and retinal dystrophy. Photophobia and nystagmus in infancy lead to progressive visual loss. Other features include sensorineural deafness, type 2 diabetes (80%), hypertriglyceridaemia, cardiomyopathy (50%), and renal failure. Bardet-Biedl syndrome is a ciliopathy disease characterised by polydactyly, infancy onset obesity and retinal dystrophy. Associated features may include cystic kidneys, renal failure, moderate learning difficulties, bladder problems, and sensorineural deafness.

EURO-WABB CONSORTIUM: Our consortium includes scientific and clinical and patient experts in each of these syndromes and also benefits from input from a wide stakeholder group.

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