Amsterdam UMC
Universitair Medische Centra

Adaptive Pathway Development: a Clinical Approach in Fabry Disease

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Disclosures

- Employed by Amsterdam UMC

- Involved in premarketing research with pharmaceutical companies
  - Sanofi, Protalix, Idorsia
- No personal fees from pharmaceutical companies

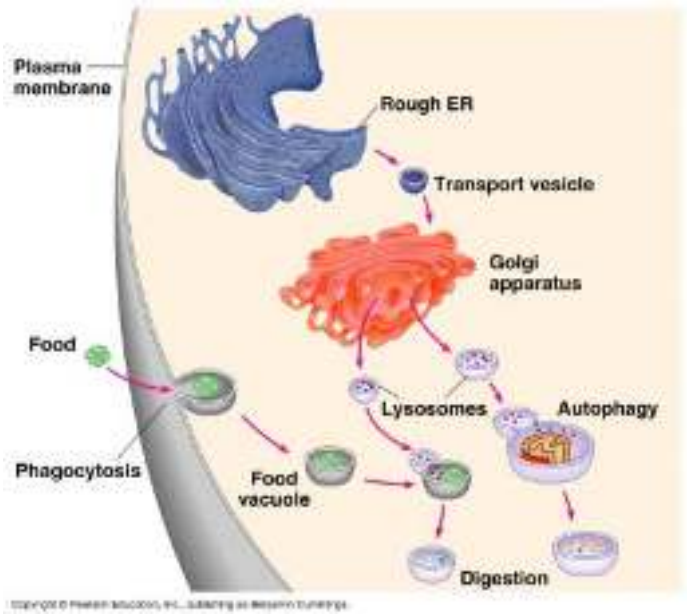
- Member of Insured Package Advisory Committee (paid)
- Chairman of SPHINX, non-profit association
- Initiator of platform “Medicine for Society”, part of Amsterdam UMC

www.medicijnvoordemaatschappij.nl

Lysosomal storage disorders

Lysosome = a garbage bin in the cell with enzymes which can break down many substances.

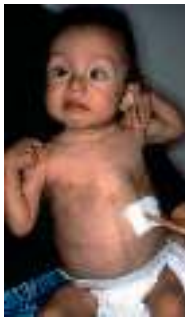
Lysosomal storage disorder (LSD) =an inherited disease characterized with a defect in a lysosomal enzyme



Phenotypic diversity is the rule

Lipidoses

Gaucher disease



Mucopoly-saccharidoses

MPS 1

Glycogen storage

Pompe disease

Enzyme therapy for Gaucher disease

Dr. Roscoe Brady injects enzyme thera

The New York Times

Business Day

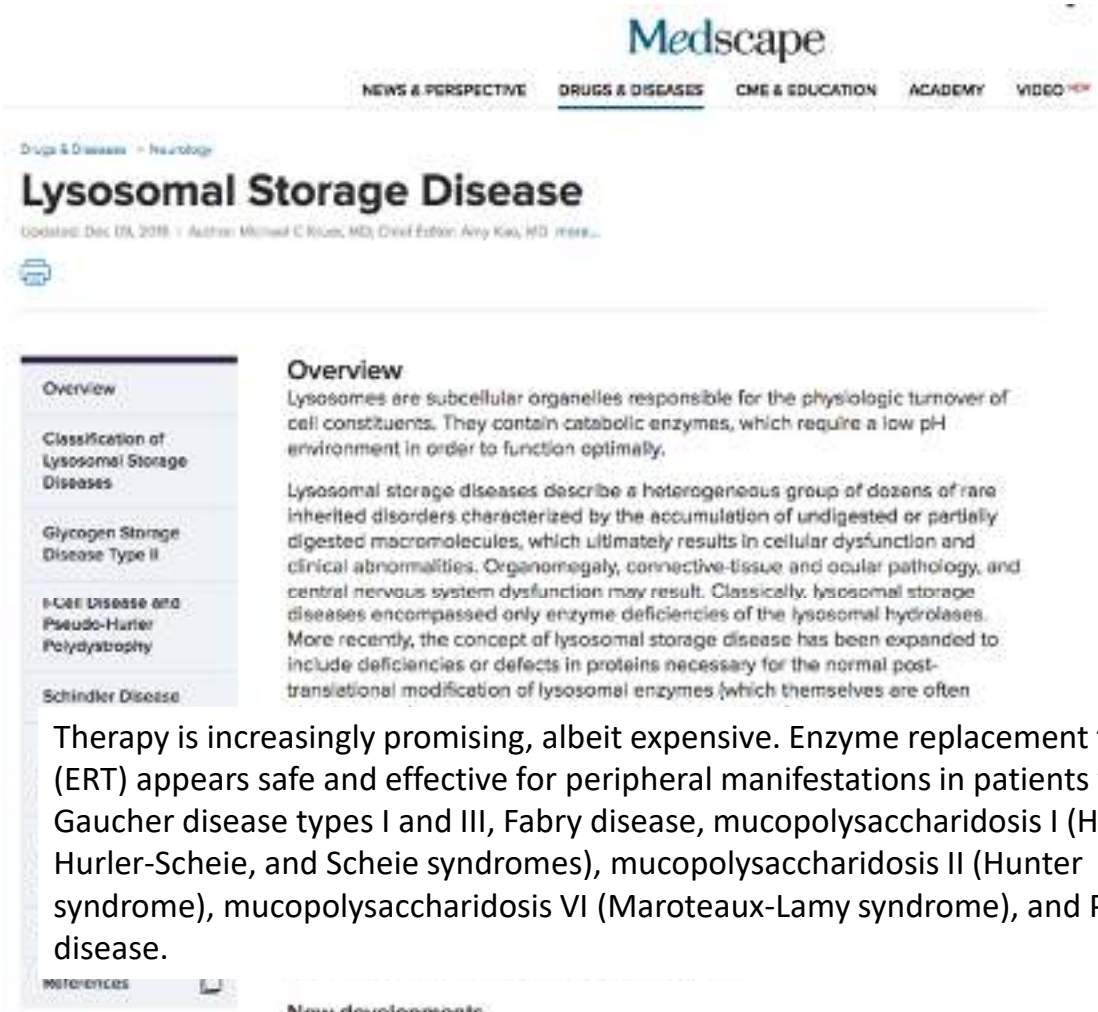
COMPANY NEWS

COMPANY NEWS; U.S. Agency Criticizes High Price of Drug

By PHILIP J. HILTS
Published: October 6, 1992

WASHINGTON, Oct. 5— A Federal agency said today that the Genzyme Corporation had priced one of its drugs so high that many patients would have to trade all their lifetime health insurance to buy the drug for two to three years.

The Office of Technology Assessment, a nonpartisan Congressional research agency, said that the pricing -- which is an average of $382,000 per patient a year -- raised serious questions about whether the Government should participate in developing drugs with little or no say in how they would finally be priced.



Therapy is increasingly promising, albeit expensive. Enzyme replacement therapy (ERT) appears safe and effective for peripheral manifestations in patients with Gaucher disease types I and III, Fabry disease, mucopolysaccharidosis I (Hurler, Hurler-Scheie, and Scheie syndromes), mucopolysaccharidosis II (Hunter syndrome), mucopolysaccharidosis VI (Maroteaux-Lamy syndrome), and Pompe disease.

Real life experience with treatment of LSD's with enzyme replacement

- Treatment is not a cure
- Phenotypes/natural disease progression is extremely variable
- Effects depend on timing and disease severity
  - Window of opportunity for treatment?
  - Treatment failure does not mean that early treatment is effective
- Diagnosis (screening) is challenging

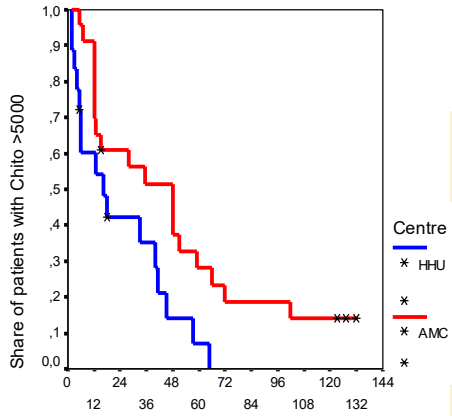
Independent collaborative efforts are needed for appropriate use of expensive treatments

Enzyme therapy for Gaucher disease in the Netherlands

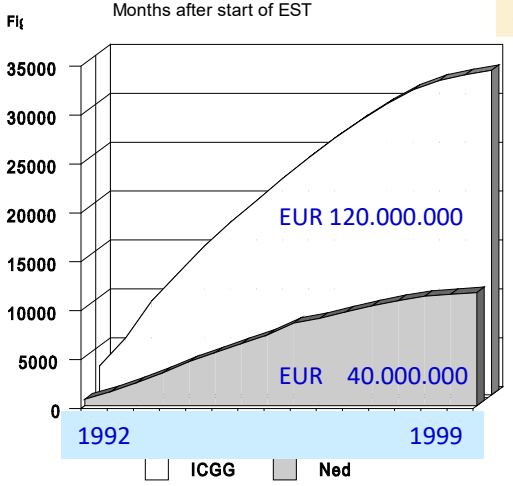
supported by Ziekenfondsraad (currently National Healthcare Institute)

- Independent studies
  - dose finding
  - biomarkers
  - home therapy
  - long term complications

→individualization of treatment



de Fost et al, Blood, 2006

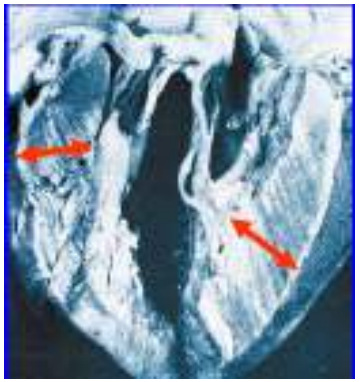


Hollak et al, Lancet 1995

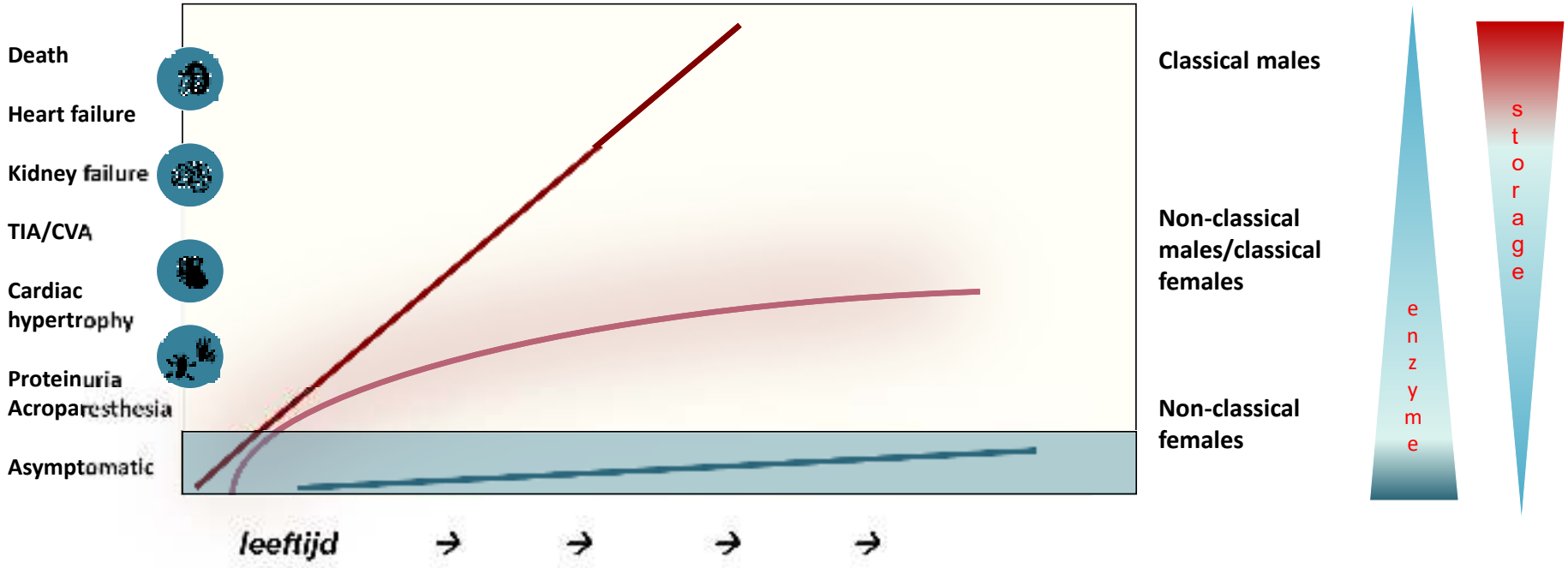
Fabry disease

X-linked deficiency of α-Galactosidase A

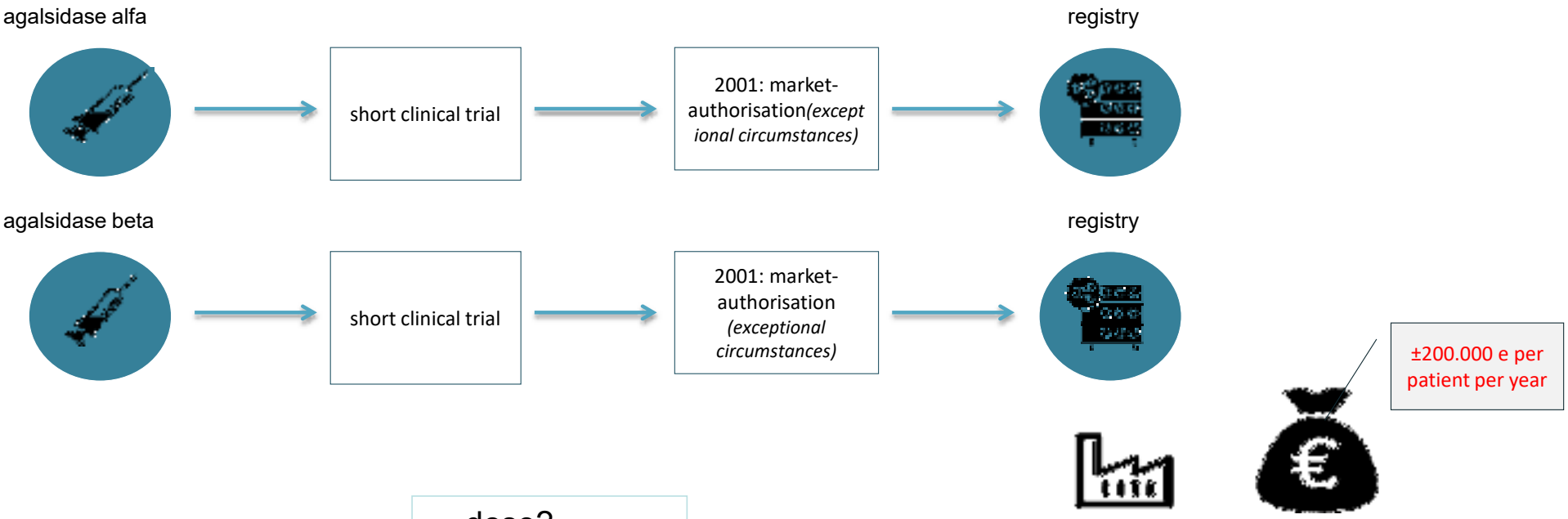
- Storage of glycolipids in vascular wall, heart, kidney:
  - Renal failure
  - Strokes
  - Cardiac failure
  - Acroparesthesias



Fabry disease course



Enzyme therapy: agalsidase alfa; agalsidase beta

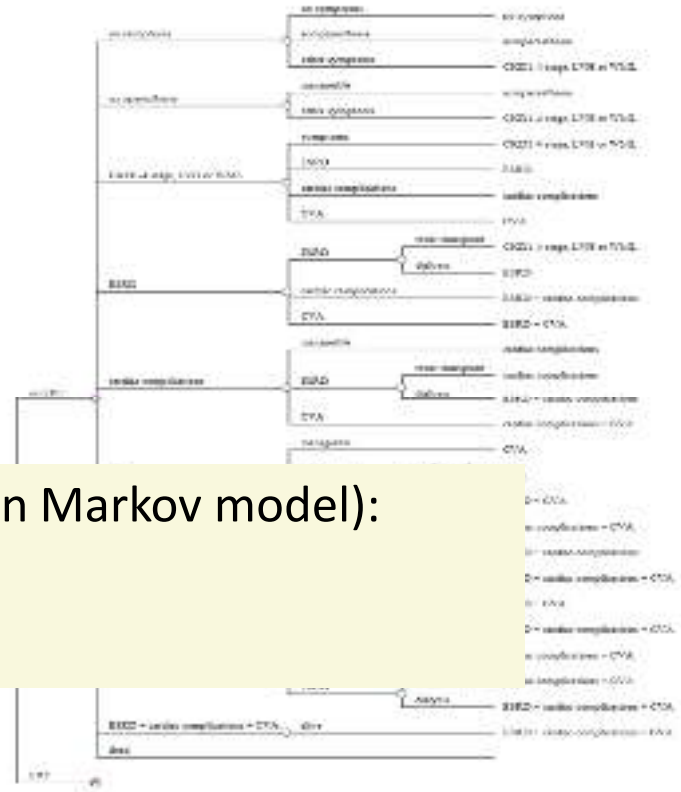


- dose?
- which patient?
- timing?

HTA study

- Dutch cohort:
  - 75 treated patiënts
  - 142 historical controls

➢Treatment delays complications



Cost effectiveness analysis (state transition Markov model):

1 QALY → € 5.5 - 7.5 million €

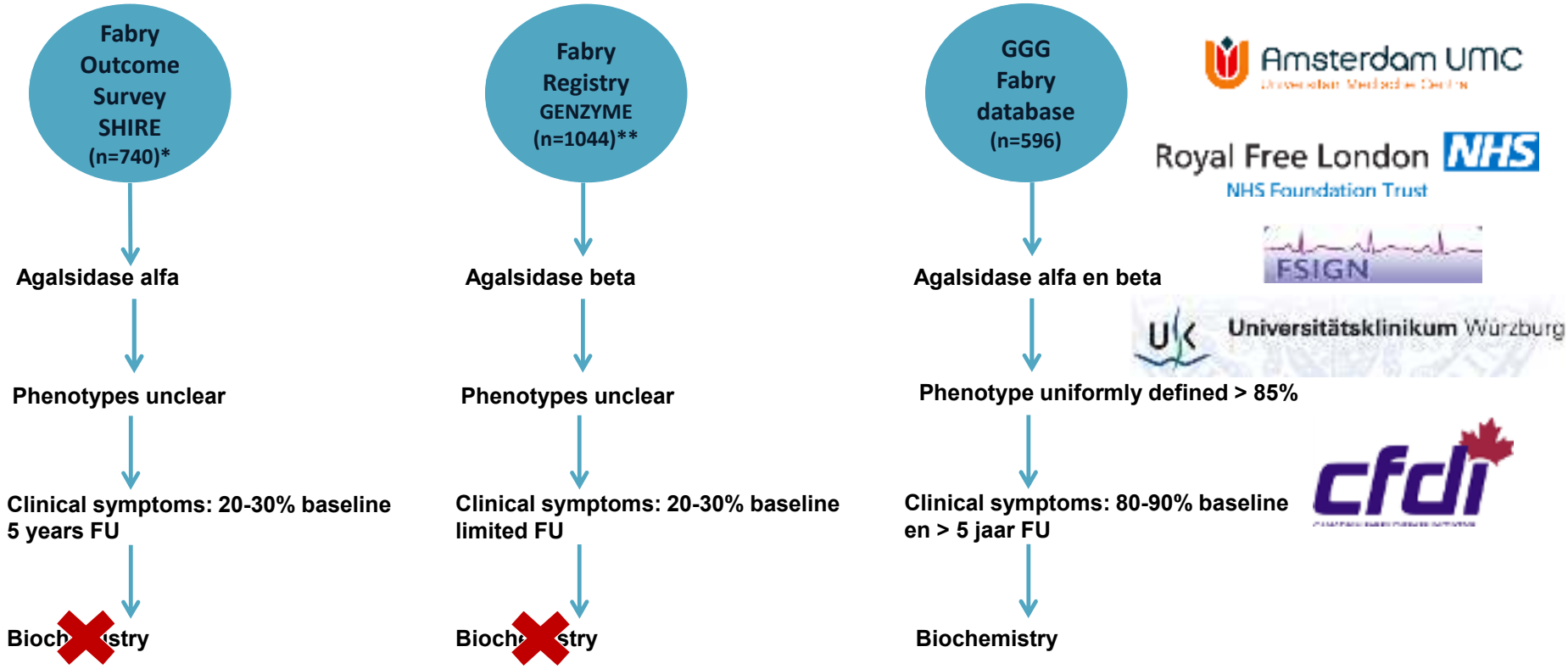
(3.3 million discounted)

Rombach SM, Hollak CE, Linthorst GE, Dijkgraaf MG. Orphanet J Rare Dis. 2013 Feb 19;8:29

July 2012: Astonished by advice to stop reimbursement of enzyme replacement therapy for Fabry and Pompe disease in the Netherlands

What's a year of life worth?

2013: GGG project: *'Treatment of patients with Fabry disease with agalsidase alfa and agalsidase beta: phenotypic diversity necessitates the development of individualized treatment guidelines*



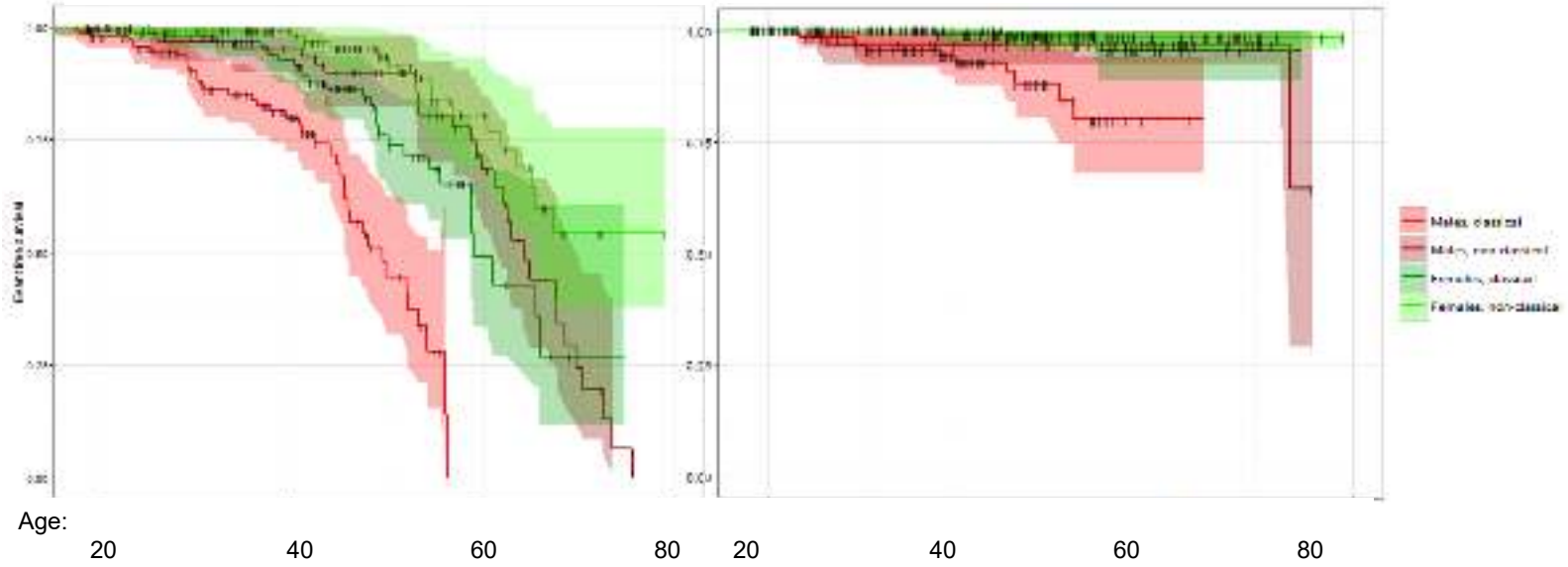
** Mol Genet Metab Rep. 2015 Mar 5;3:21-7*
***J Med Genet. 2016 Jul;53(7):495-502*

Natural disease course differs in different phenotypes

Proportion of patients with:

Major clinical complication

Renal dysfunction



137 classical males: pink
67 non-classical males: red
147 classical females: green
148 non-classical females: light green

Arends M, et al J Am Soc Nephrol. 2016 Dec 15

potentially effective for all patients

not effective in advanced disease

screening reveals many non-classical patients

not effective in cardiac fibrosis

not effective when eGFR < 30

non-classical females have a benign course

not cost-effective

antibodies may interfere

risk factors non-responders

consensus on start-stopcriteria based upon in-dependent studies

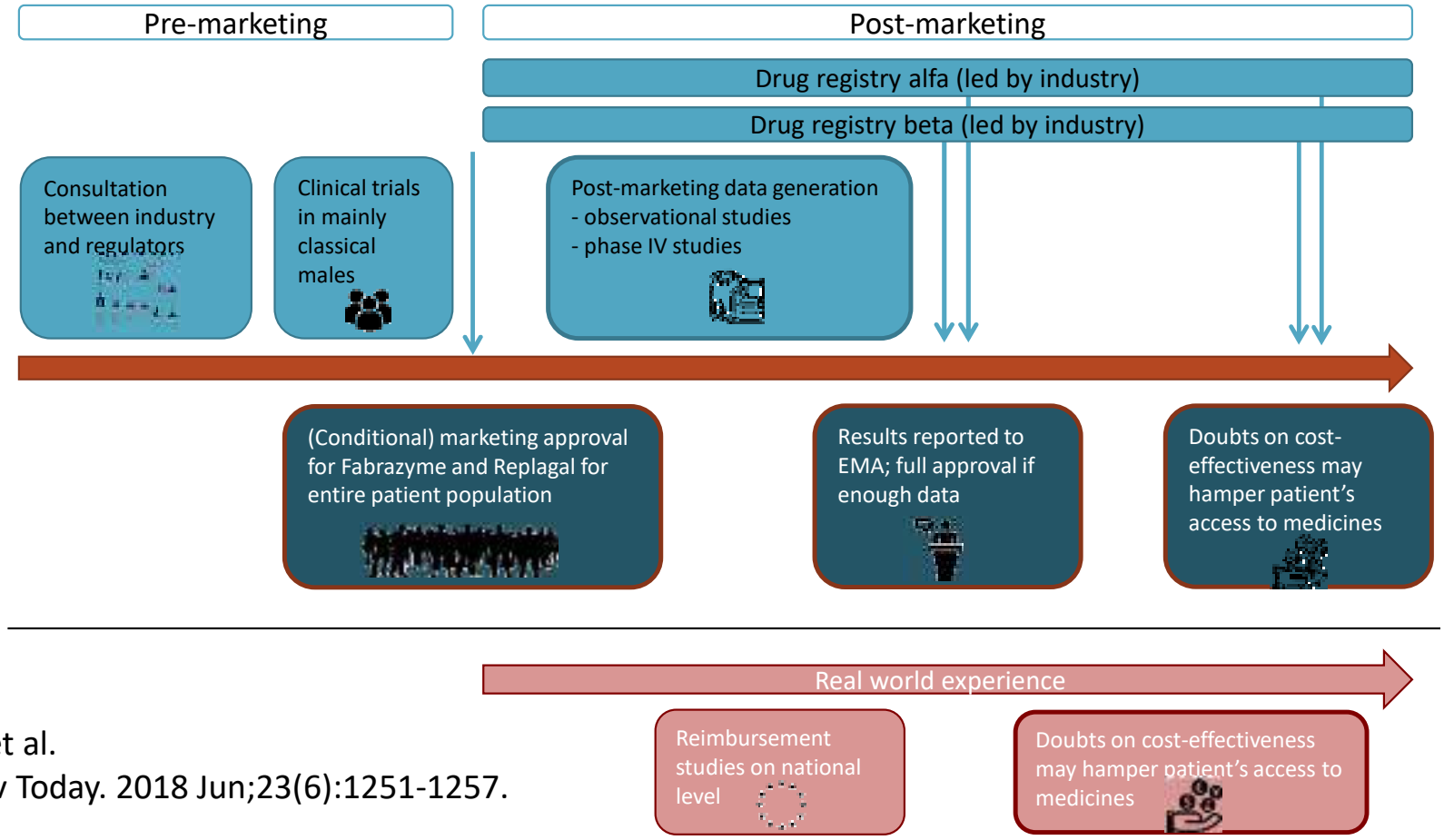
2000 2005 2010 2

Adaptive pathways to patients

- Iterative phases of evidence gathering and progressive licensing adaptations
- EMA:
  - active early dialogue with regulators, HTA bodies, patient, and healthcare professional representatives
  - use of real-world data to supplement clinical trial data
  - iterative development →initial focus on a narrow patient population followed by possible expansion of the indication to other patients

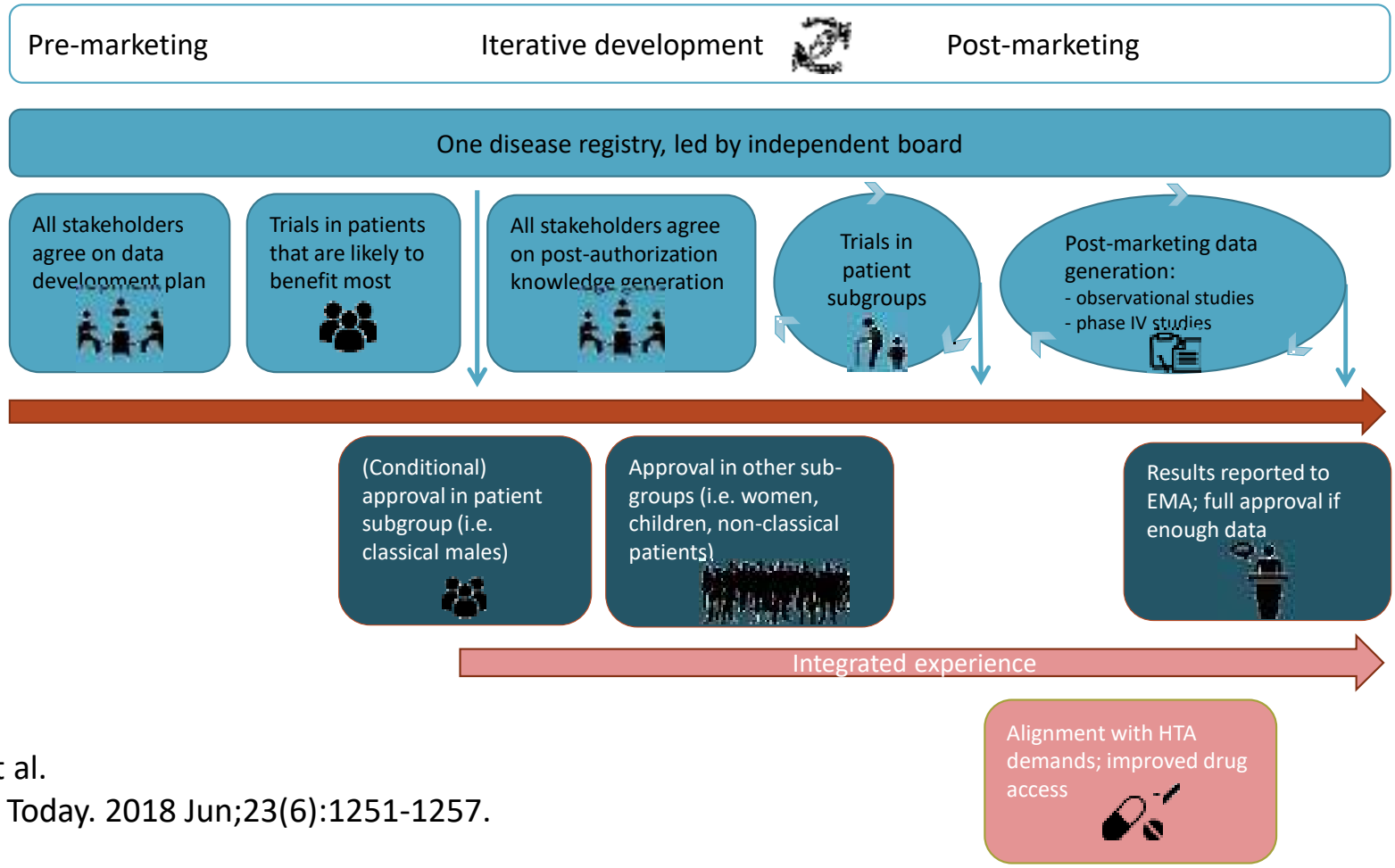
https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/mapps/

Adaptive pathway development for Fabry disease
Traditional scenario



Schuller Y et al.
Drug Discov Today. 2018 Jun;23(6):1251-1257.

Improved scenario



Schuller Y et al.
Drug Discov Today. 2018 Jun;23(6):1251-1257.

Continued evidence generation through registries: requirements

Panel: Features of post-authorisation registries

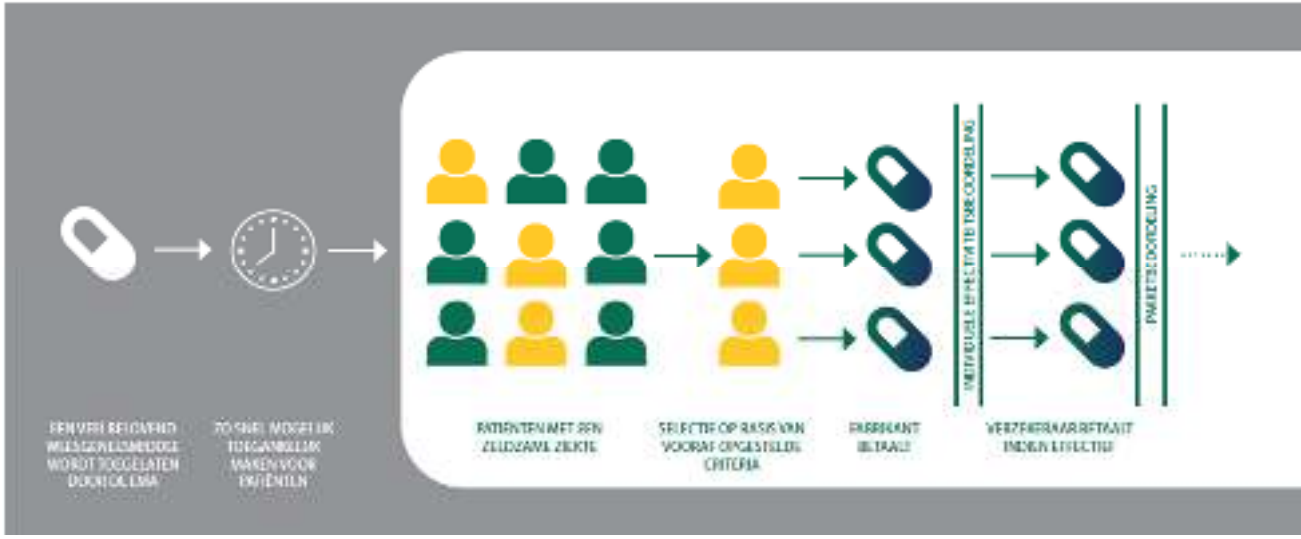
- Disease-centred registries, instead of drug-centred registries, to enable the comparison of effectiveness of different treatments for the same indication; existing registries should be integrated in or linked to systems, such as the registries proposed
- Registries supervised by patients, health-care professionals, and other relevant stakeholders, independent of corporate activity
- Analysis of data by independent statisticians
- Obligatory data entry for all doctors treating patients across Europe
- Pivotal and extended trial data and natural history data should be included in the registry
- Registries should be launched early in the development process of orphan drugs (eg, to obtain natural history data)
- Databases should contain key factors needed for cost-effectiveness studies (eg, health-related quality of life)

Hollak, Biegstraaten, Levi, Hagendijk; Lancet vol 386, November 14, 2015

Elements of the Dutch Drug Access Protocol for new cancer medicines

Early but controlled access:

- early signaling (9 months before market approval)
- development of protocol with rare disease expert center (ERN)
- dialogue with insurance companies, healthcare professionals, patients, pharmaceutical company



- **criteria for effectiveness on an individual basis**
- **pharmaceutical company provides drug for free until proven effective: reimbursed**
- **real world data: registry (inter)national**
- **report on effectiveness and cost-effectiveness after preset time scheme to payers**

Conclusions

- With the increasing number of orphan drugs we need new pathways towards
  - early (conditional) approval at the EU level
  - alternative routes to access at a national level

- This requires:
  - early dialogues with all stakeholders
  - robust system of evidence generation through independent registries
  - development of national systems of access