



***INFORMED CONSENT FOR CHILDREN AND
TEENAGERS TURNING ADULTS IN RARE
DISEASE REGISTRIES: A CLINICAL POINT
OF VIEW***

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I receive research grants from Actelion, Biomarin, Genzyme, SHIRE HGT, To-BBB

WHAT IS BRAINS FOR BRAIN?

*BRAINS FOR BRAIN IS A GROUP OF
OUTSTANDING SCIENTISTS AND CLINICIANS*

*WORKING TOGETHER WITH BIOTECH COMPANIES
TO STIMULATE AND COLLABORATE RESEARCH*

*ON PEDIATRIC NEURODEGENERATIVE
DISORDERS IN PARTICULAR LYSOSOMAL
STORAGE DISEASES.*



9TH International Symposium on Mucopolysaccharide and Related Diseases

9° Simposio Internazionale sulle Mucopolisaccaridosi e Malattie Affini
29 giugno - 2 luglio, 2006



Together for a
better life
Insieme per una
vita migliore

June 29 - July 2
2006

Venezia Lido
Italy
Congress Center



*THE IDEA WAS PROPOSED IN
VENICE, ITALY, ON JUNE 2006
DURING THE BIENNIAL
INTERNATIONAL SYMPOSIUM
ON MUCOPOLYSACCHARIDE
AND RELATED DISEASES.*

*IN VENICE ABOUT 1000
SCIENTISTS, PHYSICIANS
AND FAMILIES MET
TOGETHER TO UPDATE AND
DISCUSS ABOUT LYSOSOMAL
STORAGE DISORDERS AND
THEIR PROBLEMS.*

WHERE FROM AND WHEN?



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THERE ARE >50 LYSOSOMAL STORAGE DISEASES (LSDs) WHICH RESULT FROM A FUNCTIONAL DEFECT IN A LYSOSOMAL HYDROLYTIC ENZYME OR MEMBRANE TRANSPORT ENZYME

APPROXIMATELY ONE HALF OF THESE LSDs HAVE ASSOCIATED NEUROPATHY WHICH IS PROGRESSIVE

1 CHILD EVERY 5000 IS AFFECTED BY LSD.

IN ORDER TO TREAT THE NEUROLOGICAL DISEASE TREATMENTS MUST CROSS THE BLOOD-BRAIN BARRIER (BBB)

DURING THE MEETING A SPECIFIC WORKSHOP ON BBB WAS PROPOSED FOR THE FIRST TIME.

HIGH INTEREST WAS RAISED ON THE TOPIC AND ABOUT THE NEED TO CONTINUE TO DISCUSS.





ACTELION

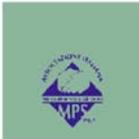
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BIOMARIN™

*THE MAJOR SPONSORS OF THE 9th
INTERNATIONAL SYMPOSIUM AGREED
IN SUPPORTING THE NEW RESEARCH
GROUP.*

Shire
Human Genetic Therapies

genzyme



BRAINS FOR BRAIN MEMBERS

85 SCIENTISTS AND CLINICIANS

11 DIRECTORS FROM BIOTECH COMPANIES

EUROPEAN COUNTRIES

DENMARK

FRANCE

GERMANY

GREECE

ISRAEL

ITALY

RUSSIA

SPAIN

THE NETHERLANDS

UNITED KINGDOM,

AUSTRIA,

EIRE

NON EUROPEAN COUNTRIES: AUSTRALIA, BRASIL, USA

FAMILY ASSOCIATIONS AND ORGANISATIONS

EUROPEAN BRAIN COUNCIL, ORPHANET, ESGLD,



MISSION OF BRAINS FOR BRAIN

- 1) **TO CATALYSE RESEARCH IN THE FIELD OF NEURODEGENERATION AND LYSOSOMAL DISEASES.**
- 2) **TO ORGANISE EFFORTS FOR THE COMPREHENSION OF THE PATHOPHYSIOLOGY PROCESSES OF NEUROLOGICAL DISORDERS IN LSD.**
- 3) **TO ORGANIZE STUDIES FOR THE IMPLEMENTATION OF KNOWLEDGE OF BLOOD BRAIN BARRIER FUNCTION**
- 4) **TO PROMOTE THE DEVELOPMENT OF NEW STRATEGIES TO OVERCOME THE BLOOD BRAIN BARRIER AND TREAT NEUROLOGICAL DISORDERS.**
- 5) **TO DEVELOP NEW APPROACHES FOR THERAPY OF THE NEUROLOGICAL COMPLICATIONS OF LSDS PATIENTS.**
- 6) **TO COLLABORATE WITH BIOTECH COMPANIES, FAMILY ASSOCIATIONS AND ORGANISATIONS SUCH AS ESGLD AND THE EUROPEAN BRAIN COUNCIL TO DISSEMINATE KNOWLEDGE ON AND LOBBYING FOR NEURODEGENERATIVE PAEDIATRIC DISORDERS**



RARE NEUROLOGICAL DISEASES OF CHILDHOOD:

"WE TREAT THE CHILD TO TREAT THE ADULT"



2 December 2010, 11:00–13:30

European Parliament, Room J6Q1
Brussels, Belgium

**MEETING ORGANIZED AT THE
EUROPEAN PARLIAMENT IN
BRUXELLES, BE, IN
COLLABORATION WITH THE
EUROPEAN BRAIN COUNCIL,
THE VENETO REGION, THE
LYSOSOMAL STORAGE
PATIENT COLLABORATIVE AND
BIOTECH COMPANIES**



THE LYSOSOME

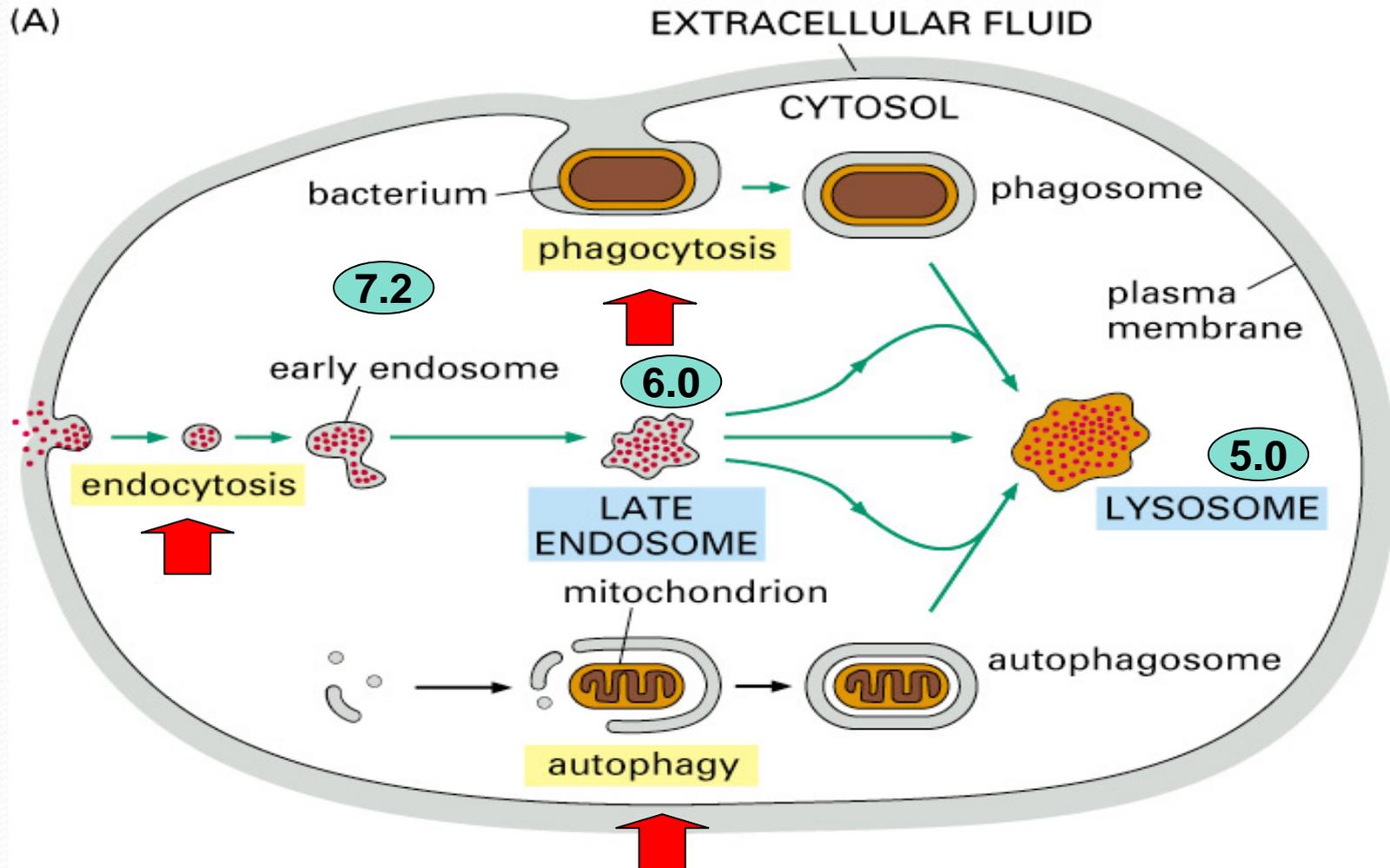


Figure 13-35 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

LYSOSOMAL DISEASES

- **Glycogenosis**
- **Glicolipidosis**
- **Mucopolysaccharidosis**
- **Oligosaccharidosis**
- **Disorders of lysosomal enzyme transporters**
- **Disorders from lysosomal membrane transporter.**

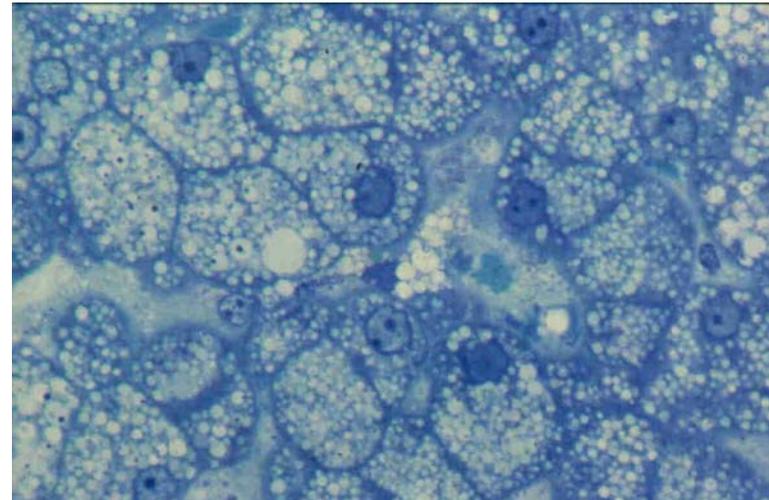
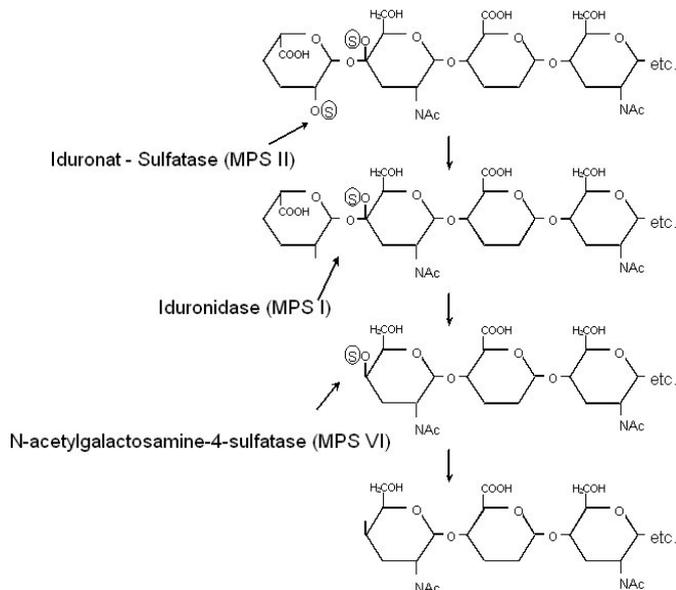
>50 DIFFERENT DISEASES

ALL TOGETHER 1:5-7000 NEWBORNS

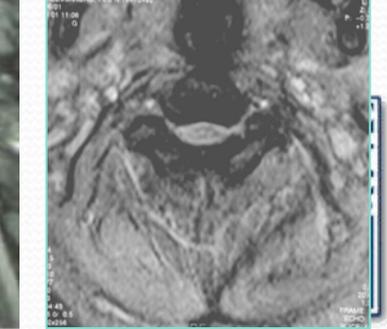
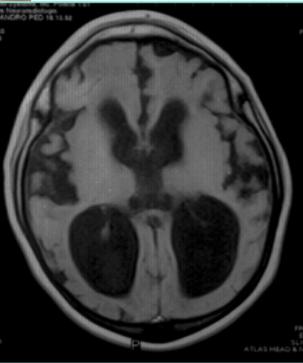
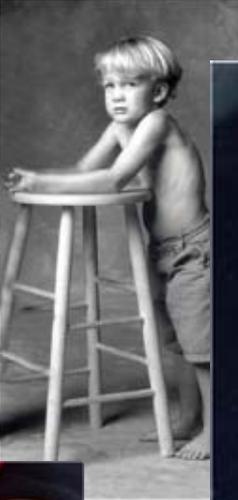
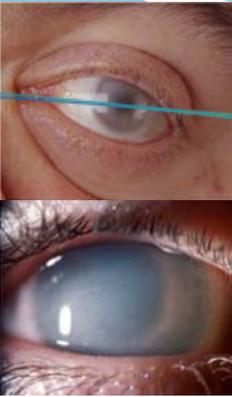


CLINICAL FEATURES

- FACIAL DYSMORPHISMS
- HYDROCEPHALUS
- DEVELOPMENTAL DELAY
- DEAFNESS
- MENTAL RETARDATION
- CORNEAL CLOUDING
- SKELETAL DYSPLASIA
- LUNG FAILURE
- HEART FAILURE
- HEPATOSPLENOMEGALY
- JOINT STIFFNESS



70% OF THE PATIENTS ARE AFFECTED BY CNS INVOLVEMENT



WHY LSDs ARE SO INTERESTING TO STUDY

- MONOGENIC DISORDERS
- ALL DISEASES ARE FULLY CHARACTERISED AT THE MOLECULAR AND BIOCHEMICAL LEVELS
- AUTOSOMIC DISORDERS, WITH EXCEPTION OF MPSII, FABRY D. AND BATTON D.
- MULTIORGAN DISORDERS
- DIFFERENT GRADE OF SEVERITY
- DIFFERENT PHENOTYPES (NEWBORN, INFANTILE, LATE INFANTILE, LATE ONSET)
- 70% INVOLVE CNS
- USEFUL TO UNDERSTAND ADULT DISEASES: GAUCHER-PARKINSON D.
- PLENTY OF ANIMAL MODEL, NATURAL AND KNOCK OUT OR TRANSGENIC
- DIFFERENT THERAPEUTIC APPROACHES (BMT, ERT, GT, CHAPERON, STOP CODON RT ETC,)
- BIOTECH COMPANIES ARE NOW INTERESTED: TRANSLATIONAL MEDICINE



DISEASE PROGRESSION



SEVERE (MPSI H)



- Early onset of symptoms
- Severe debilitation during first decade
- Early death

INTERMEDIATE (MPSI H/S)

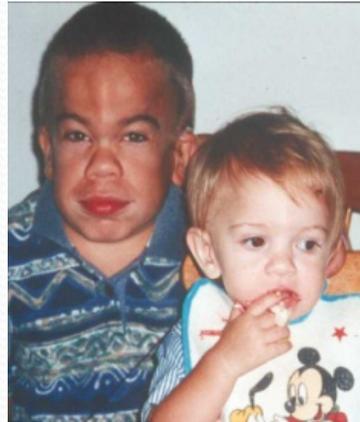
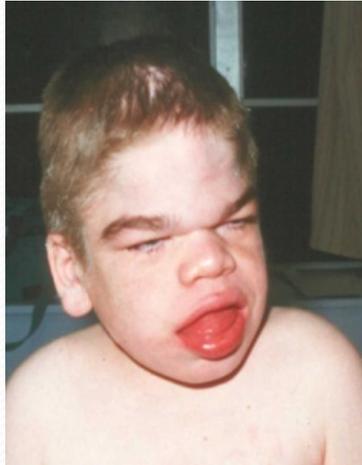


- Later onset of symptoms
- Debilitating symptoms occur later
- Survival into adulthood
- Not a mild disease, just attenuated

ATTENUATED (MPSI S)

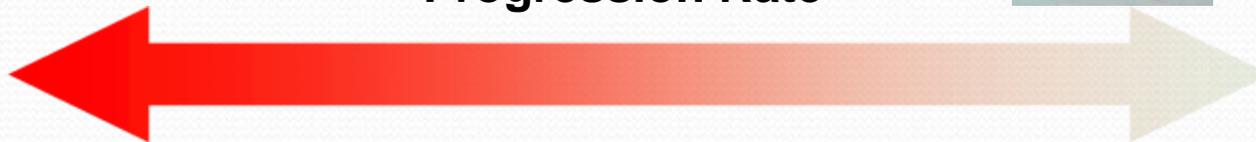


SPECTRUM OF DISEASE PROGRESSION



MPS II

Progression Rate



- Early onset of symptoms
- Severe debilitation during first decade
- Early death

- Later onset of symptoms
- Debilitating symptoms occur later
- Survival into adulthood
- **Not a mild disease, just attenuated**

SPECTRUM OF DISEASE PROGRESSION

MPS VI



Photos (right) courtesy of The National MPS Society Inc.

**Rapidly
Advancing**

Progression Rate

**Slowly
Advancing**

- Early onset of symptoms
- Severe debilitation during first decade
- Early death

- Later onset of symptoms
- Debilitating symptoms occur later
- Survival into adulthood
- **Not a mild disease**



TREATMENT OPTIONS FOR MPS

HSCT

	<u>Somatic*</u>	<u>CNS*</u>
MPS I	Yes	Yes
MPS II	Yes	No
MPS IIIA		No
MPS IIIB		No
MPS IV	No	
MPS VI	Yes	
MPS VII	?	?

*Proven clinical benefit

ERT

Available

Yes

Yes

clinical trial
ongoing

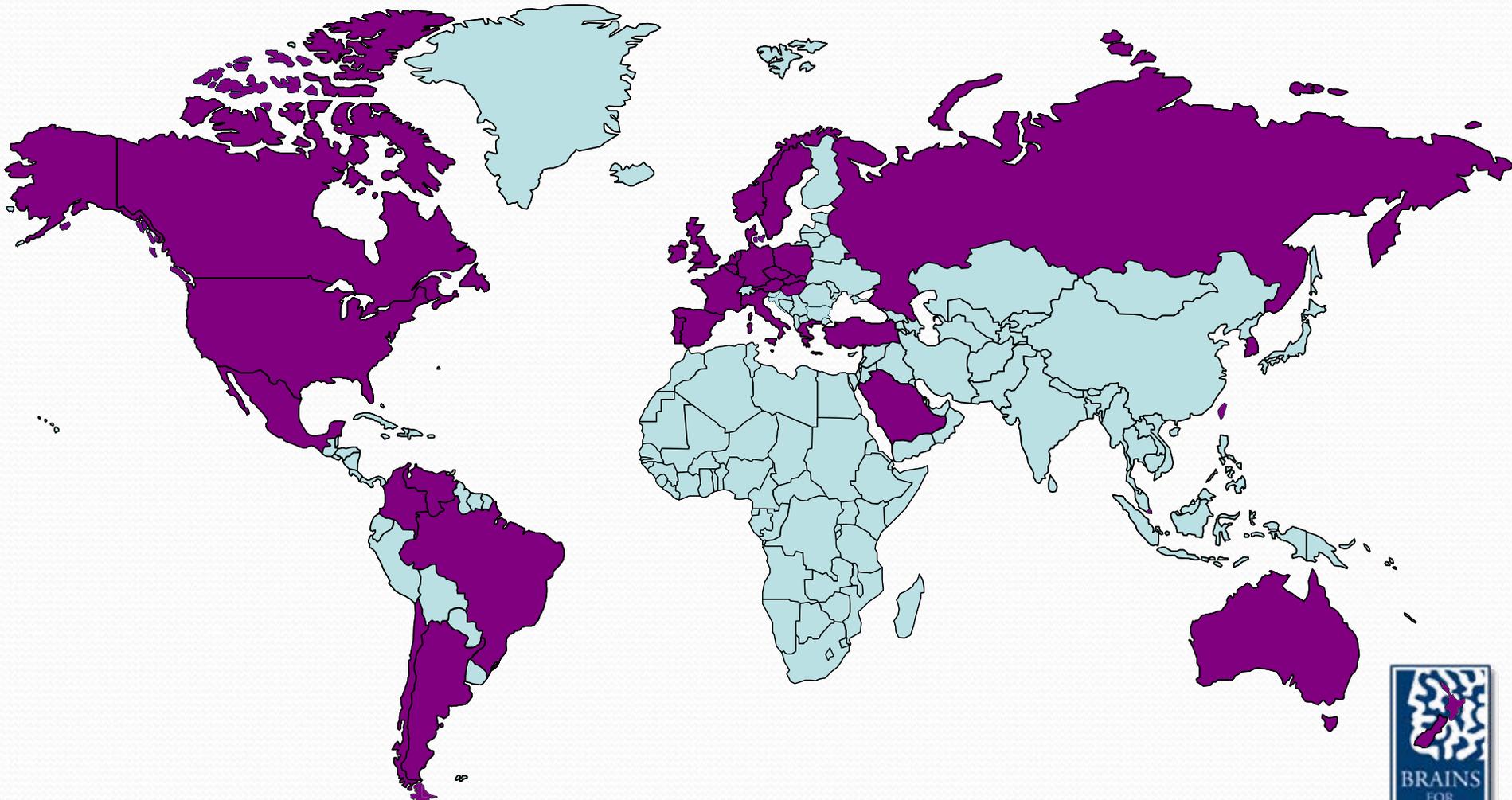
No

clinical trial
ongoing

Yes

No

923 Patients Globally, 33 countries



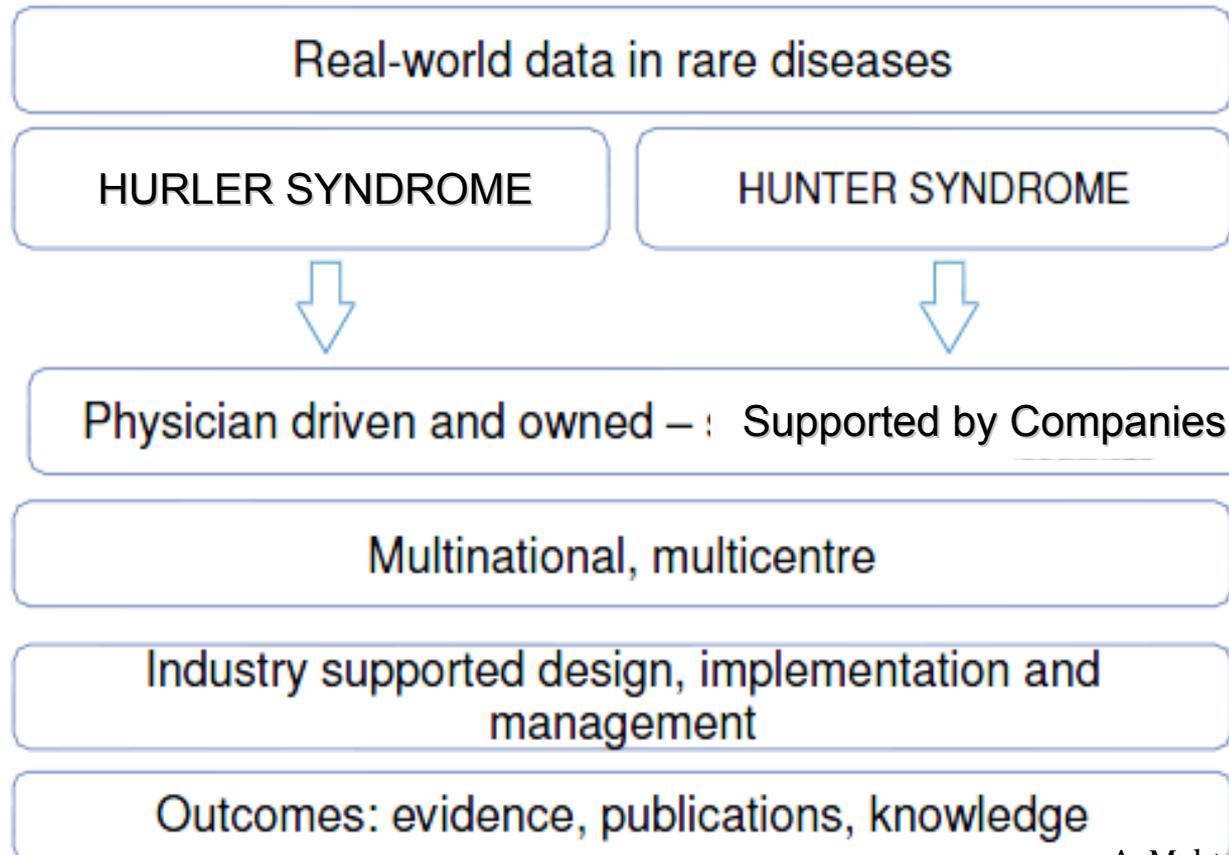
MPS I Registry data June 2010



Governance Issues

- Absolute need for independence from industry; scientific/clinical panel, statistical analyses
- Informed consent – important but difficult concept
- Multiple registries duplicate effort

Governance of registries – A clinician/academic's viewpoint



The need for real-world data

➡ ...a need to understand treatment effectiveness and long-term safety¹

➡ ...a need to understand factors that are not normally accounted for within RCTs,^{1,2} e.g.

Compliance
Patient management
Varied patient populations

➡ ...a need for clear evidence-based assessments of treatment value¹

1. Annemans, L *et al.* *ISPOR Connections*. October 15th 2007; 8-12 .
2. Gutiérrez LP, *et al.* *Pharmacoepidemiol Drug Saf.* 2007; 17: 90-102.

The value of real-world data

- What are the advantages of real-world observational studies?

Large sample size

- Increases the probability of detecting uncommon adverse events
- Allows for sub-set analyses
- Provides generalizable evidence

Longitudinal data

- To track the natural history of the disease over time
- To track the long-term effectiveness and safety of treatments
- To perform time-to-event analysis

Reflects real-world clinical decision making

Generate new hypotheses for further investigation

Essential information source for rare diseases

Outcome Surveys objectives

- To improve patient care and patient outcomes in rare diseases
 - Understand the long-term effectiveness and safety of treatments
 - Enhance understanding of the natural history of rare diseases
 - Provide high-quality data and analysis to support clinical decision making

What are the disadvantages of Outcome surveys ?

- Treatment criteria are not uniform – potential for selection bias
- May not have complete data/follow-up; particularly for patients who stop/change treatment
- May not have a control population
- Potential for data to be used for marketing
- Potential for industry influence on analytic methods
- Patients seen in diverse centres/countries

Clinical trials vs. Outcome Surveys

Randomized Controlled Trials (RCTs)

- Small group of patients
- Small number of treatment centres
- Rigid visit and dosing schedule
- Restricted concurrent treatments and comorbidities
- Treatments used as intended
- Comparatively short time-frame
- Provide evidence of the *efficacy* of treatments in a highly controlled environment to reduce bias

Outcome Surveys

- Large, varied group of patients
- Many treatment centres (multinational)
- Visit and dosing schedule as per normal clinical care
- No restrictions on concurrent treatments and comorbidities
- Treatments used as per normal clinical care
- Extended time-frame
- Provide evidence of the *effectiveness* of treatments in the real-world

Treatments in the real-world are not used in the controlled environment of a RCT

Data collection

- Approval by Ethics Committee / Institutional Review Board
- Patient consent – more difficult than it sounds
- Data collected anonymously – but must avoid duplicate records on same patient
- Documentation of patient demographics and medical history
 - Year of diagnosis
 - Signs and symptoms
 - Previous treatment
 - Comorbidities
- Prospective, serial collection of data of lab test results, examinations, investigations, treatments and patient-reported outcomes

- HOW DO WE EXPLAIN ALL OF THIS TO THE PATIENTS OR, BETTER, TO THE FAMILY?
- DO WE EXPLAIN ALL THESE INFORMATIONS TO PATIENTS AND/OR FAMILIES?
- ARE THEY REALLY INTERESTED TO THIS COLLECTION OF DATA?
- IS THERE A COMMON AWARENESS IN PATIENTS AND THEIR FAMILIES ON THE NEED OF DEVELOPING A SYSTEM TO GATHER AND INTEGRATE DATA?

- DO WE NEED TO INFORM PATIENTS AND FAMILIES ON THE DEVELOPMENT OF THESE REGISTRIES AND ABOUT THEIR OUTCOME?
- DO WE DO THIS?

WE MUST DO IT



ITALIAN LAWS

- Art. 13 of the Constitution rules the right the inviolability of the person and his/her freedom, and therefore to the inviolability of person's body inside the national laws;
- Art. 2 of the Civil Code rules that only after 18 y of age the person is able to state a valid consent;
- art. 316 (Parental permission) and art. 343 (guardian/ judge) of the Civil Code rules that up to 18 y of age, the consent can be given by parents or by a recognised tutor of by judge tutoring the minor patient

THE CONSENT PROCESS

**Informed consent is not a single event or just a form to be signed -
- rather, it is an educational process that takes place between
the investigator and the prospective subject.**

The basic elements of the consent process include:

- full disclosure of the nature of the research and the subject's participation,
- adequate comprehension on the part of the potential subjects, and
- the subject's voluntary choice to participate.



PROCEDURES TO OBTAIN CONSENT

- Subject has the legal and mental capacity to give consent
 - legally authorized representative;
- Sufficient opportunity is provided to consider
- The possibility of coercion or undue influence is minimized
- Language understandable to the subject
- No “exculpatory” language



DOCUMENTATION OF CONSENT

Documentation of "legally effective informed consent" usually involves the use of a written consent form signed by the subject or the subject's legal representative.

- The consent form is merely the documentation of informed consent and does not, in and of itself, constitute informed consent.
- The fact that a subject signed a consent form does not mean that he/she understood what was being agreed to or truly gave their voluntary consent. (Spertus Study)

CONTENT OF INFORMED CONSENT FORMS IN LSD REGISTRIES

Information to subjects should include explanation of:

- Type of research and purpose of trial
- Treatments and trial/CSP procedure
- Treatment of genetic informations:
 - Importance of genotype information
 - No discrimination
 - Consent can be withdrawn at any time also to only genetic data
- Explanation of all the tests performed and listed in the registry
- Subjects responsibilities
- Risk and expected benefits
- Payment and expected expenses
- Participation is voluntary –withdrawal at any time w/o penalty
- Access to medical records for SDV purposes
- Confidentiality is maintained

REQUIREMENTS INFORMED CONSENT FORM

Information to subjects should include explanation of.

- Patient ID number
 - Code known only by the responsible physician
- Importance of the database collection
 - Who might have access to data: physician, CRO, Company monitor, statisticians, NIHS, etc.
- Use of integrated data for publication purposes
- Identification of siblings and link data to siblings (another consent)
- Consent to gather data into CRF or web software-password
 - Risk of access by third parties on web
- Patients/guardians can ask any information regarding:
 - How data are kept,
 - Origin of the data,
 - Correction or modifications of data
 - No correction can be done on clinical-generated data
- Participation is voluntary –withdrawal at any time w/o penalty
 - If withdrawn participation, registry can use the data up to the withdrawal.

REQUIREMENTS INFORMED CONSENT FORM

Information to subjects should include explanation of:

- Subject will be informed in timely manner if new information becomes available that may be relevant to willingness to participate in trial
- Person(s) to contact for further information regarding the trial
- Foreseeable circumstances under which subject's participation in the trial might be terminated
- Expected duration of participation in the trial
- Approximate number of subjects involved in the trial



VULNERABLE POPULATIONS



VULNERABLE POPULATIONS

- Federal regulations involving human subjects in research include specific protections for pregnant women and fetuses, and children.
- In addition, the IRB expects the investigator to provide additional information regarding cognitively impaired individuals in research or others who are likely to be vulnerable to coercion or undue influence.

CHILDREN

Definition:

- "Children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

CHILDREN

Parental Permission:

- Adequate provisions are to be made to secure permission from the parents or guardians of each child.
 - For minimal risk research or risk research with direct benefit, the **IRB may allow** permission from one parent.
 - For risk research without direct benefit, permission from both parents is required.

RESPECT FOR CHILDREN

- Declaration of Helsinki (2000)
 - Obtain informed consent from parent (§24)
 - If child capable, obtain assent (§25)
- The National Commission (1977, 1979)
 - Parental Permission (but within limits)
 - ✓ Protect child's health and safety
 - Child Assent (not as a right, but a benefit)
 - ✓ Nurture child's moral growth and developing autonomy

ROYAL COLLEGE OF PHYSICIANS

Age > 7 years

Acquisition of the
consent also from a
minor and not only from
parents

TOPICS COVERED IN TEENAGE INFORMATION AND CONSENT FORM (EXAMPLE FROM MPS I REGISTRY)

- What is the purpose of the Registry
- Will I benefit from the Registry
- Are there any problems with being in the Registry?
- How will my identity be kept secret?
- What is done with the data?
- What happens if I wish to pull out of the Registry?
- Informing my GP
- Language should be simpler and addressed to the minor
- The presence of a NPSI might be helpful

DIFFERENT PROCEDURES ACROSS EUROPE (EXAMPLES FROM MPS I REGISTRY)

- Many Ethics Committees in various European countries require Teenage consent forms, however, not all participating sites/EC's
- Age range for teenage consent: 13-18 years
- Parents need to sign adult version of consent form for their child's participation
- Once child reaches majority age, they need to be reconsented using the adult consent form
- Use of teenage consent is at discretion of physician: determine if child is capable to understand and sign

EXAMPLES OF EC RECOMMENDATIONS IN EUROPE (EXAMPLES FROM MPS I REGISTRY)

- Germany: need to obtain consent form for Teenagers
- Belgium: separate consent for teenagers
- UK: teenage consent
- Scotland: age of majority is 16 years
- Ireland: recommended to re-consent the patients/parents every 5 years, regardless of age of patient

CONSENT FROM: STEPS FROM CHILD – TEENAGE - ADULT

Child

The child should be informed about the trial to the extent compatible with the child's understanding

Teenager

13 -18
years

The teenager should be informed about the trial to the extent compatible with the child's understanding and, if capable, the subject should sign and personally date the written informed consent.

Adult

≥ 18 years

Once majority age is reached, adult consent should be signed

CONCLUSIONS

- Rare diseases are good models to discuss ethical issues.
- The development of new therapies require data collections and analysis which can be performed only in specific registries.
- Data collection is important to determine the efficacy, the safety and the influence of therapies on natural histories of diseases.
- Patients must understand why data collection is needed
- The informed consent must be collected by professionals who are able to answer to any question patient/parent/guardian might have.
- Informed consent must contain all the information regarding the registry.
- Informed consent must be obtained by minor patients if able to understand.
- Informed consent is a tool to improve health Outcomes, Patient Safety and reduce liability exposure
- Guidelines about collection of informed consent from teenagers and young adult should be produced.

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