ERDERA
European Rare Diseases
Research Alliance

Overview of Rare and Genetic Diseases in Pediatric Patients

Persephone Augoustides-Savvopoulou
Emeritus Professor Medical Faculty Aristotle University of Thessaloniki
President of Panhellenic Advocate for Inherited Metabolic Diseases “KRIKOS ZOIS”

Co-funded by the European Union

ERDERA has received funding from the European Union’s Horizon Europe research and innovation programme under grant agreement N°101156595.
Views and opinions expressed are those of the author(s) only and do not necessarily reflect those of the European Union or any other granting authority, who cannot be held responsible for them.

Content

- Brief introduction to rare diseases
- Challenges on reaching a timely and accurate diagnosis - with case studies
- Therapeutic options
- Take-away messages

What is a rare disease?

- EU: A disease affecting **fewer than 1 in 2,000** people within the general population

- USA: a disease affecting fewer than 200,000 people within the general population

Why are rare diseases important?

1

RARE but MANY!

~7000 RD

36 million people in EU

1 in 17 Europeans during their lifetime

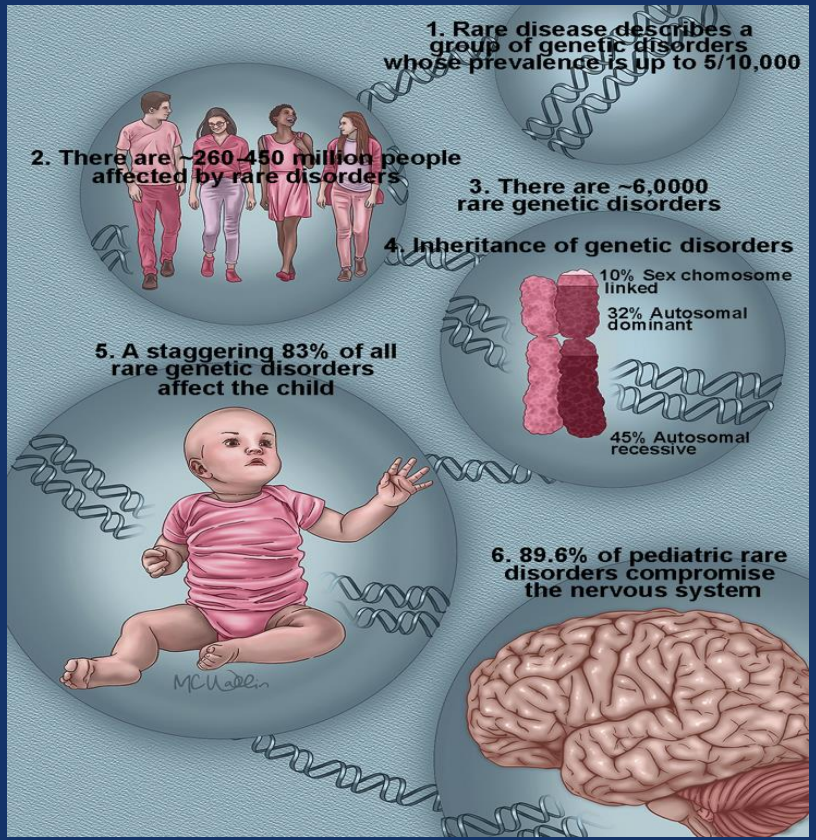
2

UNKNOWN to most – including health professionals

3

INVISIBLE diseases….

90% without therapy



- Globally 260-480 million people affected by a rare disorder
- ~ 6-8000 rare genetic disorders
- 72-80% affect children
- 90 % of pediatric RD affect the nervous system

Rare Genetic Diseases: Nature's Experiments on Human Development
iScience . 2020 May 1;23(5):101123. doi: 10.1016/j.isci.2020.101123

How do you get a rare disease?

- **Chromosomal** disorders
- **Single gene** inheritance disorders
- **Multifactorial** genetic inheritance disorders
- **Mitochondial** genetic inheritance
- De novo mutation

Importance of a timely diagnosis...

- Avoidance of **diagnostic odyssey**
- Enables
  - **timely access to specialized care before irreversible damage**
  - **prevention**

Patient Journey through diagnosis

> *"It's a waiting game, but you tell a mum to wait when she's waited 15 years. It's difficult. – Nuria*

> *"People began to ask which side of the family it came from...It was a difficult time for us as parents. – Alexa*

> *"A diagnosis may be bad news, it may be very bad news or it may be no news. But all of that's OK and there's help and support for whatever spectrum you end up on. – Peter*

> *"We went around, travelling across the entire city to find a nursery for our son. It was impossible to have him accepted. – Gaston*

Information and training for patient organizations

Helplines

Information on secondary findings

Next Steps Toolkit

EUROGENTEST Guidelines

Experience Based Co-Design

RareConnect .org

ENSERIO study. Time to Diagnosis

Undiagnosed Photo Project

Protocol to support ultra-rare diagnosis

Training for professionals

EURORDIS

SolveRD

CHEO

European Patient Advocacy Group

EuroGentest

GLOBAL COMMISSION

UNIAMO

WILHELM FOUNDATION

VSOP

feder

SWAN

UDNI

Prevention : diagnosis enables prenatal diagnosis of future pregnancies

siblings with same metabolic disease….☹

Prevention by neonatal screening..
e.g. phenylketonuria (PKU)

WITHOUT NEONATAL SCREENING ☹

WITH NEONATAL SCREENING ☺

Case studies

All these patients had the same disease….OTC deficiency

- Male 21m old vomiting, somnolence, lethargy
- Adult male 33y old 1st episode of encephalopathy, death
- Adult male aged 27y sibling of above deceased male asymptomatic
- 2 male neonates coma, death
- 2 asymptomatic female siblings of above deceased neonates
- Female 40y encephalopathy, mother of affected male son
- Female 3y episodes of aggressive behaviour, vomiting, coma, death

Case study 1

Proband (index patient):

Male born full-term , pregnancy birth unremarkable, normal development

Healthy parents non-consanguineous

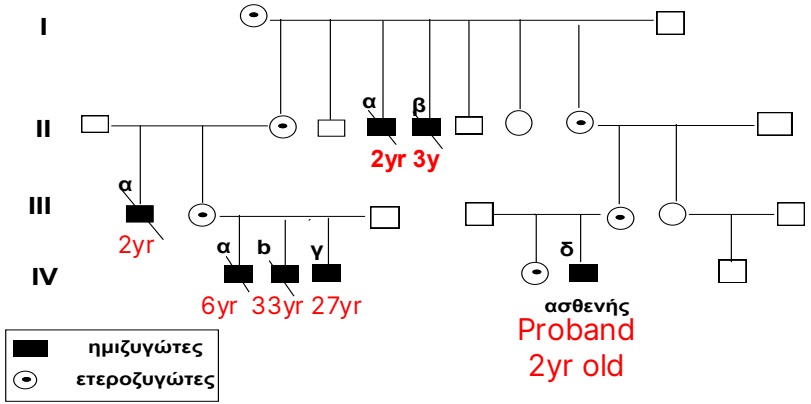
At 21m old episode of vomiting and somnolence after febrile diarrhoea

20 days later, similar episode…

Clinical suspicion for metabolic disease…

PEDIGREE (Family tree) OF PROBAND

X—LINKED PROFILE i.e. Inheritance from the mother



5 DEATHS aged 2-33yrs old - 4 GENERATIONS

Undiagnosed encephalopathy

Initial biochemical tests for a metabolic disorder indicative of a urea cycle disorder

Blood gases pH 7.48 (r.v. .7.35-7.45)

Blood NH4 230 μmol/l (r.v. <35)

Lactate

Urine sugars

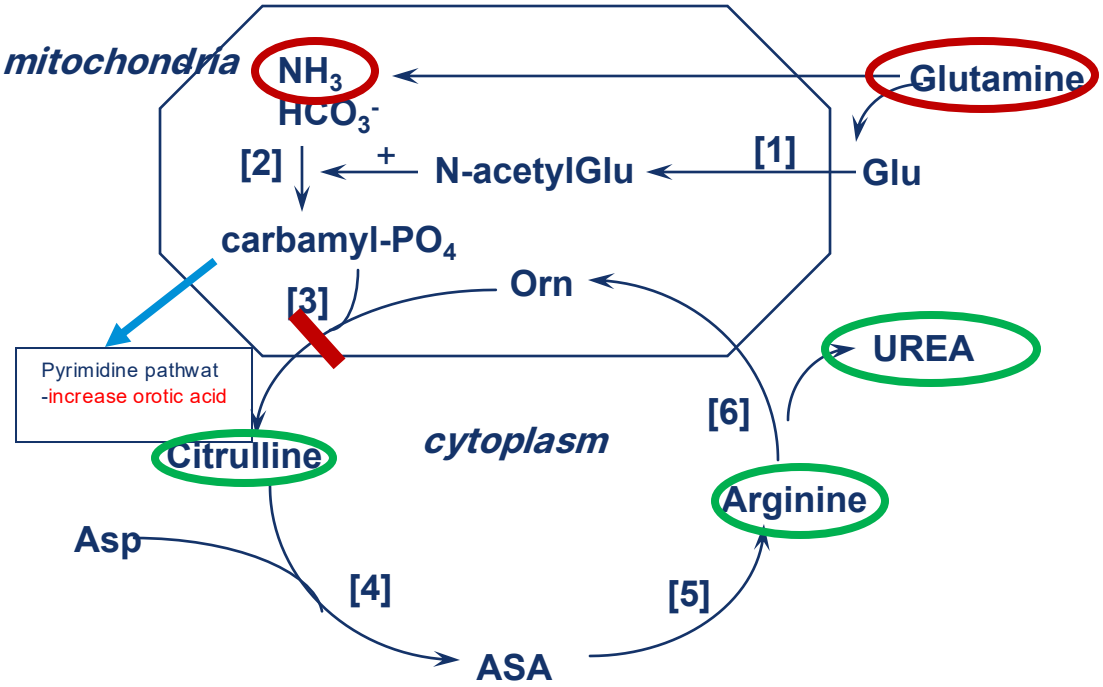
Aminoacids plasma ↑Gln ↑Ala ↓Cit Arg

Organic acids ↑urine orotic acid

Carnitine

Acylcarnitines

SUSPECT METABOLIC PATHWAY - UREA CYCLE



Profile indicative of ***Ornithine transcarbamylase (OTC) deficiency***

Molecular confirmation of diagnosis

M. Tuchman, Biochemical Genetics Lab, Washington University, USA

Isolation of pathogenic mutation in *OTC* gene

Exon 8 codon #: 277, DNA sequence change: CGG to TGG Aminoacid / Frame change: Arg to Trp *Restriction site: Ital $ Fnu4Ht*

Late-onset OTC deficiency

Investigation of high – risk family members…

Hemizygote OTC :The *asymptomatic* affected adult cousin of proband (with 2 deceased siblings)

OTC heterozygote (carriers) :the female sibling and aunt (mother of 2 deceased cousins of proband)

Management and evolution..

Diet decreased protein intake + arginine/citrulline

Specific protocol for metabolic episodes

Proband now 30y old with University degree + post graduate diploma

Hemizygotel male cousin married with a healthy male offspring

Lessons learnt…..

Clinical suspicion: encephalopathy with **episodes** of vomiting, somnolence, behavioural disorders, coma …

Thorough family history

Investigation of high-risk family members **irrespective of age, even if asymptomatic!**

All these patients had the same disease….
Lysinuric protein intolerance -LPI

- **Soldier 23 yrs old** - *psychotic episodes-epilepsy…*
His older male **sibling** 27 yrs old –*episodes of vomiting, lethargy, seizures* ***frequent comas….***

- **Male 8 yrs**. Vomiting, lethargy…
His **asymptomatic** male **sibling** aged 10 yrs…

- **Female 6.5 yrs** – delayed somatic development, osteroporosis, pulmonary proteinosis, ***multiorgan failure, death….***

Case study 2..

Soldier 23yrs –2nd offspring of **consanguineous** parents (2nd cousins)

From 16yr old "behavioural problems" **accentuated during traditional holidays** (XMAS, Easter…)

During his military service psychotic episodes, paranoic hallucinations, stereotypic movements, stupor, astyrixia a.o.)

Persistent seizures - **status epilepticus..**

Symptoms linked to high protein meals!

Clinical suspicion for a metabolic disorder..

Clinical examination...

- **somatotype: thin with short stature (1.50m), bespectacled**

-**moderate hepatosplenomegaly** (abdominal MRI increased liver and spleen dimensions,
7 focal liver lesions possible hemangiomata)

- X-ray chest, bones, cardiac ECHO, brain MRI : normal findings

Opthalmological assessment : bilateral punctate lens opacities. chorioretinal atrophy vascular stenosis in fundus

Biochemical Metabolic profile indicative of **Lysinuric protein intolerance (LPI)**

	Plasma (μmol/l)	Urine (μmol/mmol cr)
NH_4^+	155 (τ.α <35)	-
Gln	1853 (τ.α.335-745)	624 (τ.α.20-76)
Gly	422 (τ.α.152-362)	1186 (τ.α.43-173)
Ala	650 (τ.α.152-362)	409 (τ.α.16-68)
Lys	91 (τ.α..36-269)	2176 (τ.α.7-58)
Orn	30 (τ.α.38-101)	53 (τ.α.0-5)
Arg	12 (τ.α.37-141)	21 (τ.α.0-5)
Orotic acid	-	+++

Molecular investigation of SLC7A7 gene

Generosa Andria University of Naples

SSCP screen negative - 20-25% false negative

Further investigation of SLC7A7…

2 novel mutations – double heterozygosity

804C T (Thr188Ile) - **mother**

1612 A (Tyr457Stop) - **father**

LPI diagnosis confirmed ! ☺

Management and evolution..

Diet: decreased protein intake + arginine/citrulline

Specific protocol for metabolic episodes

Significant improvement

Follow up problematic because of geographical distance and finally lost to follow-up...

Investigation of male sibling 27y….

- **Significant differences** with the proband: Mentally retarded male, tall stature (1.80μ), barrel chest and thin extremities
- **From age 7y** episodes of vomiting, abdominal pain, headaches, drowsiness and frequent comas
- Clinical suspicion for a metabolic disorder **8 years later**….(!)

At age 15y diagnosed as **"hyperammonemia of unknown etiology'**

- Treated with low protein diet and sodium benzoate

Diagnosis of older sibling…..lysinuric protein intolerance

- **Aminoacid profile indicative of LPI**
- **Molecular confirmation of diagnosis of LPI :**
  Isolation of identical family mutations of *SLC7A7 gene*

Lessons learnt…

- LPI can manifest with behavioural disturbances with psychotic phenomena– red flag for psychiatrists!

- Symptoms resemble urea cycle defect but with complicated phenotype due to macrophage activation (**multisystemic disease with potential complications from any system - lungs, kidneys. liver. Immune system**..)

  - Thorough clinical history **particularly dietary habits !**

  - Clinical heterogeneity in the same family

  Clinical and laboratory follow up of factors indicative of macrophage activation ..... (ferritin, LDH,platelets,aminotransferases,hypoalbuminemia , fibrinogen.,proteinuria, cytopenia, coagulation, immunological assessment..a.o..)

  Intraspecialty collaboration .....

KRIKOS ZOIS "Think Ammonia" webinar to increase awareness of potentially lethal hyperammonemia syndromes
https://www.livemedia.com/krikoszoisammonia

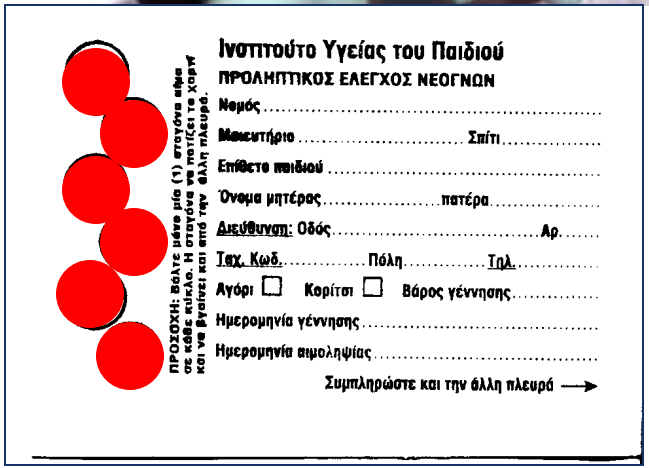
DIAGNOSIS of rare genetic pediatric diseases

- **Selective screening** based on clinical findings (caveat…can lead to diagnostic odyssey with misdiagnosis…..)
- **Genetic screening of patients**
- **Newborn screening**

Newborn screening:
revolution in presymptomatic diagnosis

1962 NEWBORN SCREENING for PKU - one metabolite one test

Robert Guthrie pioneer of NBS
'Guthrie test' for phenylketonuria (PKU)(1962)



Ινστιτούτο Υγείας του Παιδιού
ΠΡΟΛΗΠΤΙΚΟΣ ΕΛΕΓΧΟΣ ΝΕΟΓΝΩΝ

Νομός .....

Μαιευτήριο ..... Σπίτι .....

Επίθετο παιδιού .....

Όνομα μητέρας ..... πατέρα .....

Διεύθυνση: Οδός ..... Αρ. .....

Ταχ. Κωδ. ..... Πόλη ..... Τηλ. .....

Αγόρι ☐ Κορίτσι ☐ Βάρος γέννησης .....

Ημερομηνία γέννησης .....

Ημερομηνία αιμοληψίας .....

Συμπληρώστε και την άλλη πλευρά →

ΠΡΟΣΟΧΗ: Βάλτε μόνο μία (1) σταγόνα αίμα σε κάθε κύκλο. Η σταγόνα να πατίζει το χαρτί και να βγαίνει και από την άλλη πλευρά.

NEWBORN SCREENING (NBS) TODAY

- **Expanded national NBS programs screen for about 50 diseases using blood tests based on metabolic biochemical markers** of diseases

- **Genetic screening** **(**next generation sequencing or whole genomic screening)

Expanded NBS

Are more diseases better?

- Criteria
- Ambivalent biochemical findings
- False positive and false negative findings
- Quality of NBS centers
- Availability of therapeutic intervention and follow-up

EURORDIS AND NBS…..

Newborn Screening programmes should include ACTIONABLE diseases ….

Genetic NBS –potential issues.....

- Data storage
- Access to the information
- Ownership until the children reach adulthood

THERAPEUTIC OPTIONS FOR RARE DISEASES….

About 90% without therapy…

but…with more than **1,400 different genetic metabolic diseases** affecting a variety of biochemical pathways, **the field of metabolic diseases represents a dynamic and expanding field** of genetic research for which an **increasing number of treatments have become available**

600 metabolic epilepsies - 37% inherited metabolic disorders

- In total, 111 metabolic epilepsies (18% of all) have specific treatments that may significantly change health outcomes if diagnosed in time.

- Genes (Basel). 2022 Mar; 13(3): 5082022 Overview of Metabolic Epilepsies doi: 10.3390/genes13030508 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6286965/
- Front Neurol. 2018; 9: 1016. Metabolic Evaluation of Epilepsy: A Diagnostic Algorithm With Focus on Treatable Conditions doi: 10.3389/fneur.2018.01016 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8952328/

Potentially treatable inborn errors of metabolism causing intellectual disability (ID)

Genetic etiologies constitute the most frequent cause and are demonstrable in more than 50% of individuals with ID

- **81 metabolic diseases with intellectual disability as major clinical feature**. (aminoacids, organic acids, vitamins/co-factors, cholesterol & bile acids, ,glucose transport and regulation, hyperhomocystenemias, lysosomes, mitochondria, peroxisomes,urea cycle, neurotransmission, pyrimidines, metals, fatty aldehydes)

- **Metabolic screening tests reliably provide clues** for diagnosis for **62% (50/81) of all treatable IDs.**

For the remaining 31 treatable IDs (38%), a specific 'one test per one disease' approach is required

Through a **multidisciplinary approach and expertise in IMDs the diagnostic yield in individuals with ID exceeded 10%,** standing in sharp contrast to frequently quoted yields of **0.5%.**

Equal access to better care: ERNs..

European Reference Networks

- **Virtual networks** involving Reference Centres across Europe
- **Objective: to tackle complex and rare patient cases**
- **Instead of patients travelling medical knowledge and expertise travel !**

European Reference Networks

ERN EURO-NMD	ERN BOND
ERN EYE	ERN CRANIO
ERN GENTURIS	Endo-ERN
ERN GUARD-HEART	ERN EpiCARE
ERN ITHACA	ERKNet
MetabERN	ERN-RND
ERN PaedCan	ERNICA
ERN RARE-LIVER	ERN LUNG
ERN ReCONNET	ERN Skin
ERN RITA	ERN EURACAN
ERN TRANSPLANT-CHILD	ERN EuroBloodNet
VASCERN	ERN eUROGEN

1500 ERNs in 27 EU countries+Norway

European Reference Network

MetabERN

European Reference Network
for Hereditary Metabolic Disorders

The most comprehensive network of specialised centres on inherited metabolic rare diseases

metab.ern-net.eu

Cross-border health care

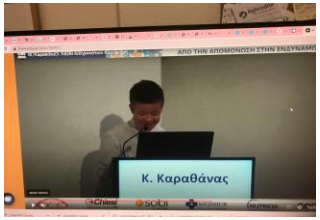
European Reference Networks

- **EU citizens have the right to access healthcare in any EU country and to be reimbursed for care abroad by their home country**
- Information: Directive 2011/24/EU

CONTINUING EDUCATION.....

KIDSBari

TEDDY NETWORK
European Network of Excellence for Paediatric Research



https://www.cvbf.net/ypag-kids-bari/

Project: **Second paediatric expert patients training workshop (in person) Date: 11 – 15 July 2022** Location: **Université de Lyon**, 8, Avenue Rockefeller 69008 Lyon, France

Grateful to the iCAN crew for the amazing opportunity! ✨
We have **learned a lot about Rare Diseases, their scientific aspects, ethics, research, and innovation**.🫁
Through the highly interactive sessions, we have shared many **ideas to improve pediatric clinical research.**
We learned about Animation and Storytelling, worked on the conception and development of a serious game, and **reviewed paediatric clinical trial materials** to provide suggestions to make them more useful and comprehensible. 👨‍⚕️ 👩‍⚕️

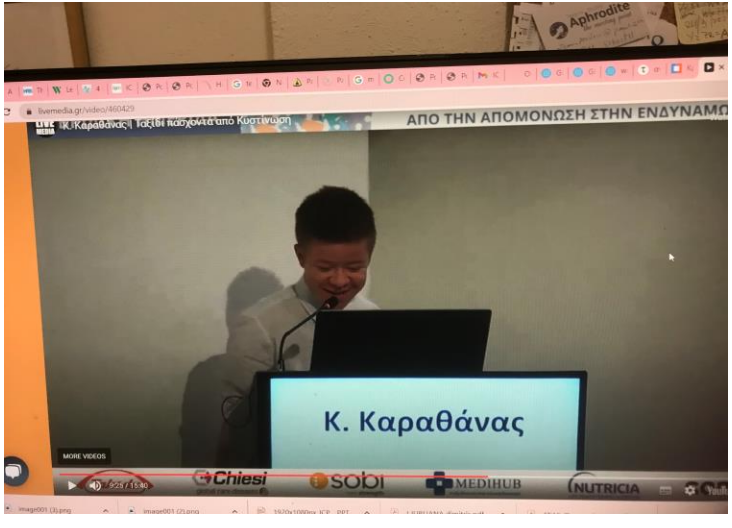
Patient Engagement…..

FROM
FOR THE PATIENT……

TO
WITH THE PATIENT


ΥΒΡΙΔΙΚΗ ΗΜΕΡΙΔΑ
Α. Κατσώρας
ΥΒΡΙΔΙΚΗ ΗΜΕΡΙΔΑ
ΚΛΗΡΟΝΟΜΙΚΑ ΜΕΤΑΒΟΛΙΚΑ ΝΟΣΗΜΑΤΑ
ΑΠΟ ΤΗΝ ΑΠΟΜΟΝΩΣΗ ΣΤΗΝ ΕΝΔΥΝΑΜΩΣΗ
Σάββατο 4 Ιουνίου 2022
Photopress©Yannis Tsouflidis


ΦΑΚΕΛΟΣ ΑΣΦΑΛΙΣΗΣ ΥΓΕΙΑΣ
Επόμενη Μέρα
Γ. Αγγούρης
Photopress©Yannis Tsouflidis


ΑΠΟ ΤΗΝ ΑΠΟΜΟΝΩΣΗ ΣΤΗΝ ΕΝΔΥΝΑΜ
Κ. Καραθάνας
Chiesi
sobi
MEDIHUB
NUTRICIA


Ε. Κυπραίου-Μπούτλα
ΥΒΡΙΔΙΚΗ ΗΜΕΡΙΔΑ
ΚΛΗΡΟΝΟΜΙΚΑ ΜΕΤΑΒΟΛΙΚΑ ΝΟΣΗΜΑΤΑ
ΑΠΟ ΤΗΝ ΑΠΟΜΟΝΩΣΗ ΣΤΗΝ ΕΝΔΥΝΑΜΩΣΗ
Σάββατο 4 Ιουνίου 2022
ΚΡΙΚΟΣ
Photopress©Yannis Tsouflidis


Photopress©Yannis Tsouflidis

Engagement of parents for efficient therapy of metabolic diseases

https://www.youtube.com/watch?v=BPmFBKWBHJM

The Charlie Foundation for Ketogenic therapies and Matthew's Friends..

united LEUKODYSTROPHY FOUNDATION

The Ryan Foundation

Charlie FOUNDATION

[redacted]

Key players in the rare disease cause…

- **Patients and their families/caregivers**
- **Patient advocacy groups**
- Clinicians/investigators
- Academia/ principal investigators
- Biopharmaceutical industry
- Government/policy makers

Collaboration the key to success!

Take-away messages……Needs.

- Ensure patients get the **right diagnosis faster**
- Increase **awareness of rare diseases and training of healthcare professionals**
- **Improve access** to specialist care, treatments and drugs.with **better coordination** of care
- Standardization of NBS screening policies and genetic screening i**n national health care systems.**
- More **genetic counsellors**
- **Integration and expansion of ERNs** into European health care and social systems and facilitated access to cross-border health care
- **Intraoperable patient registries with geographical mapping of patients** with rare diseases
- **Engagement, of young patients** in decision making
- Information sharing and community provision for everyday supportive care for patients and family members to make the **everyday challenges more visible**
- **Support of patient groups !!**

AND….. AND……☺

Our Vision.....

Increased empowerment of the rare disease patient community with key role of YPA for **science-driven** legislation and policy that advances the **unbiased development** of and **access to lifesaving diagnoses, treatments, and cures!**

ERDERA

European **Rare Diseases** Research Alliance

Thank you!

PANHELLENIC ADVOCATE FOR KRIKOS ZOIS INHERITED METABOLIC DISEASES

www.krikoszois.gr

Co-funded by the European Union

ERDERA has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement N°101156595.
Views and opinions expressed are those of the author(s) only and do not necessarily reflect those of the European Union or any other granting authority, who cannot be held responsible for them.