Regulatory Challenges in Paediatric Research:

Innovative Medicines for Children

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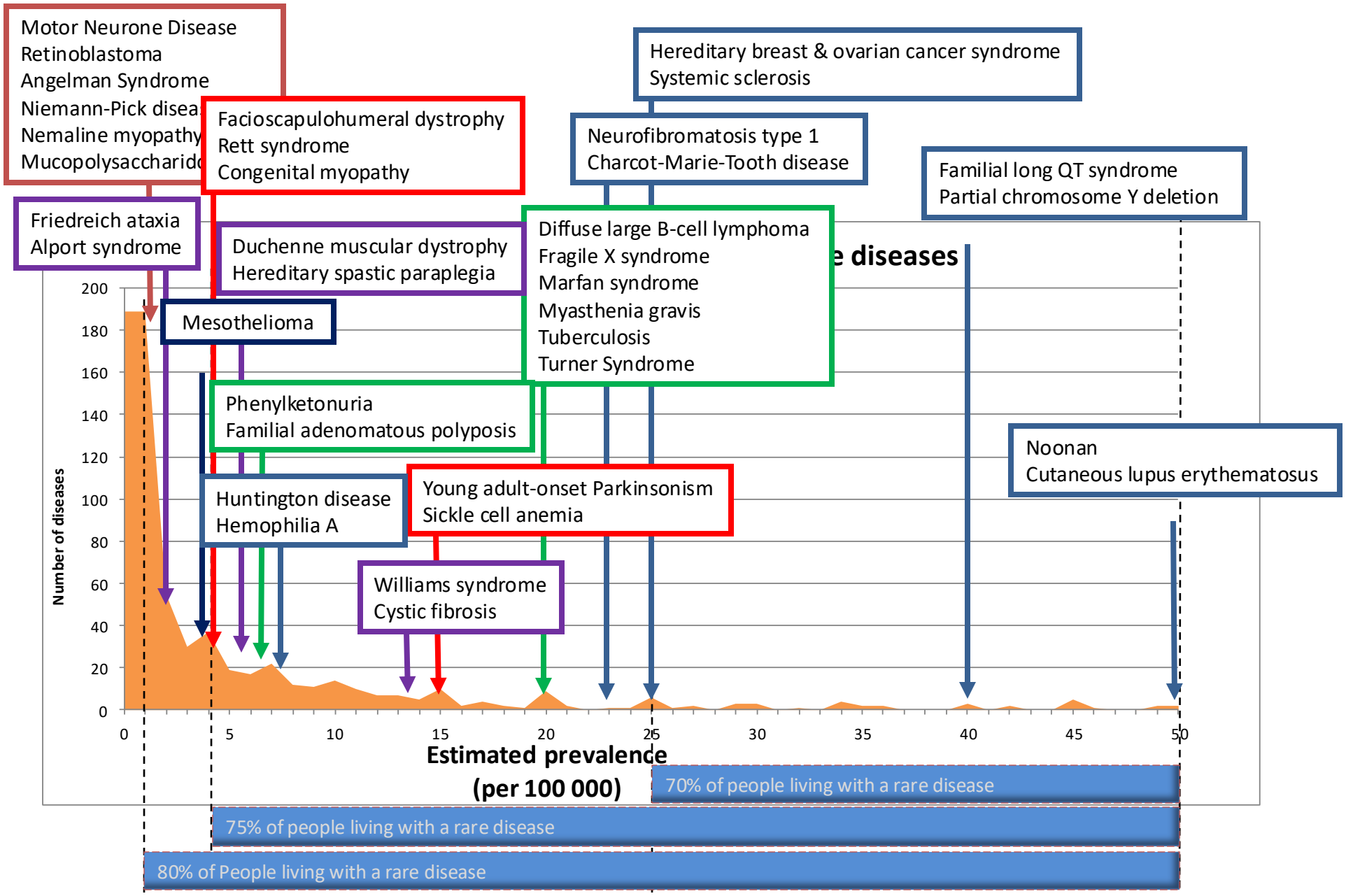
Nothing to  disclose


Motor Neurone Disease
Retinoblastoma
Angelman Syndrome
Niemann-Pick disea
Nemaline myopathy
Mucopolysaccharido
Facioscapulohumeral dystrophy
Rett syndrome
Congenital myopathy
Hereditary breast & ovarian cancer syndrome
Systemic sclerosis
Neurofibromatosis type 1
Charcot-Marie-Tooth disease
Familial long QT syndrome
Partial chromosome Y deletion
Friedreich ataxia
Alport syndrome
Duchenne muscular dystrophy
Hereditary spastic paraplegia
Diffuse large B-cell lymphoma
Fragile X syndrome
Marfan syndrome
Myasthenia gravis
Tuberculosis
Turner Syndrome
e diseases
Mesothelioma
Phenylketonuria
Familial adenomatous polyposis
Noonan
Cutaneous lupus erythematosus
Huntington disease
Hemophilia A
Young adult-onset Parkinsonism
Sickle cell anemia
Williams syndrome
Cystic fibrosis
Number of diseases
0
20
40
60
80
100
120
140
160
180
200
0
5
10
15
20
25
30
35
40
45
50
Estimated prevalence
(per 100 000)
70% of people living with a rare disease
75% of people living with a rare disease
80% of People living with a rare disease

ATMP regulation 1394/2007

- ATMP
  - products in gen therapy (GTMP)
  - products in somatic cell therapy (sCTMP)
  - products in tissue engineering (TEP)
  - combined products (Combined)
  - 'Manipulated': minimum 1 of the 2 criteria

"substantial manipulation" :
NOT: cut, centrifuge, sterilise, freeze,… (Annex I)
BUT: cell expansion, ex vivo cell activation or –differentiation, …

not the same essential function in receiver and donor

Gene Therapy

Biological medicinal product with the following characteristics:

a) it contains an active substance which contains or consists of a **recombinant nucleic acid** used in or administered to human beings **with a view to regulating, repairing, replacing, adding or deleting a genetic sequence**;

b) its therapeutic, prophylactic or diagnostic effect **relates directly to the recombinant nucleic** acid sequence it contains, or to the product of genetic expression of this sequence. Not include vaccines against infectious diseases.

EMA Marketting Authorization GT

YESCARTA® (axicabtagene ciloleucel)

Breyanzi (lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION

casgevy (exagamglogene autotemcel) suspension for IV infusion

Abecma (idecabtagene vicleucel)

IMLYGIC
elimogene laherparepve
SUSPENSION FOR INJECTION
PFU/mL and 10⁸ PFU/mL single-use vi

Strimvelis®
EMA APPROVED

zolgensma®
(onasemnogene abeparvovec-xic)
suspension for intravenous infusi

LIBMELDY

ROCTAVIAN™
(valoctocogene roxaparvovec-rvox)
Suspension for intravenous infusion

skysona

CARVYKTI™
(ciltacabtagene autoleucel)

HEMGENIX
etranacogene dezaparvovec-drlb

TECARTUS™
(brexucabtagene autoleucel)

Upstaza

KYMRIAH™
(tisagenlecleucel)

LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

Vyjuvek®
beremagene geperpavec-svdt

zynteglo®
(betibeglogene autotemc
suspension for IV infus

AUCATZYL®
obecabtagene autoleucel
suspension for IV infusion

Cell Based Medicinal Products

- **Somatic cell therapy** medicinal products:
- -**substantially manipulation** cells or tissues **or not intended** to be used for **the same essential function**(s);
- -administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action.
- **Tissue engineered** product:
- -**engineered (substantially manipulated)** cells or tissues, and
- -administered to human beings with a view to r repairing or replacing a human tissue.

EMA Marketting Authorization CT

ZALMOXIS

CHONDROCELECT™

When evidence makes a difference

Cartilage lesions of femoral condyle ICRS III-IV

TIGENIX

Living Medicines

EBVALLO®

tabelecleucel

PROVENGE®

(sipuleucel-T)

ALOFISEL

HOLOCLAR

maci

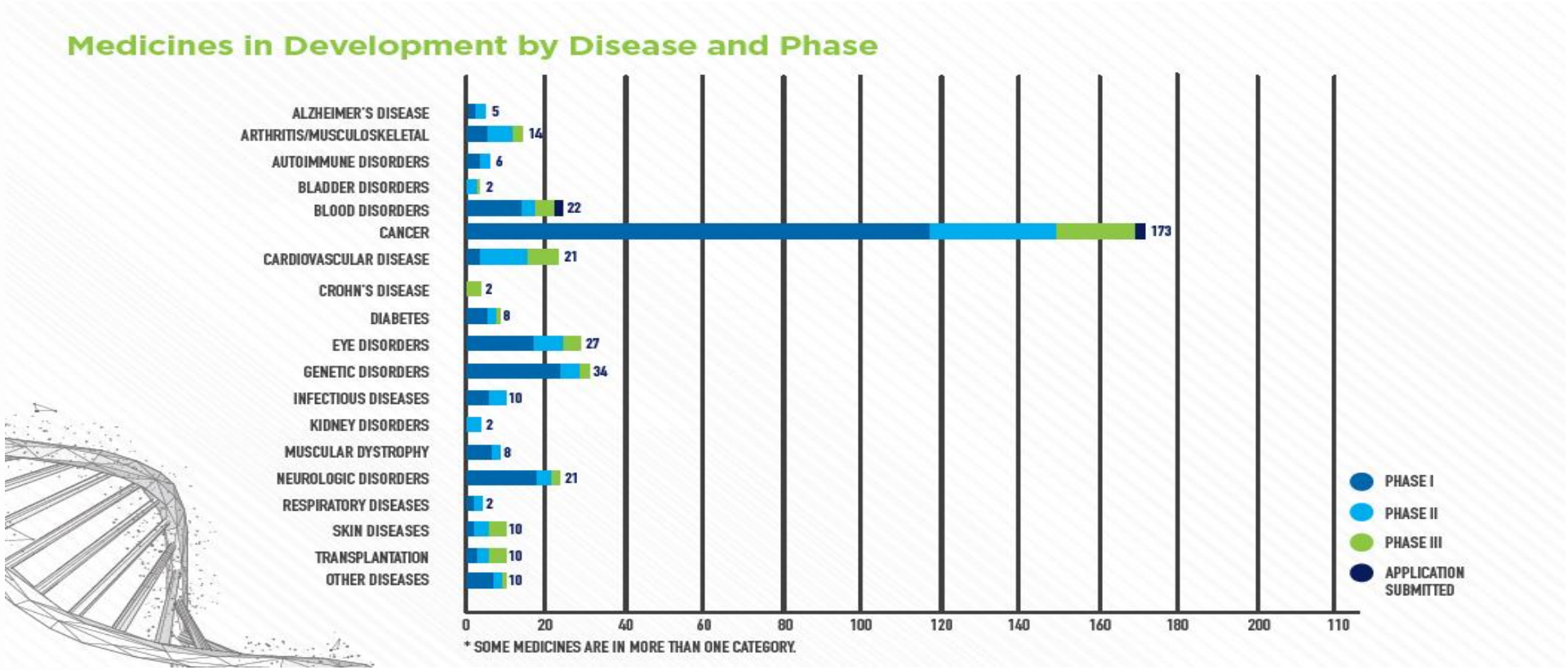
autologous cultured chondrocytes on porcine collagen membrane

Combined ATMP

- Incorporates a medical device (according to Article 1(2)(a) of Dir. 93/42/EEC)
- **And**
- includes viable cells or tissue parts
- **or**
- In case of non-viable cellular/tissue part, the primary mode of action is attributed to the cell component as either pharmacological, immunological, metabolic or as repair, replacement, regeneration.

Hospital Exemption

Pipeline by disease and phase




European Commission
European Reference Networks
European Reference Networks
Annika Nowak
European Commission
Health and Food Safety

Cross-Border Healthcare

General Comments Cross-Border Healthcare

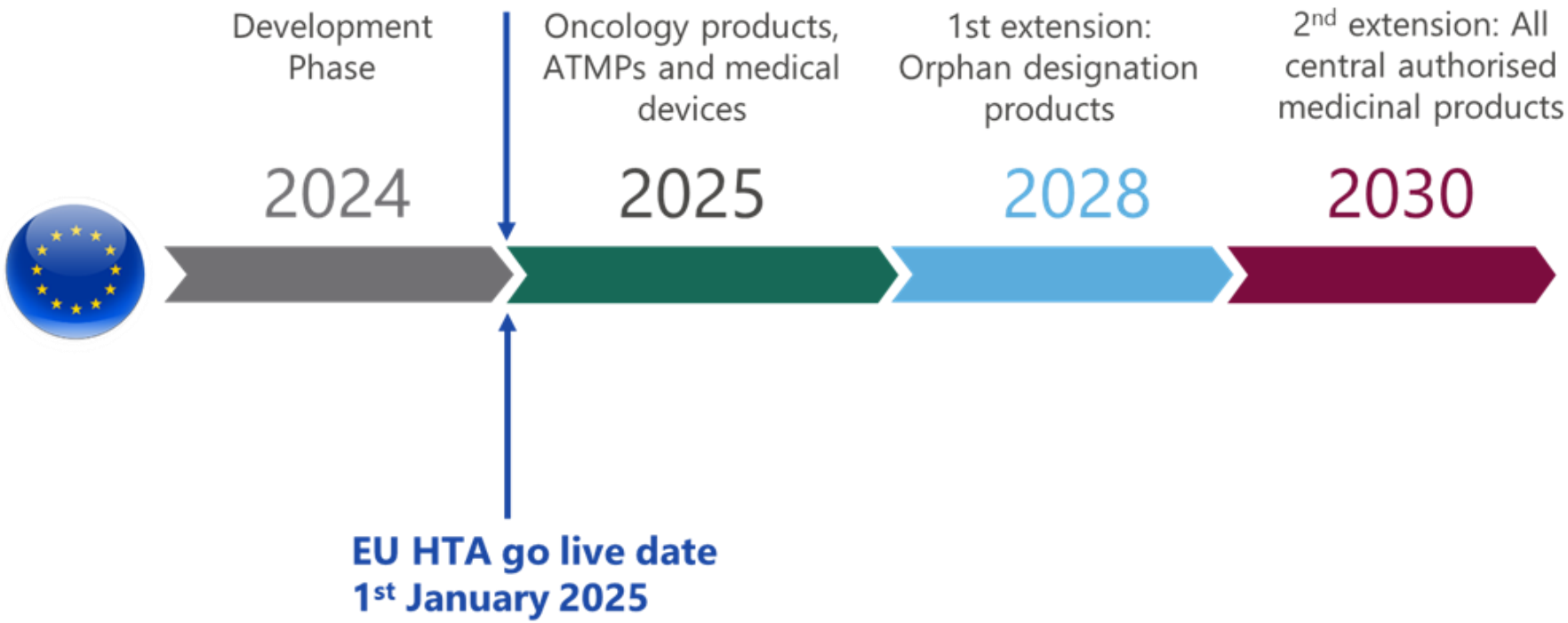
- Revision and strengthening of the regulation
- Multi-annual cross-border care authorisations
- Ending upfront payments
- Reform prior authorisations
- Expand scope to clinical trials
- Give legal status to European Reference Networks

European BioTech Act

General Remarks Bio Tech Act

- Integrate with relevant existing specialized clinical networks, including ERNs
- Facilitate structured real world data generation, in complementarity with existing Union data
- Ensure that scientific and industrial progress translates into meaningful benefits for patients
- Maintain high standards of scientific assessment, ethical review and patient safety
- Exchange of best practices across Member States on the preparation, handling, administration
- Structure involvement of patient and healthcare professional representatives
- Help developers navigate complex and overlapping regulatory requirements

Joint Clinical Assesment



Legal routes	Differences in treatment cost	Payment system	MEA confidentiality	Other
Social Security Regulations (EC) 883/2004 and 987/2009 ("S2 route") Treatment center abroad considers the patient as insured under the local, national healthcare system. The payer of the home country is bound to pay the total treatment cost (i.e. tariffs) of the guest country.	• Different medical costs can be covered by the payer of the home country • Reimbursement basis + VAT as agreed in the guest country • Does not cover travel costs	• Patient prepayment (usually) not required	• Risk of double compensation • No revenue for the manufacturer in the home country	
Directive 2011/24/EU Treatment center abroad will consider the patient as a private patient, so patient needs to prepay the treating hospital. A specific VAT rate for private patients might apply. The patient must cover the difference in total cost in the guest country and total cost in the home country.	• Reimbursement basis + VAT as agreed in the home country • Patient needs to cover the difference in cost between home and guest country (reimbursement basis + VAT private patient) • Does not cover travel costs	• Patient prepayment required	• Risk of double compensation • No revenue for the manufacturer in the home country	
National fund Additional safety nets on top of the regular health insurance system (e.g. SSF in BE)	• Can cover travel and accommodation costs • Possibly limited budget (e.g. closed envelope system) • Not a structural solution	• Patient prepayment usually not required	• Not addressed	
Backpack method The home country hospital will order the product with the manufacturer in the home country. The product will be delivered to the treating hospital in the guest country. The patient is considered as treated in the home country.	• Reimbursement basis + VAT as treated in the home country • But only relevant for pharmaceutical product	• Patient prepayment is not required	• Pharmaceutical company in the home country has revenue for MEA execution	• Legal restrictions
Direct agreement with hospital The payer of the home country sets up an agreement directly with the treatment center abroad. The payer of the guest country is not involved.	• Treatment cost can be agreed between payer's home country and treating hospital	• Patient prepayment is not required	• Risk of double compensation • No revenue for the manufacturer in the home country	• Only specific centers (limits the options) • Workload can rise with an increasing no of centers

ATMPs in the Hospital Pharmacy

Storage:

Nitrogen vapor & -80 °C

Handling:

Sensitive products / Patient specific

Preparation:

Risk assesment (Biohazard/Cleaning)

Logistics:

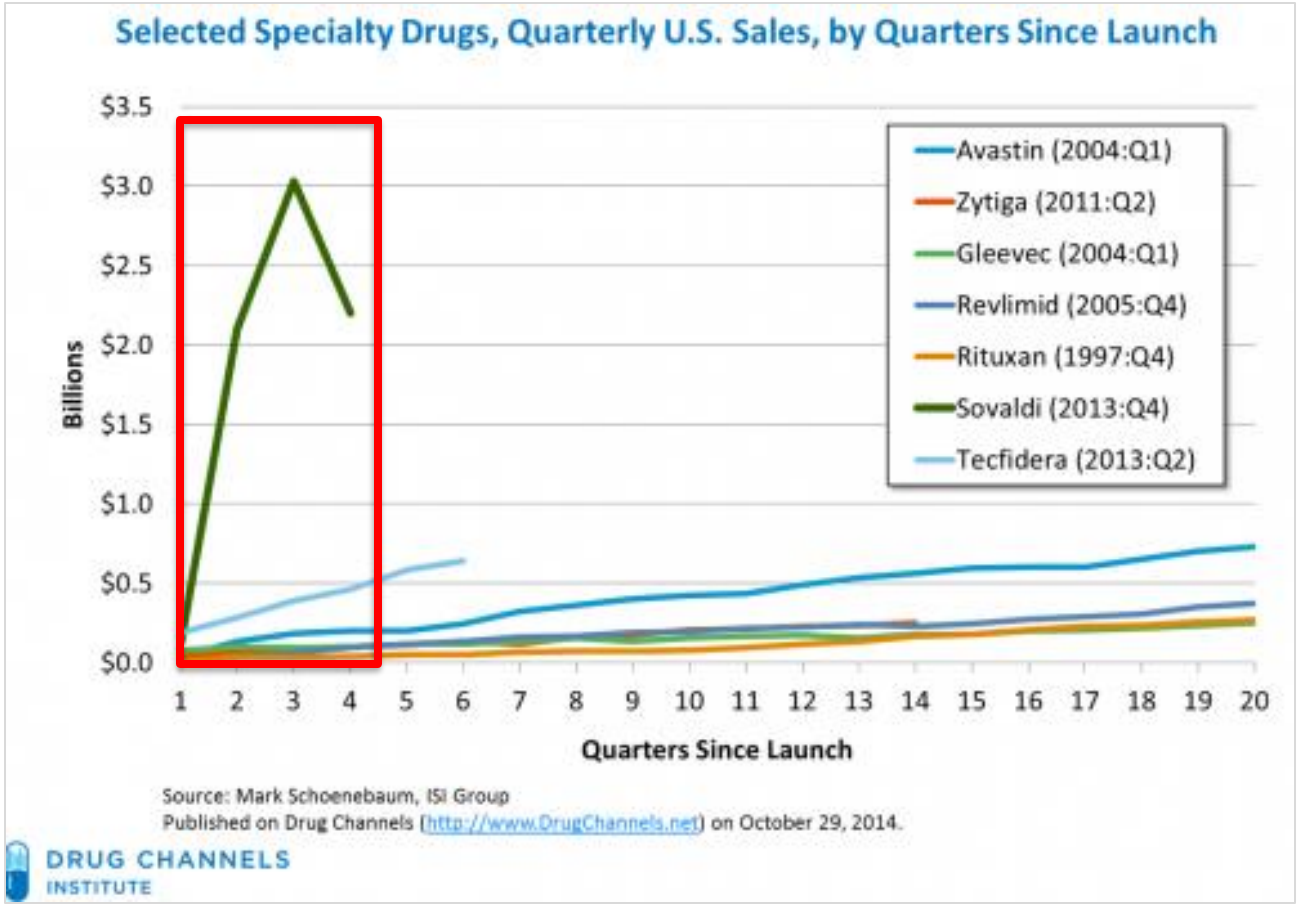
Short shelf life / Communication / €

BIOBank

BUDGET Impact Gene Therapies

Indication	Product	Regulatory approval	Market price[a]	Estimated number of eligible patients (US + Europe)
ADA-SCID[b]	Strimvelis (Orchard Therapeutics)	EMA-2016	€594,000	30–40
Leber amaurosis	Luxturna (Sparks Therapeutics)	FDA-2017 EMA-2018	$850,000	>2,000
SMA[c]	Zolgensma (Novartis)	FDA-2019	$2.1 million	>1,500
B-ALL[d]	Kymriah (Novartis)	FDA-2017 EMA-2018	$475,000	1,000
DLBCL[e]	Kymriah (Novartis)	FDA-2017 EMA-2018	$373,000	1,200
	Yescarta (Gilead)	FDA-2017 EMA-2018	$375,000	
β-thalassemia[f]	Zynteglo (Bluebird)	EMA-2019	€1.58 million	>10,000

THE PROBLEM OF CURING: IMMEDIATE FUNDING FOR UNCERTAIN LONG-TERM VALUE DELIVERED



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SYRIA
CYPRUS
LEBANON
ISRAEL
JORDAN
MOROCCO
ALGERIA
TUNISIA
MALTA
IHSI (International Horizon Scanning Initiative)
mapchart.net

r/r ALL

Timeline: reimbursement requests through e-health, with recording of patient assessments

Cell Chain		E-Health §100	E-Health §200	E-Health §300
Product request	Cells accepted on site	Electronic reimbursement request	Notify response and patient situation (NCCN criteria)	Notify response and patient situation (NCCN criteria)

Patient selected → Delivery day → Perfusion day → + 6 months → + 12 months

Patient assessments			
		Blood/ Bone marrow examination	Blood/ Bone marrow examination

Invoice/reimbursement request	X	X	X
	280.000€	20.000€	20.000€

Future challenges in Care sector

- Most expert centres have no budget / no extra staff
- Tensions on the budget at hospital level / detrimental for RD
- Coordination requires long-term financial support
- No interoperability between local hospital systems

Ethics no longer a value

Innovative Medicines for Children