XIth FORESIGHT TRAINING COURSE

25-27 October, 2018 Pavia Italy

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ORPHAN MEDICINES DEVELOPMENT

THE SCIENCE OF HOPE

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I have no real or apparent relevant financial relationships to disclose

DOI

www.ema.europa.eu/docs/en_GB/document_library/contacts/athanasioud_DI.pdf

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" ARE PATIENTS SATISFIED FROM THE IMPLEMENTATION OF EU POLICIES ON ORPHAN MEDICINES DEVELOPMENT AND AVAILABILITY SO FAR? "

http://www.aimsmeeting.org/rare-diseases/

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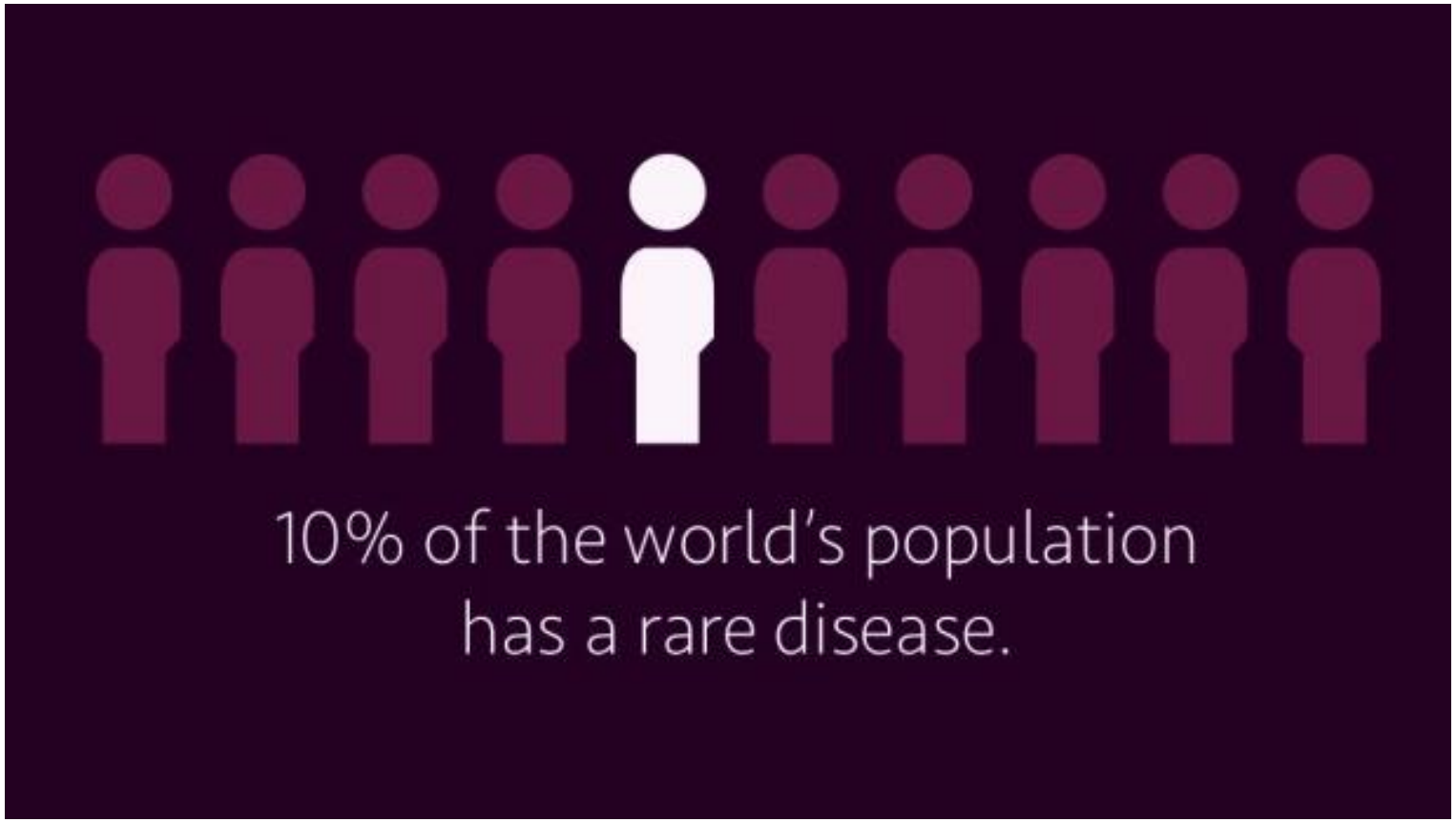

https://patientsrising.org/living-with-a-rare-disease/

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350 Million People Globally are fighting Rare Diseases

https://patientsrising.org/living-with-a-rare-disease/

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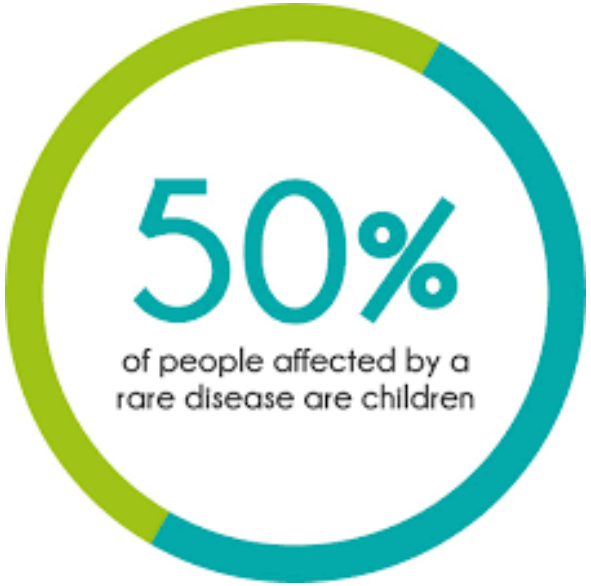

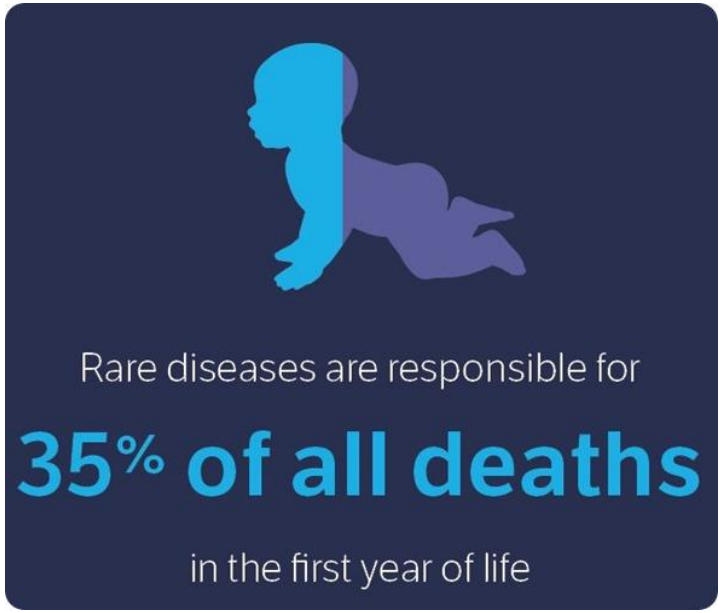

Global genes / https://blog.cirm.ca.gov

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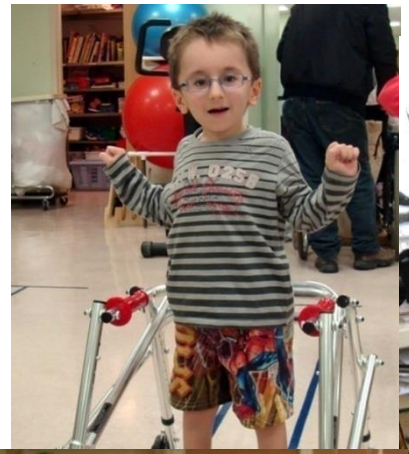
OUR NUMBERS

95%

8%

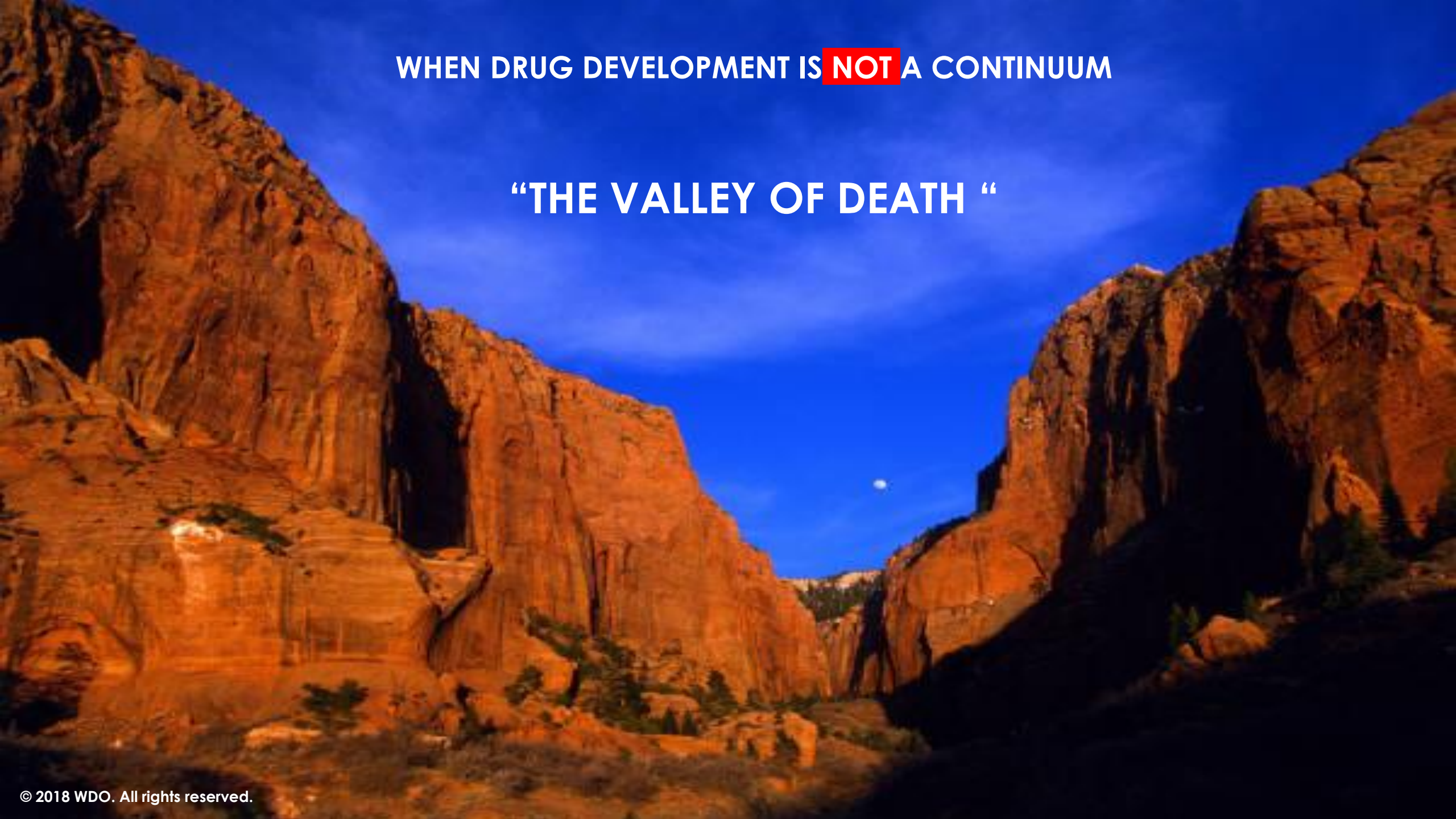


35%

75%

30%

http://globalgenes.org/rare-diseases-facts-statistics/ http://www.raredisease.org.uk/about-rare-diseases.htm



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DRUG DEVELOPMENT IS A CONTINUUM
"THE VALLEY OF DEATH "

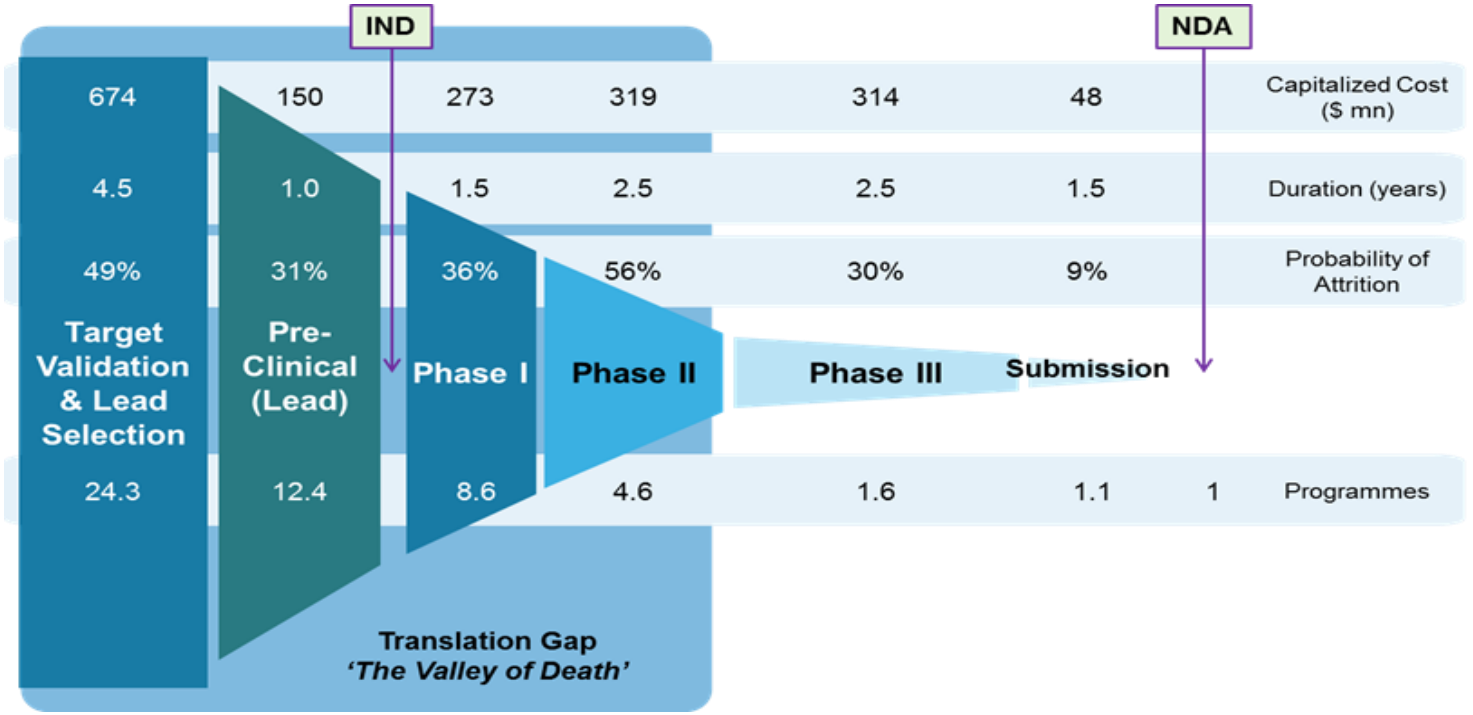

Figure 1. Drug development cycle and the 'valley of death'. Schematics of the drug development lifecycle, duration of each one of the stages, capitalized costs and probability of failure. Adapted from {Paul, 2010 #886} and Michael J. Fox Foundation.

Source : www.lonza.com

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UNDERSTANDING THE SITUATION

- Analysis of the Environment
- The Economics
- The Process

Source: Getting new drugs through the 'valley of death' New initiative addresses growing gap between academic and clinical research By Quinn Eastman | Emory Medicine | Jan. 27, 2014

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ANALYSIS OF THE ENVIRONMENT

- **The current economic conditions**
  - **Biomedical innovation has become riskier and more expensive**
  - Zero growth rates
  - Government funding has been declining
  - Cost pressures from healthcare reforms
- **The current biomedical RD conditions**
  - Industry shies away from the sponsorship of early clinical research citing increasing risks and costs
  - Expiration of patents, regulatory hurdles and rising costs of clinical trials
  - Pharma leaders focus on drug candidates that have passed some of the early regulatory hurdles

Source: Getting new drugs through the 'valley of death' New initiative addresses growing gap between academic and clinical research By Quinn Eastman | Emory Medicine | Jan. 27, 2014

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THE ECONOMICS - MARKET SIZE

- **8%** are living with a rare disease
- **30** million people in the EU
- **350** million globally
- Rare diseases affect more people than all cancers & HIV combined
- Market value in **2022 at $209bn** with an **11% growth/year**
- The cost to develop and win marketing approval for a new drug is **$2.6 billion** (drug failures and exploratory expenses are included)

Extracts from
(a) *Eurordis fact sheet http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf*
(b) *Rare Diseases: Facts and Statistics*, Global Genes (https://globalgenes.org/rare-diseases-facts-statistics/) and
(c) *Rare Diseases: understanding this Public Health Priority* (http://www.eurordis.org/sites/default/files/publications/princeps_document-EN.pdf)
(d) Evaluate Pharma Orphan Drug Report 2017 http://www.evaluategroup.com/public/Reports/EvaluatePharma-Orphan-Drug-Report-2017.aspx

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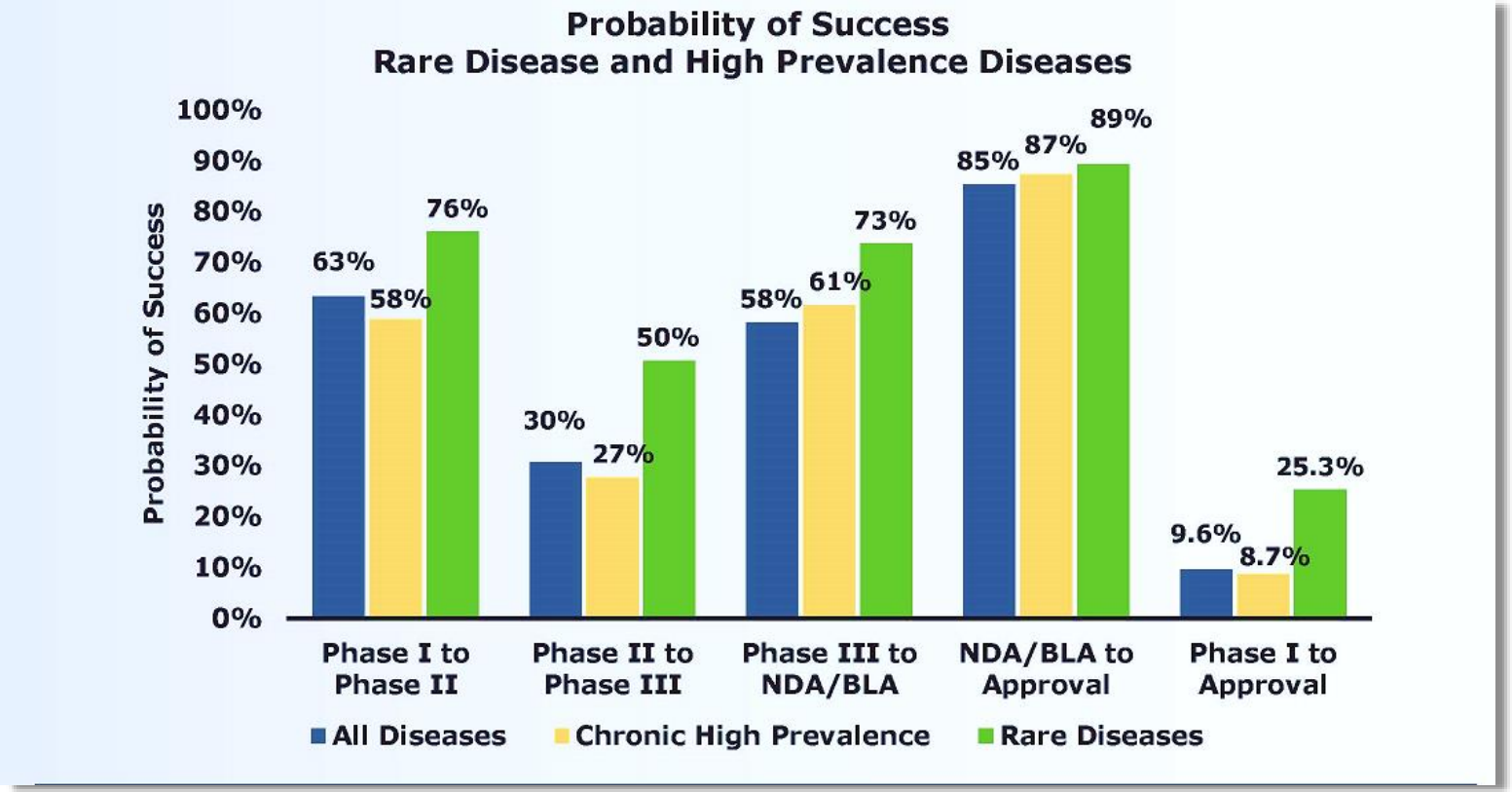
PROBABILITIES



2016 Business Report BIO, Biomedtracker, Amplion 2016 Clinical Development Success Rates 2006-2015
https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf

Does it make economic sense to invest in RD?

- Commercial benefits of an orphan designation (IP protection, low regulatory cost, adaptive and fast access schemes etc.).
- The orphan drug market is expected to peak at $209bn in 2022 with an **11%** growth/year
- Investing in a drug for rare diseases in the early phases the difference can even be **double** than any other drug development option.
- The accumulative probability from **Phase I to Approval is 300% higher**.

2016 Business Report BIO, Biomedtracker, Amplion 2016 Clinical Development Success Rates 2006-2015 Evaluate Pharma Orphan Drug Report 2017
http://www.evaluategroup.com/public/Reports/EvaluatePharma-Orphan-Drug-Report-2017.aspx

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THE DMD EXAMPLE

- DMD Market Size: The market is expected to grow from **$8.2 million for 2014** to nearly $1 billion by 2019, across the six major markets of the US, Germany, France, UK, Italy and Spain

- This represents a Compound Annual Growth Rate (CAGR) of **160.5%**

- Budget Impact ?

Market Research Global Data: Duchenne Muscular Dystrophy-Opportunity Analysis and Forecasts to 2019. http://www.marketresearch.com/product/sample-9127881.pdf
Global data Duchenne Muscular Dystrophy - Opportunity and Market Analysis to 2019 April 17, 2015 REFERENCE CODE GDHC038POA | PUBLICATION DATE APRIL 2015

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THE REAL IMPACT

- The economic impact of DMD is quite remarkable even though it is a rare disease

- The total estimated economic burden in 2012:

Germany	$ 278,058,000
Italy	$ 154,465,000
UK	$ 200,478,000
US	$ 1,217,373,000

- Almost **$2 billion** for 4 countries in 2012

- The cost to develop and win marketing approval for a new drug is **$2.6 billion** (drug failures and exploratory expenses are included)

Landfeldt, Erik, et al. "The burden of Duchenne muscular dystrophy An international, cross-sectional study." Neurology 83.6 (2014): 529-536.
Pammolli, Fabio, Laura Magazzini, and Massimo Riccaboni. "The productivity crisis in pharmaceutical R&D." Nature reviews Drug discovery 10.6 (2011): 428-438.
Tufts University Center for the Study of Drug Development, 2014 (http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study)

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THE PROCESS

REGULATORY NEEDS IN PEDIATRIC DEVELOPMENT

- Neonatals
- Pediatric Cancers
- Rare Diseases

REGULATORY SUCCESS IN PEDIATRIC AND ORPHAN DEVELOPMENT ?

Example : Between 2007 and 2015

150 PIPs agreed for medicinal products with ODD

Number of completed PIPs for medicinal products with ODD: 8

Number of authorisations of paediatric indications: 9 (+6 in 2016)

3 orphan medicinal products: Two-year extension of the market exclusivity period

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Since 2000

2067 Orphan designations

171 Orphan designations included in authorised indication

153 Authorised OMPs

61 To be used in children

4 Removed from the market

43 Marketed, but no longer "orphans"

To date

110

Products with a marketing authorisation and an orphan status in the European Union

19 October 2018

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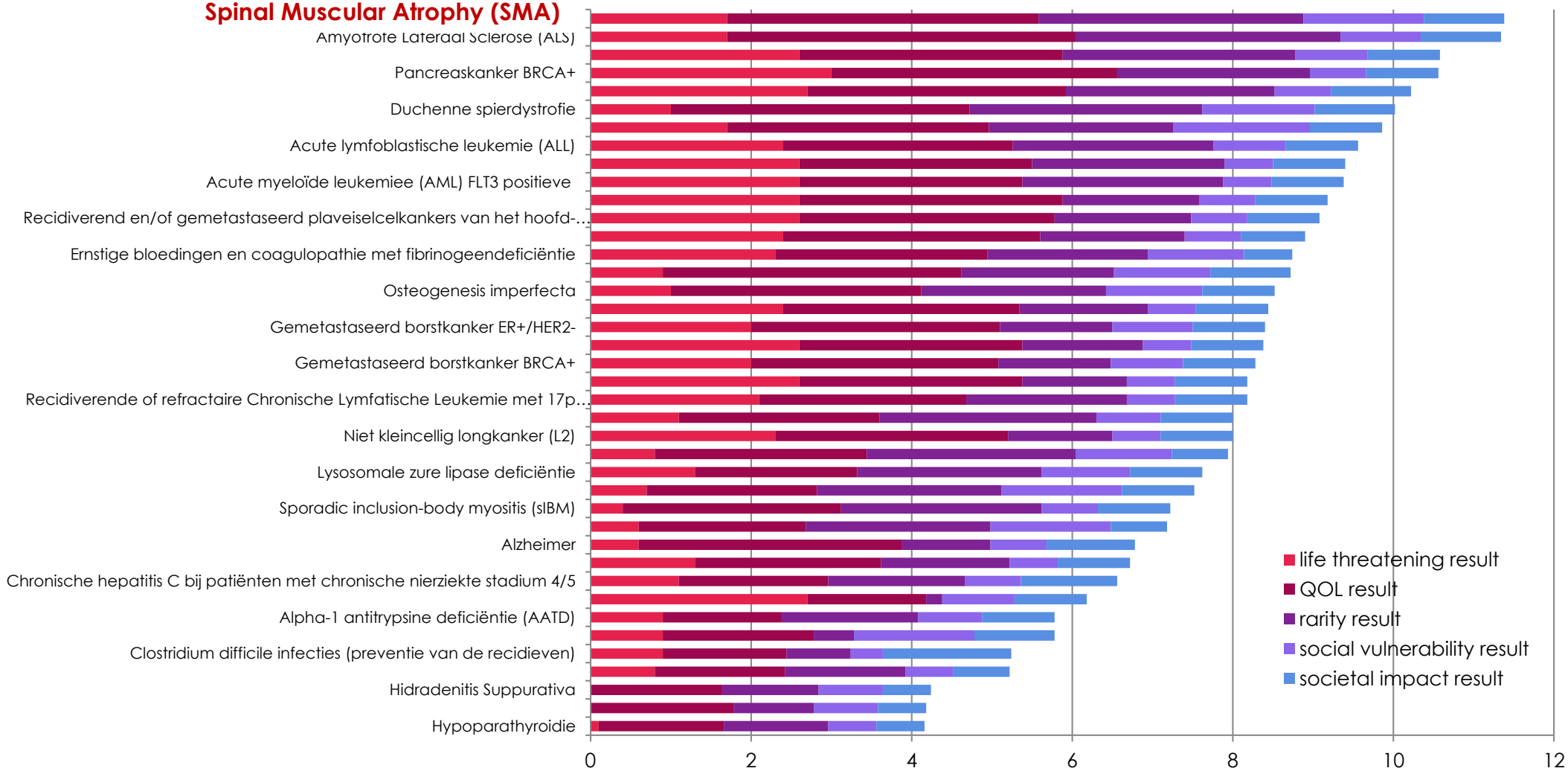
Spinal Muscular Atrophy (SMA)



Reality Check the SMA Example

Access & Reimbursement Details by Country

Germany	AMNOG process finalized. Reimbursed access in line with the label – 5q spinal muscular atrophy (SMA)
Croatia	Reimbursed access – Type I, II, III (<18 yrs)
Cyprus	Access through Individual Reimbursement
Czech Republic	Reimbursed access – Types I, II and IIIa (subject to clinical criteria)
Denmark	Reimbursed access – pre-symptomatic, Type I and II (subject to clinical criteria)
England & Wales	Awaiting NICE Appraisal Committee decision
Finland	Reimbursed access for patients up to, and including, 17 years old, aligned with PALKO positive recommendation.
France	Negotiations underway; current reimbursed access given to Types I, II and III through post-ATU
Greece	Reimbursed access for pre-symptomatic, Types I and II; negotiations for Type III underway
Hungary	Biogen & NEAK agreement signed. Final access decisions will be made by NEAK as
Israel	Reimbursed access – Types I, II and III
Italy	Reimbursed access – Types I, II and IIIz
Lithuania	Access through individual reimbursement – Types I, II and III
Netherlands	Negotiations underway Reimbursed access Type I, II and III (subject to clinical and age criteria)
Northern Ireland	Negotiations underway
Norway	Reimbursed access – Types I, II and III (0 to 18 years of age)
Romania	Spinraza included in the national list of reimbursed medicines and therapeutic protocol published (Types I,II and III)
Scotland	Reimbursed Access Type I (later-onset patients funded via the Individual Treatment Fund); negotiations for Type II, III
Serbia	Access through a named patient programme
Slovakia	Reimbursed access – Types I, II and IIIa as of August 1st 2018
Slovenia	Reimbursed access – Types I, II and III that are treated in paediatric centres
Spain	Reimbursed access – Types I, II and III

https://www.treatsma.uk/2018/07

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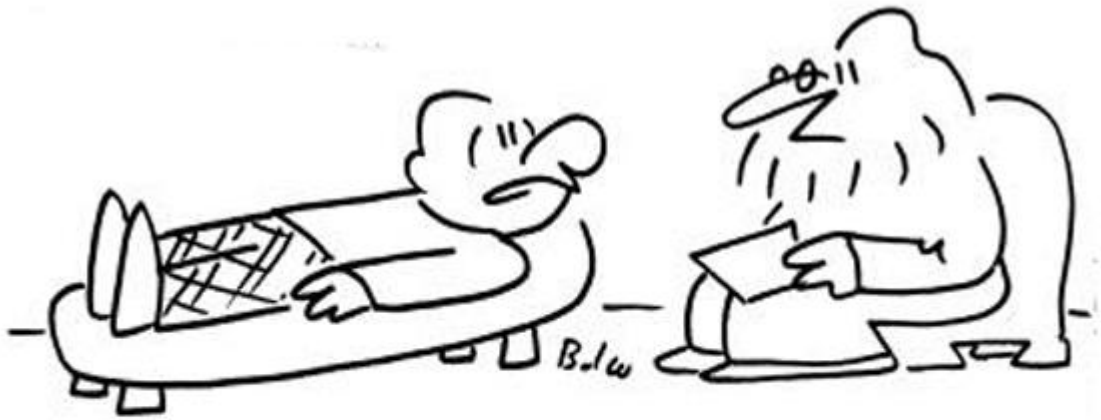

"I want you to put me in touch with reality, but be ready to break the connection *fast*."

https://www.gamasutra.com/blogs/BenChong/20140323/213713/Indie_Reality_Check__Guidelines.php

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RARE BAROMETER VOICES INITIATIVE – SURVEY PROGRAMME

- Juggling care and daily life: The Balancing Act of the Rare Disease Community
- Access to treatment: Unequal care for European rare disease patients

SORTING BY SUB-POPULATION: PARENTS OF CHILDREN LIVING WITH A RARE DISEASE

Social Survey : **1151 Parents of a child** living with a rare disease
Access Survey : **652 Parents of a child** living with a rare disease

Rare Barometer Voices
A EURORDIS INITIATIVE

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THE SERIOUS IMPACT TO EVERYDAY LIFE

9 in 10 Parents of a child living with a rare disease report **difficulties in more than one aspect** of their **everyday** life

62% Parents of a child living with a rare disease spend more than **2h/day on illness-related** tasks **(29% more than 6h/day)**

The role of the **primary carer** for a child living with a rare disease is primarily assumed by the **mother**

79 %

Hygiene

Administration of treatments

Helping patients to move

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ACCESS TO TREATMENT / PAEDIATRIC PATIENTS

In 2016, **13%** of rare disease patients did not get the medical treatment they needed because **they could not pay for it** (**versus 6%** in the general population)

And **18%** did not get the medical treatment they needed because **the waiting list was too long** (**versus 9%** in the general population)

24% of rare disease patients surveyed could not get the medical treatment they needed in 2016 because the treatment was not available where they live

VS. 7% in the general population

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COMMISSION REPORT "*Still* ***the use of rewards was limited to 55 % of the completed PIPs*** *…the* ***PUMA*** *concept with its specific reward* ***has failed to deliver****."*

COMMISSION REPORT *"Regulation works best in areas where the needs of adult and paediatric patients overlap. Especially, in diseases that are* ***rare and/or unique to children*** *and which in many cases are equally supported through the orphan legislation,* ***major therapeutic advances often failed to materialise*** *yet.""*

Vytenis Andriukaitis, Commissioner *for Health and Food Safety*
`*"When we consider the advances in adult oncology, it* ***upsets me deeply*** *that we have* ***not made*** *the same progress in* ***treating the cancers that affect children****," commented . "In the* ***next 10 years we must focus on making similar breakthroughs for children."***

The ***MEP who was rapporteur for the Paediatric Regulation - Françoise Grossetête***
"I am ***all the more afraid*** *that the* ***ongoing incentives review*** *carried out by the Commission, together with the current* ***anti-innovation climate****, with particularly* ***harsh criticisms*** *against the Orphan Drugs Regulation,* ***would harm children access to medicines in Europe****,".*

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THE MAIN ISSUES

- Lack of funding
- Lack of knowledge and training
- Data fragmentation
- Deficient diagnostic systems

NEED TO WORK ON

- Effective and targeted regulation and access pathways
- Suboptimal coordination between EMA-FDA-HTA-PAYERS
- Challenges in Access to and Affordability of Medicines for RD
- Challenges in assessing clinical relevance and cost effectiveness

FOCUS MORE ON

- Population definition, different subsets
- Disease progression models
- Innovative & adaptive trial designs models that should already be fit for modelling and extrapolation
- Non-clinical models validity-development
- Primary and secondary “clinically meaningful” & “validated” endpoints, Biomarkers related to clinical outcomes
- Dose assessment – definition in relation with ages, also in relation with biological drugs

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FUTURE

BUILD A PREDICTABLE PATHWAY WHERE DRUG DEVELOPMENT MEETS THE ORPHAN NEED

- Develop a holistic approach with an early involvement of all stakeholders
- Look for innovation in scientific platforms , networks and technologies
- Look and work for innovation in strategy, policy, access and **thinking**
- Think of Drug Development Process as a continuum
- Understand, Quantify and Measure
- Develop a holistic approach with an early involvement of all stakeholders
- Understand the positions of all the stakeholders
- De-risk the process
- Build a drug development strategy based on trust with a common goal
- **Build a predictable pathway where the development meets the Orphan Need**

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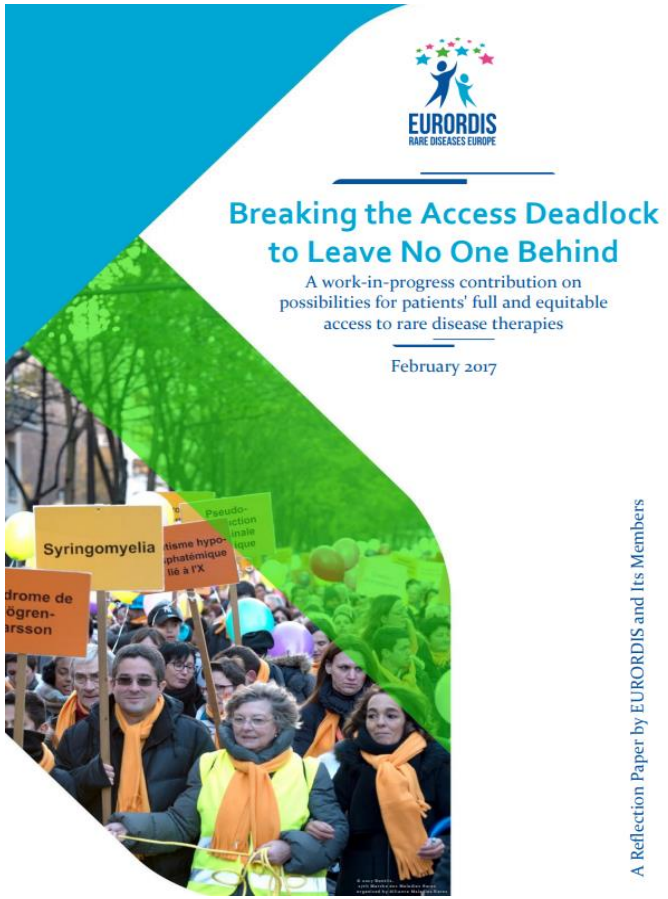
EURORDIS POSITION PAPER ON ACCESS

FOUR PILLARS TO SUCCESS

The new position paper sets out a four-pillar approach that encompasses:

- A new blueprint to cut costs and fast-track R&D (read more);
- Early dialogue and cooperation between healthcare systems on the determination of value of a medicine and on patient access (read more);
- A transparent European cooperation framework between national healthcare systems for the determination of fair prices and of sustainable healthcare budget impacts (read more)
- A continuum approach to evidence generation linked to healthcare budget spending (read more).



http://www.aimsmeeting.org/rare-diseases/

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THANK YOU!

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