Infinite Possibilities: The Past, Present, and Future of Rare Disease Therapeutics

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RARE DISEASES *by the* NUMBERS

50%

of the people affected by rare diseases are **children**

Approximately

7,000

rare diseases & disorders have been identified

in the U.S. are living with rare diseases

in Europe are living with rare diseases

#DYK:

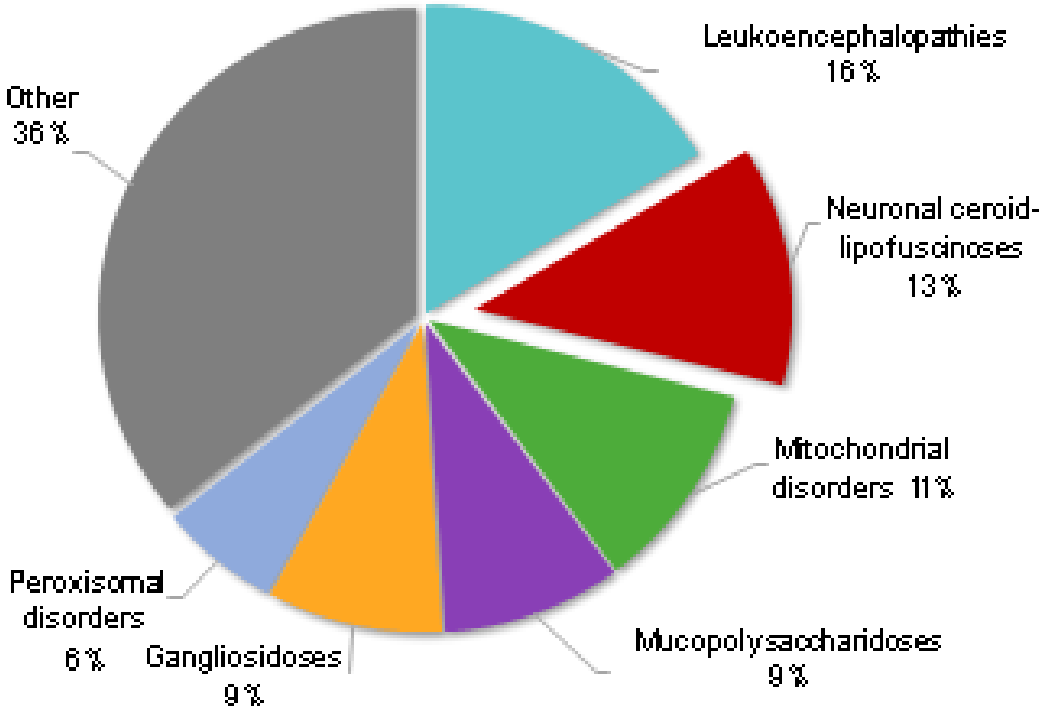
If all of the people with rare diseases lived in one country, it would be the

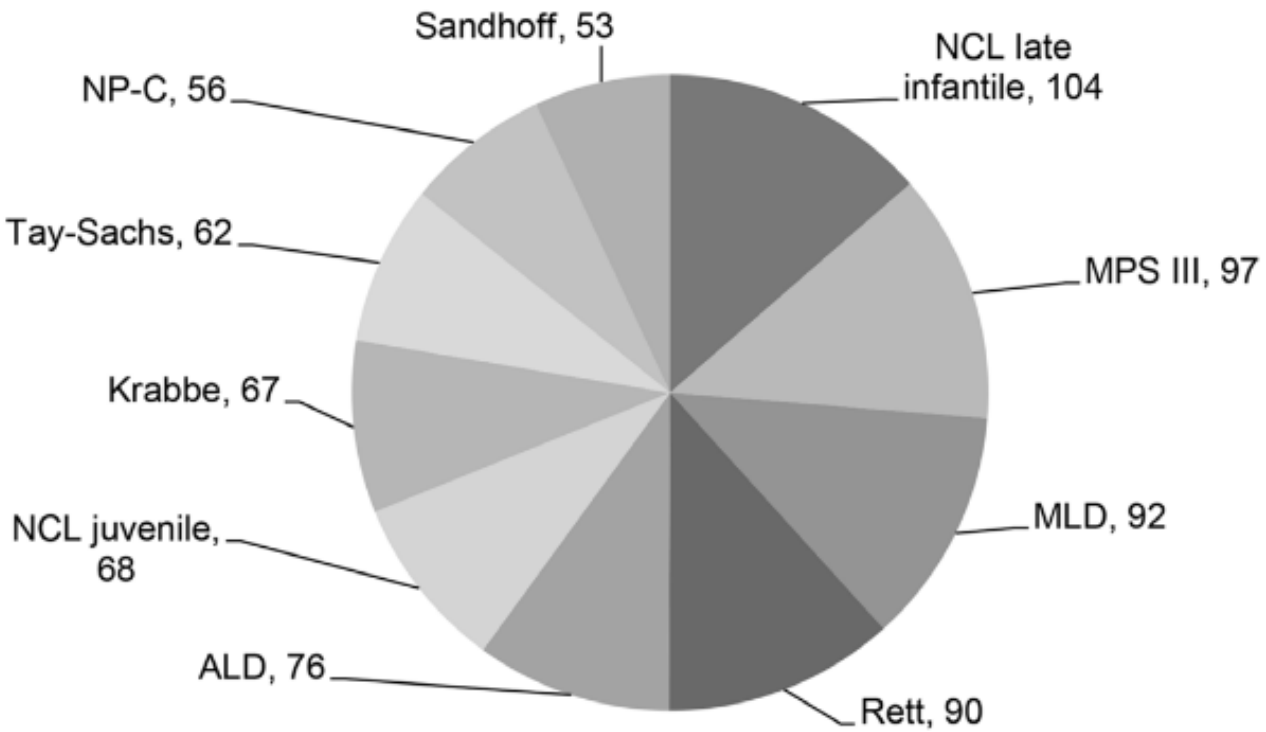
world's 3rd most populous country

Source: Global Genes. https://globalgenes.org/rare-diseases-facts-statistics/

PAST

Diagnoses in children with progressive intellectual & neurologic deterioration (PIND)





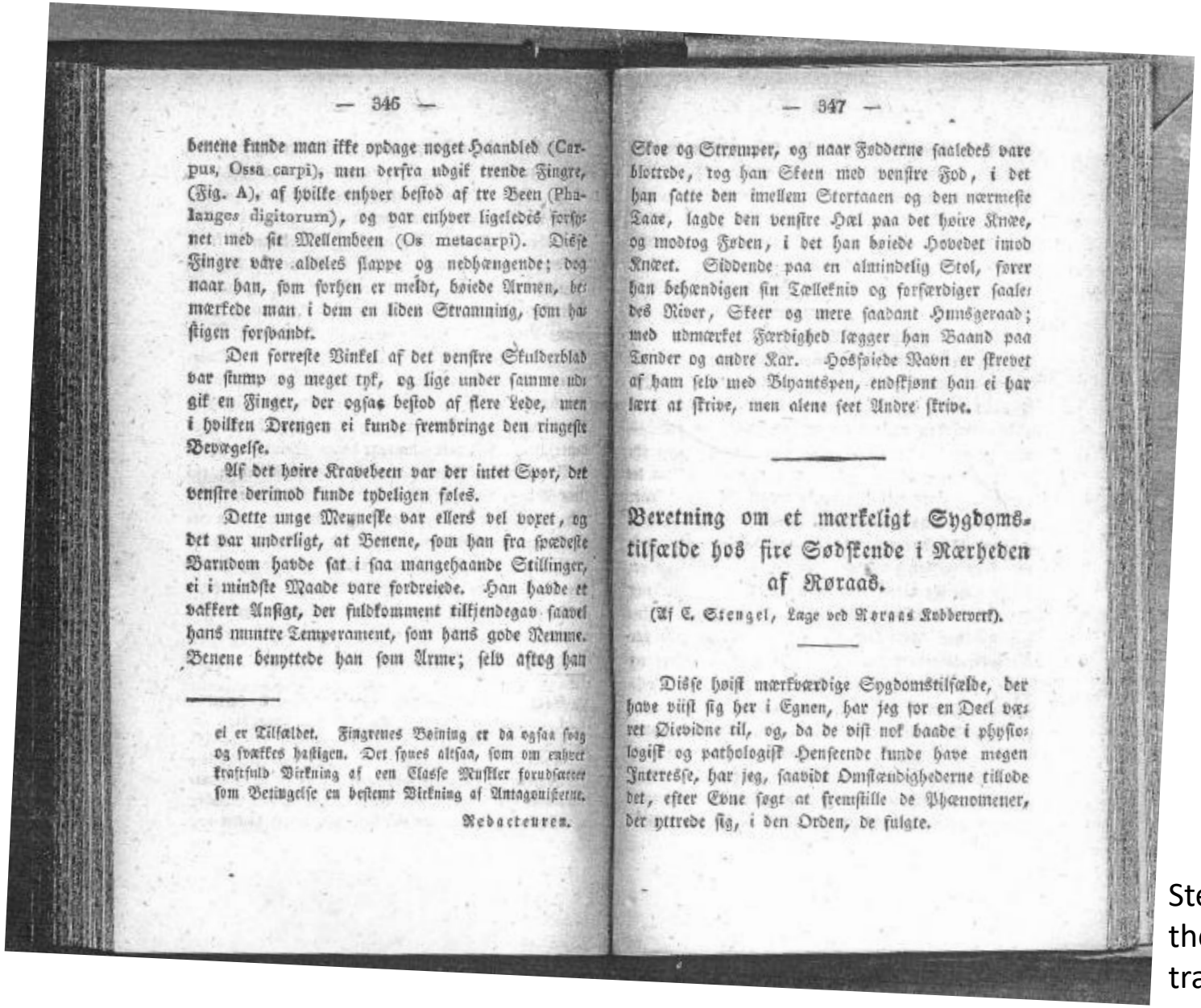
12-year UK epidemiologic study of PIND, 147 different diagnoses were recorded in 1114 of 2636 patients <16 years.

Top 10 diagnoses in n=1819 children diagnosed with PIND in the UK 1997 - 2017.

Verity C, et al. *Arch Dis Child*. 2010;95:361–364.

Verity C, et al. *Arch Dis Child*. 2018

Neuronal Ceroid Lipofuscinosis – Historical Perspective



— 346 —

benene kunde man ikke opdage noget Haandled (Carpus, Ossa carpi), men derfra udgik trende Fingre, (Fig. A), af hvilke enhver bestod af tre Been (Phalanges digitorum), og var enhver ligeledes forsynet med sit Mellembeen (Os metacarpi). Disse Fingre vare aldeles slappe og nedhængende; dog naar han, som forhen er meldt, bøiede Armen, bemærkede man i dem en liden Stramning, som hastigen forsvandt.

Den forreste Vinkel af det venstre Skulderblad var stump og meget tyk, og lige under samme udgik en Finger, der ogsaa bestod af flere Lede, men i hvilken Drengen ei kunde frembringe den ringeste Bevægelse.

Af det høire Kraveben var der intet Spor, det venstre derimod kunde tydeligen føles.

Dette unge Menneske var ellers vel voxet, og det var underligt, at Benene, som han fra spædeste Barndom havde sat i saa mangehaande Stillinger, ei i mindste Maade vare fordreiede. Han havde et vakkert Ansigt, der fuldkomment tilkjendegav saavel hans muntre Temperament, som hans gode Nemme. Benene benyttede han som Arme; selv aftog han

ei er Tilfældet. Fingrenes Boining er da ogsaa svag og svækkes hastigen. Det synes altsaa, som om enhver kraftfuld Virkning af een Classe Muskler forudsætter som Betingelse en bestemt Virkning af Antagonisterne.

Redacteuren.

— 347 —

Skoe og Strømper, og naar Fødderne saaledes vare blottede, tog han Skeen med venstre Fod, i det han satte den imellem Storta aen og den nærmeste Taae, lagde den venstre Hæl paa det høire Knæe, og modtog Føden, i det han bøiede Hovedet imod Knæet. Siddende paa en almindelig Stol, fører han behændigen sin Tælleknib og forfærdiger saaledes River, Skeer og mere saadant Husgeraad; med udmærket Færdighed lægger han Baand paa Tønder og andre Kar. Hosføiede Navn er skrevet af ham selv med Blyantspen, endskjønt han ei har lært at skrive, men alene seet Andre skrive.

Beretning om et mærkeligt Sygdomstilfælde hos fire Sødskende i Nærheden af Røraas.

(Af C. Stengel, Læge ved Røraas Kobberverk).

Disse høist mærkværdige Sygdomstilfælde, der have viist sig her i Egnen, har jeg for en Deel været Øievidne til, og, da de vist nok baade i physiologisk og pathologisk Henseende kunde have megen Interesse, har jeg, saavidt Omstændighederne tillode det, efter Evne søgt at fremstille de Phænomener, der yttrede sig, i den Orden, de fulgte.

Otto Christian Stengel (1826)

1st description of NCL

Stengel O. Report about a strange illness in four siblings in the vicinity of Røros [in Norwegian]. Hager P, Andersen T, trans. *Eyr*. 1826;1:347-352

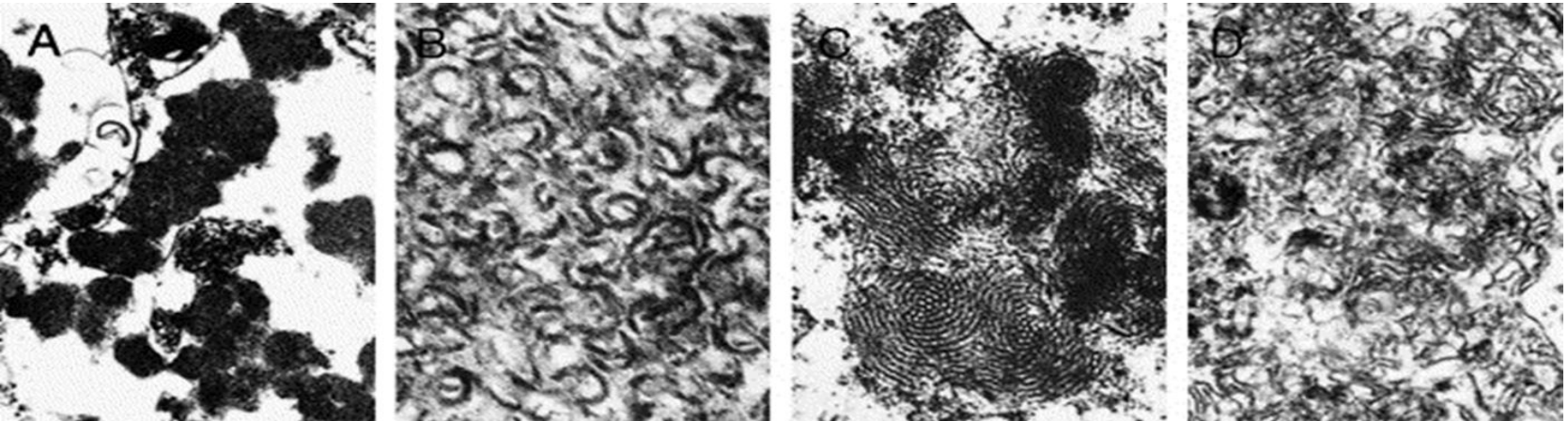
Neuronal Ceroid Lipofuscinosis – Historical Perspective

- Otto Christian Stengel (1826) – 1st description of NCL
- Batten (1903) – 1st report with pathology
- Vogt (1905), Spielmeyer (1905)
- Jansky (1908), Bielschowsky (1913) – reported a similar late-infantile onset disorder
- Kufs (1925) – reported a similar adult-onset disorder
- Haltia and Santavuori (1973) – described infantile-onset form

Mink JW, et al. *J Child Neurol* 2013;28(9):1101-1105.

Neuronal Ceroid Lipofuscinoses

- Group of lysosomal storage diseases
- Most prevalent neurodegenerative disorder of childhood, 1:12,500
- Unifying clinicopathologic features
  - clinical symptoms
  - progressive neuronal loss
  - autofluorescent storage material



A: GRODs

B: curvilinear profiles

C: fingerprint patterns

D: rectilinear profiles

Haltia et al, Biochim et Biophys Acta 2006; 1762: 850–856

NCL type	Intervention	Indication	Sample size	Duration of follow-up	Conclusion	Reference
Case Series						
JNCL	Antioxidants	Disease modification	74	6-18 yrs	Inconclusive	Santavuori 1988
Open label, single group clinical trials						
JNCL	Polyunsaturated fatty acids	Disease modification	5	1 yr	Inconclusive	Bennett 1988
LINCL, JNCL	Antioxidants	Disease modification	3	0.5 - 1.75 yrs	Inconclusive	Naidu 1988
JNCL	Polyunsaturated fatty acids	Disease modification	6	4 -7 yrs	Possibly effective	Bennett 1994
Open label, historical control clinical trial						
JNCL	Antioxidants	Disease modification	43	8 yrs	Possibly effective	Santavuori 1989
Open label, parallel group clinical trials						
JNCL	Antioxidants	Disease modification	46	Unknown	Possibly effective	Santavuori 1977
JNCL	Antioxidants	Disease modification	125	4 - 11 yrs	Partially effective	Santavuori 1985
Randomized, placebo controlled, clinical trial						
JNCL	Antiparkinsonian drugs	Parkinsonism	8	11-13 wks per treatment period x3	Ineffective	Zweije-Hofman 1982

Augustine, et al. *J Child Neurol* 2013

PAST

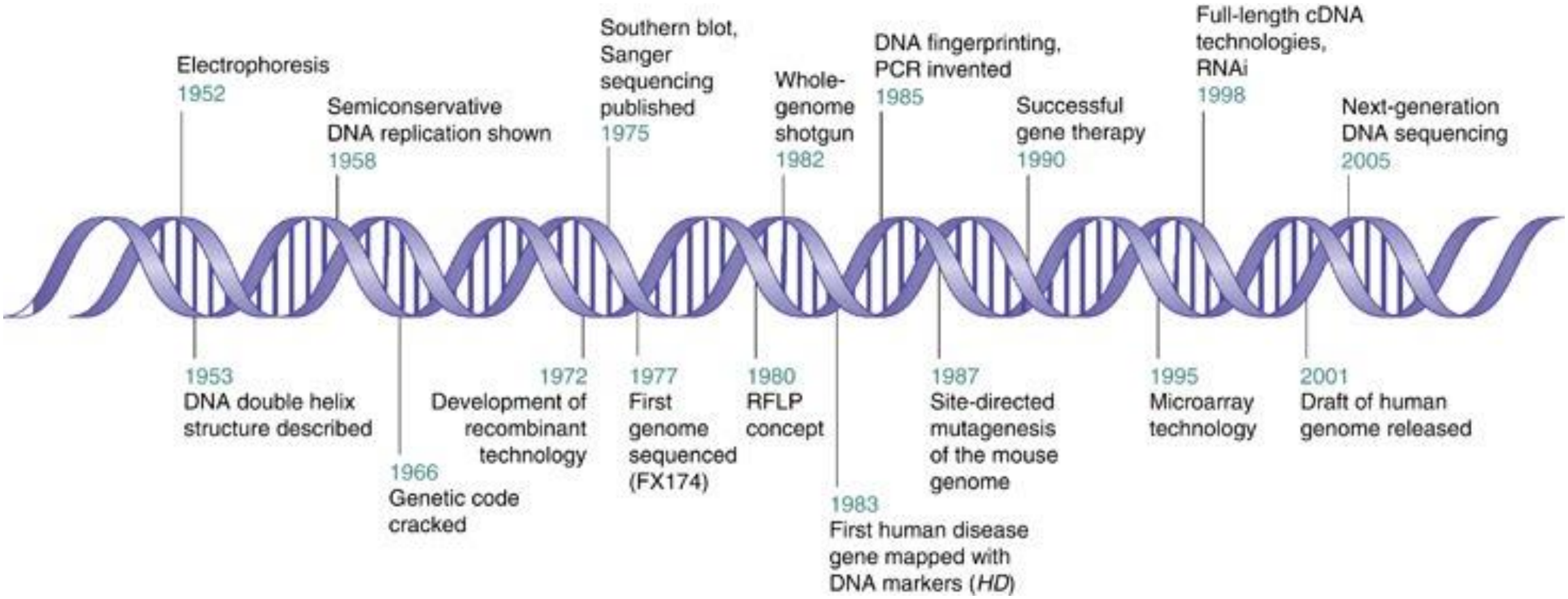
Describing phenomenology, grouping characteristics, and linking to pathological findings

PRESENT

Diagnostic Odyssey

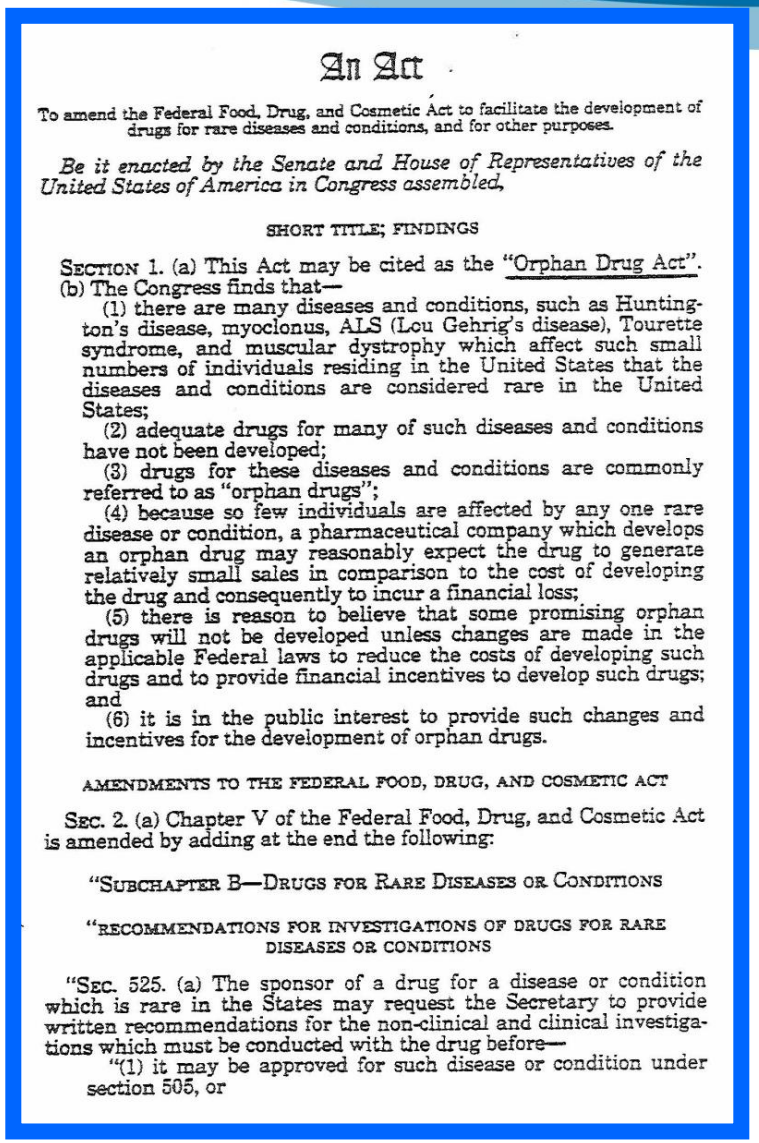
- Average 5-7 years to diagnosis
- 40% have misdiagnosis
- Up to 50% never achieve a specific disease diagnosis

Genetic discoveries



The Orphan Drug Act (ODA)

- Decade prior to 1983 – only ~1 drug/year independently developed by pharmaceutical sponsors
- Legislation needed to promote rare disease drug development
- The Orphan Drug Act signed into law on Jan. 4, 1983



An Act

To amend the Federal Food, Drug, and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SHORT TITLE; FINDINGS

SECTION 1. (a) This Act may be cited as the "Orphan Drug Act".
(b) The Congress finds that—
(1) there are many diseases and conditions, such as Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome, and muscular dystrophy which affect such small numbers of individuals residing in the United States that the diseases and conditions are considered rare in the United States;
(2) adequate drugs for many of such diseases and conditions have not been developed;
(3) drugs for these diseases and conditions are commonly referred to as "orphan drugs";
(4) because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss;
(5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs; and
(6) it is in the public interest to provide such changes and incentives for the development of orphan drugs.

AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

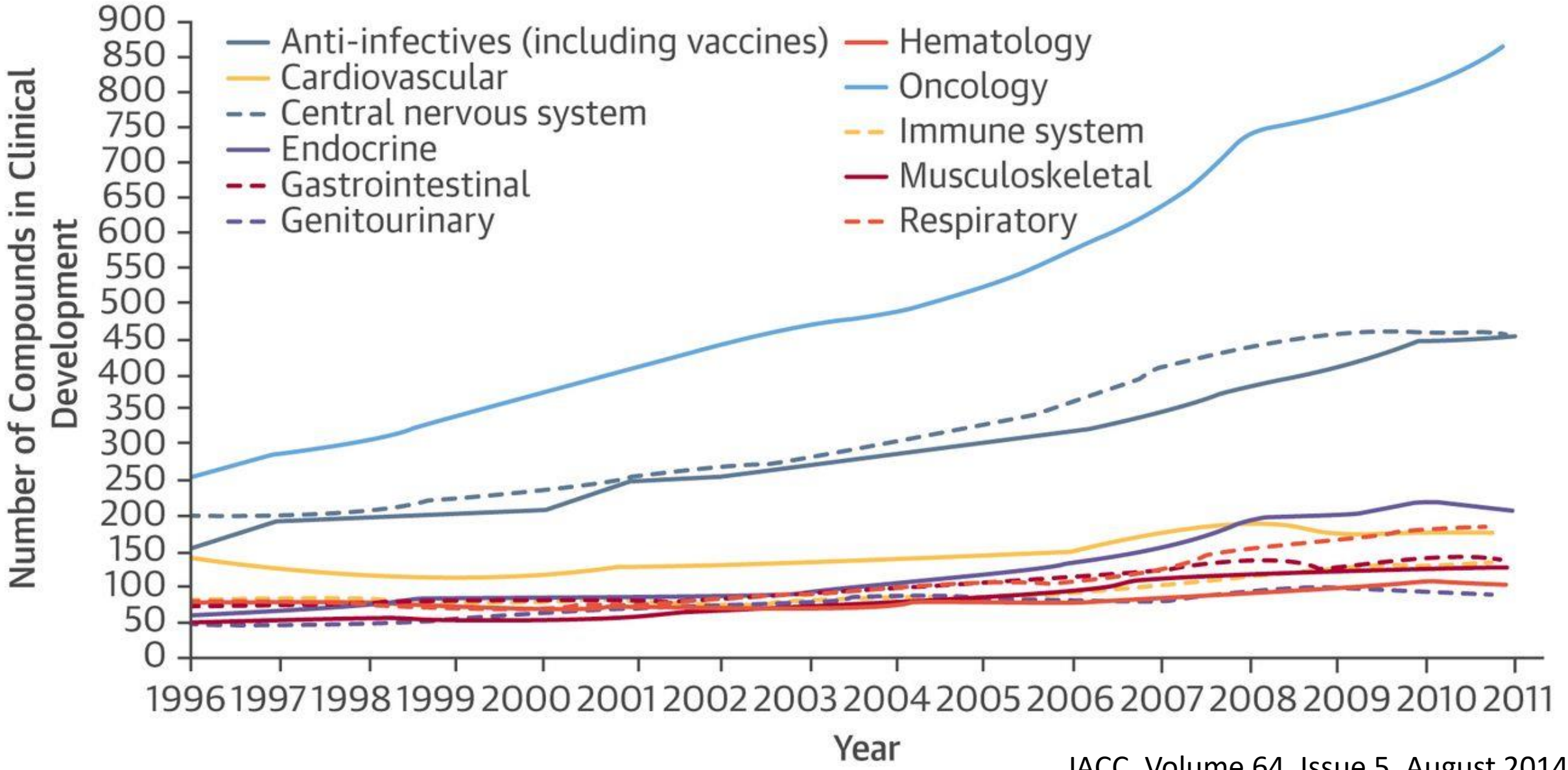
SEC. 2. (a) Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by adding at the end the following:

"SUBCHAPTER B—DRUGS FOR RARE DISEASES OR CONDITIONS

"RECOMMENDATIONS FOR INVESTIGATIONS OF DRUGS FOR RARE DISEASES OR CONDITIONS

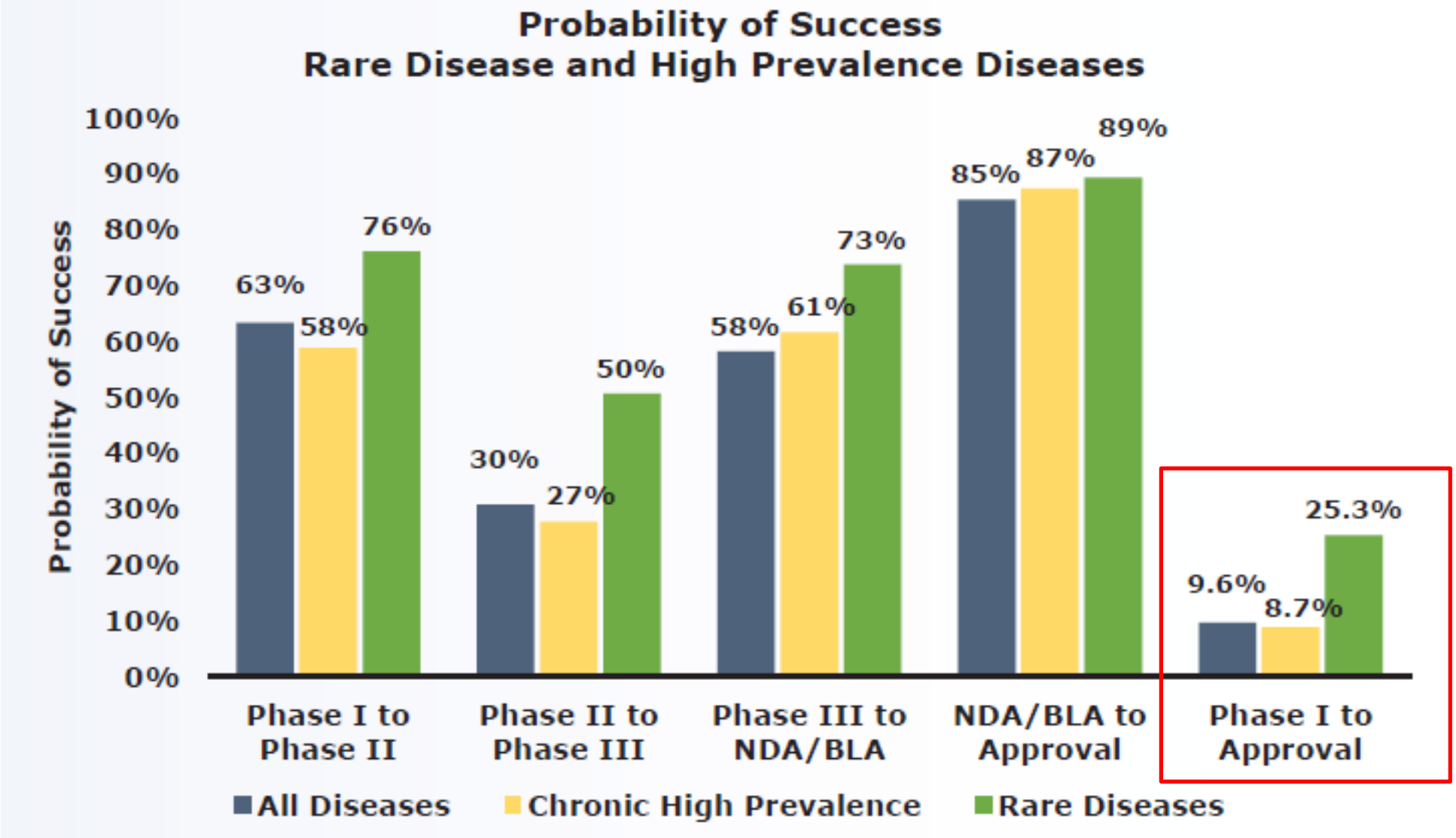
"SEC. 525. (a) The sponsor of a drug for a disease or condition which is rare in the States may request the Secretary to provide written recommendations for the non-clinical and clinical investigations which must be conducted with the drug before—
"(1) it may be approved for such disease or condition under section 505, or

Development for CNS disorders is rising



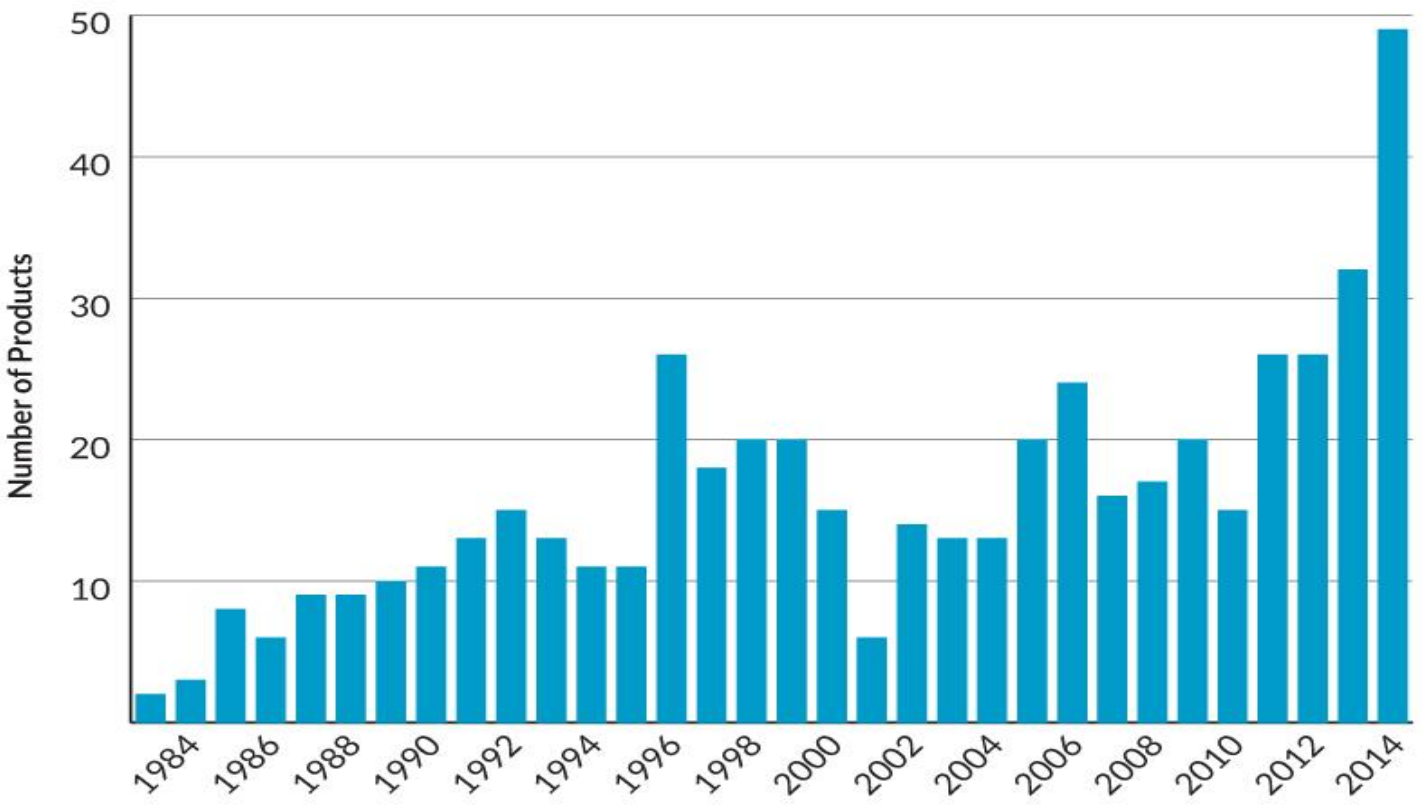
JACC. Volume 64, Issue 5, August 2014

Higher rates of success for rare diseases



http://www.raredr.com/news/orphan-approval; Clinical Development Success Rates 2006-2015, BIO

Orphan Product Approvals



XADAGO® (safinamide) tablets

INGREZZA™ (valbenazine) capsules

NUPLAZID™ (pimavanserin) tablets

OCREVUS™ ocrelizumab

Zinbryta® (daclizumab)

BRIVIACT® (brivaracetam)

Radicava™ (edaravone) IV infusion 30mg/100mL

Brineura™ (cerliponase alfa)

EXONDYS 51™ (eteplirsen) Injection

Emflaza™ (deflazacort)

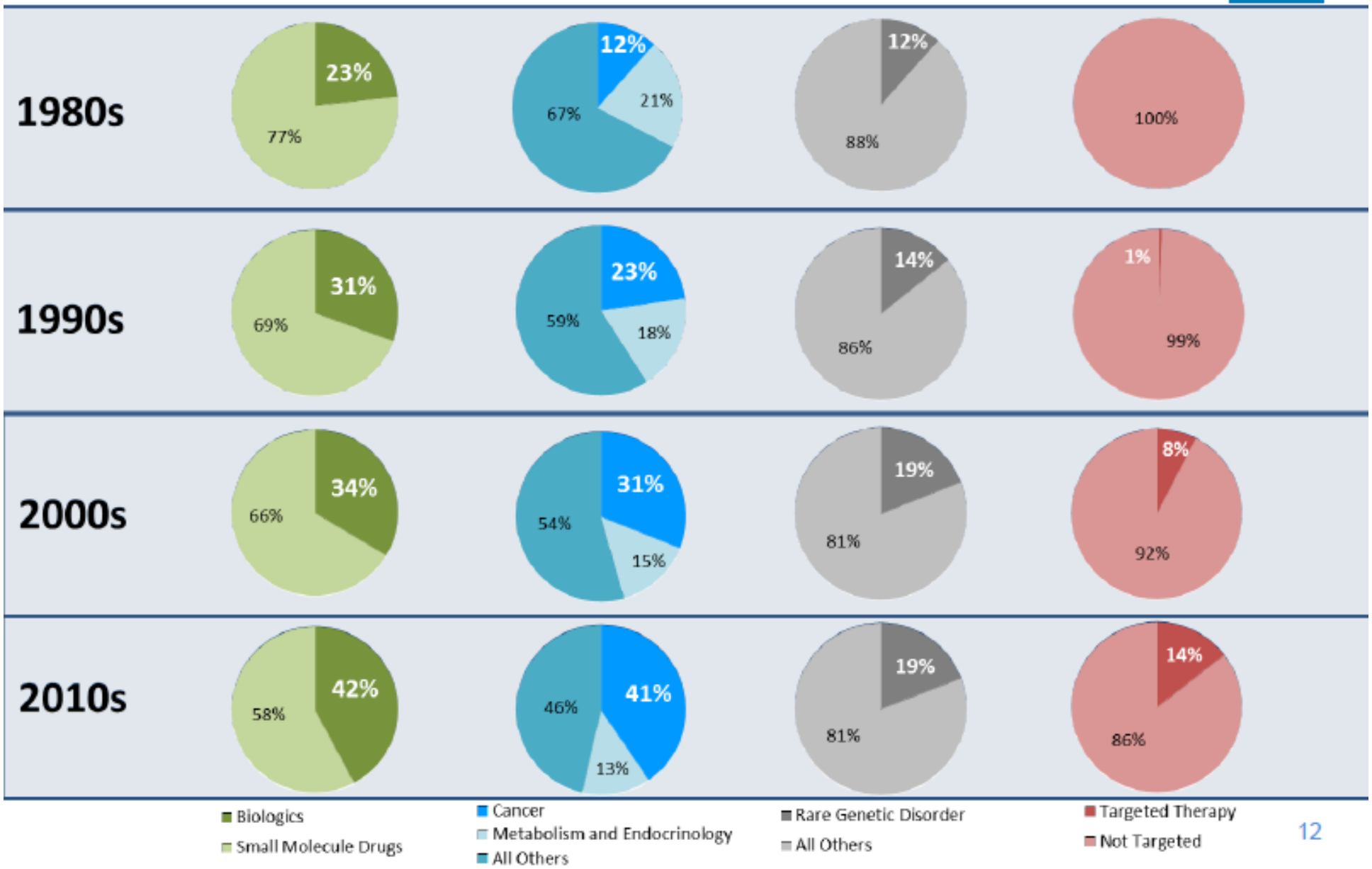
SPINRAZA® (nusinersen) injection 12 mg/5 mL

Austedo™ (deutetrabenazine) tablets

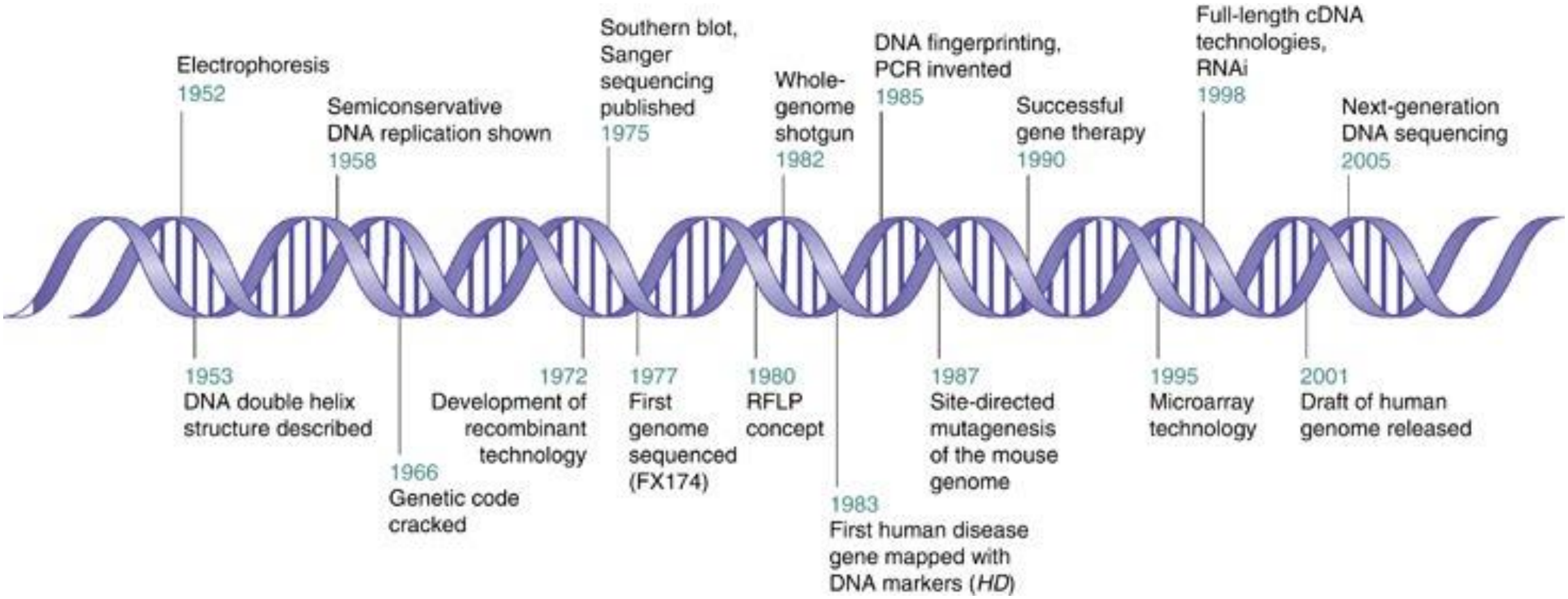
The Orphan Drug Act has had strong impact and rare disease approvals are on the rise

Source: FDA Law Blog

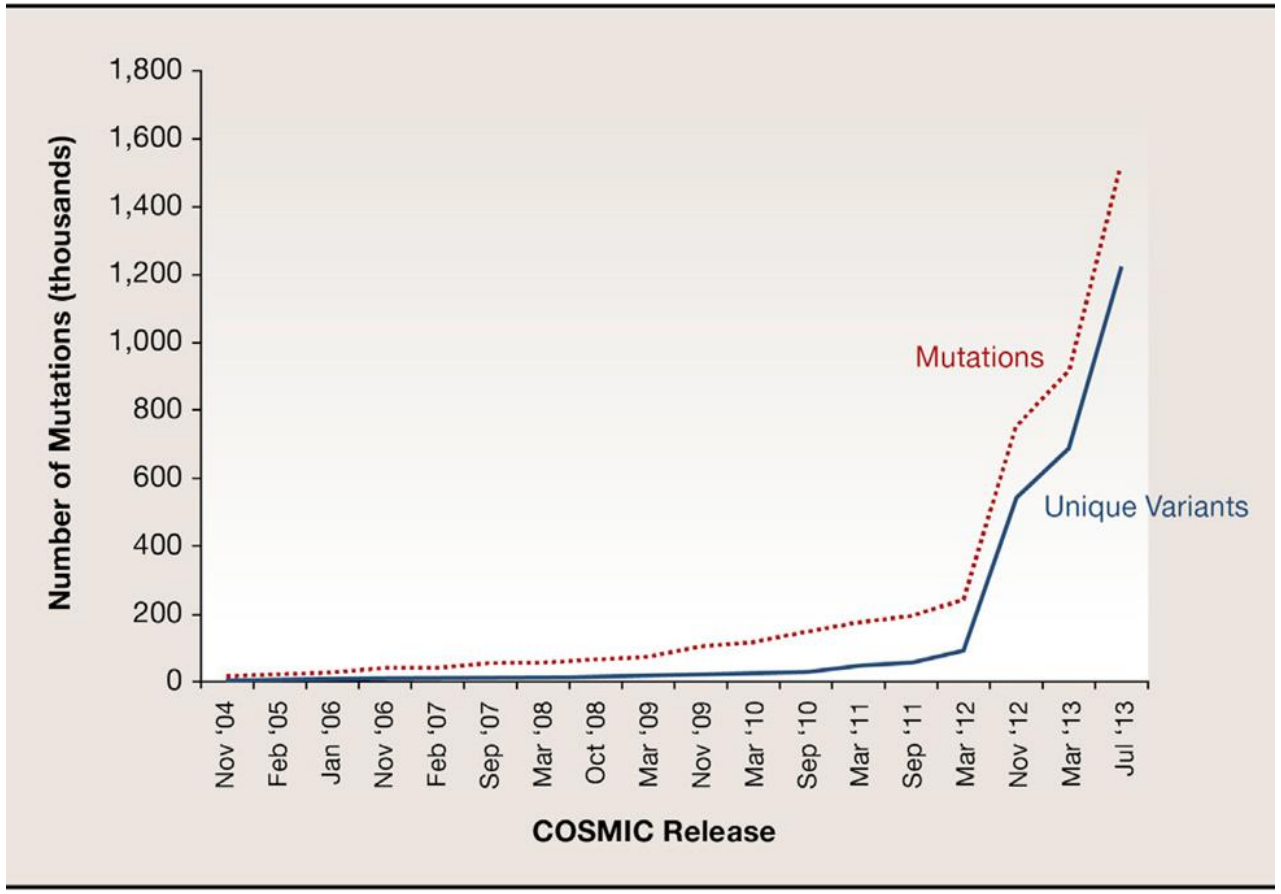
Orphan Drug Approval Characteristics Have Shifted Over Time



Genetic discoveries



Impact of the Next Generation Sequencing Era



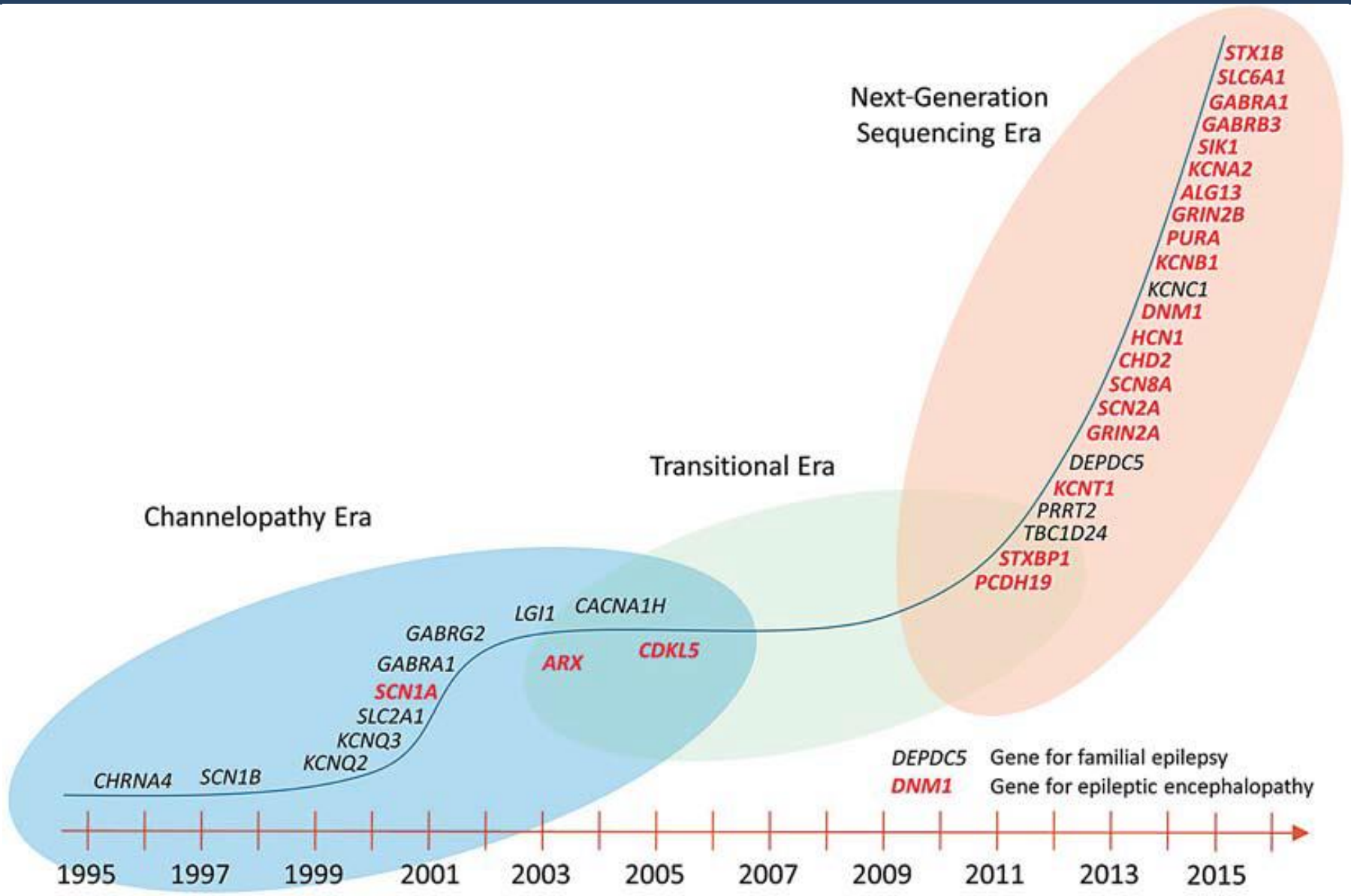
Inheritance Pattern	January 2007	July 2013
Autosomal	1,851	3,525
X Linked	169	277
Y Linked	2	4
Mitochondrial	26	28
Total	2,048	3,834

OMIM Phenotypes for which the Molecular Basis is Known (2007 & 2013)

The # of recognized unique mutations and unique variants is rising

DC Koboldt, et al. Cell 2013; 155(1):27-38

Timeline of gene discovery in epilepsy



Mol Syndromol 2016;7:172–181

Gene	Age at Onset	Chromosome	Protein	Ultrastructure
CLN1	Infantile Late infantile, juvenile, and adult	1p32	PPT1	Granular Osmophilic deposits (GRODS)
CLN2	Late infantile Juvenile	11p15	TPP1	Curvilinear profiles
CLN3	Juvenile	16p12	Transmembrane protein (lysosomal)	Fingerprint profiles
CLN4 (DNAJC5)	Adult (AD) (Parry)	20q13.33	Cysteine string protein	Rectilinear profiles
CLN5	Late infantile (Finnish variant)	13q22	Soluble protein (lysosomal)	Rectilinear profiles, Curvilinear profiles, Fingerprint profiles
CLN6	Late Infantile Adult (Kufs)	15q21	Transmembrane protein (endoplasmic reticulum)	Rectilinear profiles, Curvilinear profiles, Fingerprint profiles
CLN7	Late Infantile (Turkish variant)	4q28	MFSD8, membrane protein (lysosomal)	Fingerprint profiles
CLN8	Late infantile (Northern epilepsy)	8q23	Transmembrane protein (endoplasmic reticulum)	Curvilinear profiles
CLN10	Congenital	11p15	Cathepsin D	GRODS

Current NCL Classification

New Classification of NCL Disorders

According to GENES and CLINICAL TYPE

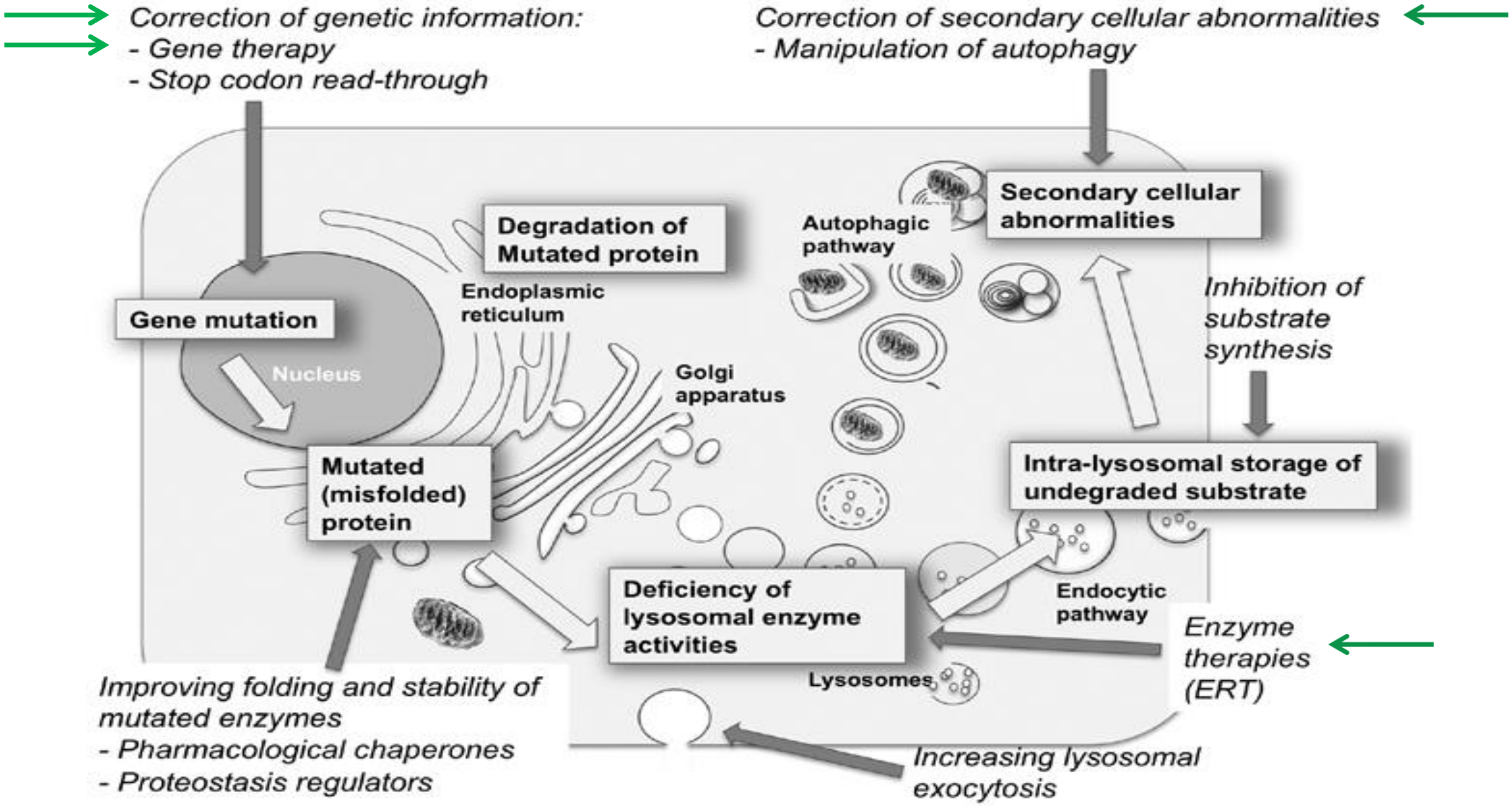
Designation of disease

Genetic type	*Mutated gene*	*Clinical type (age of onset)*
• **CLNX**	• **CLNX disease**	• **Infantile** (6–24 months) • **Late infantile** (2–5 years) • **Juvenile** (5–7 years) • **Adult**

Example: **CLN2 disease, late infantile**

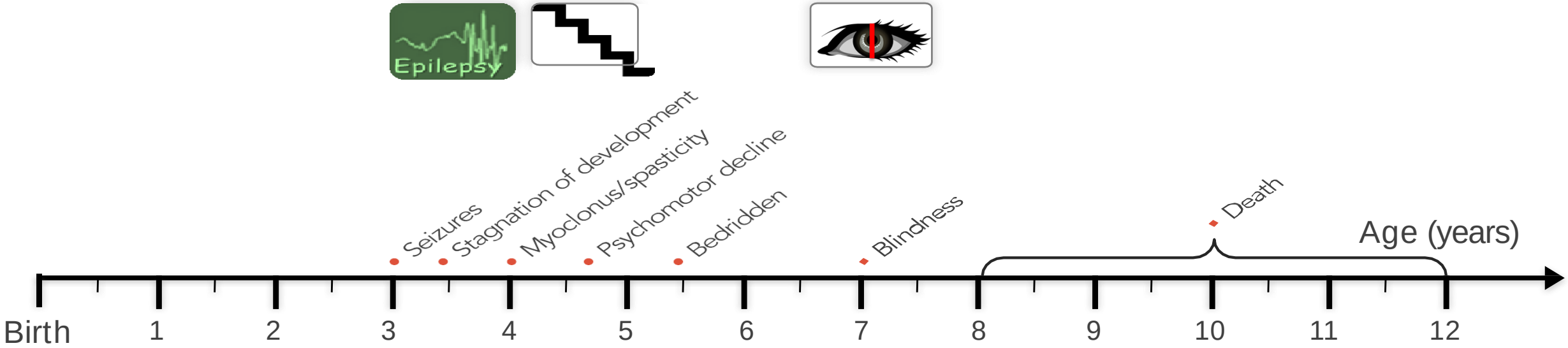
Williams RE, Mole SE. *Neurology.* 2012;79:183-191.

Rational Therapeutic Targets for NCLs



G Parenti et al. Int J Mol Med. 2013; 31: 11-20.

Clinical Presentation Of CLN2 Disease/TPP1 Deficiency



Early features (2-4 years):

- Early language delay
- Seizures, often polymorphic
- Increasing developmental concerns
- Referral for diagnostic investigations
- Developmental stasis

Rapidly Progressing (3-5 years):

- Drug-resistant seizures
- Loss of milestones
- Progressive dementia
- Movement disorder
- Sleep disorder
- Worsening mobility
- Pain and irritability

Prolonged Late stage :

- Gastrostomy dependent
- Dysphagia
- Loss of communication
- Loss of voluntary movement
- Ongoing seizures and myoclonus
- Spasticity, contractures

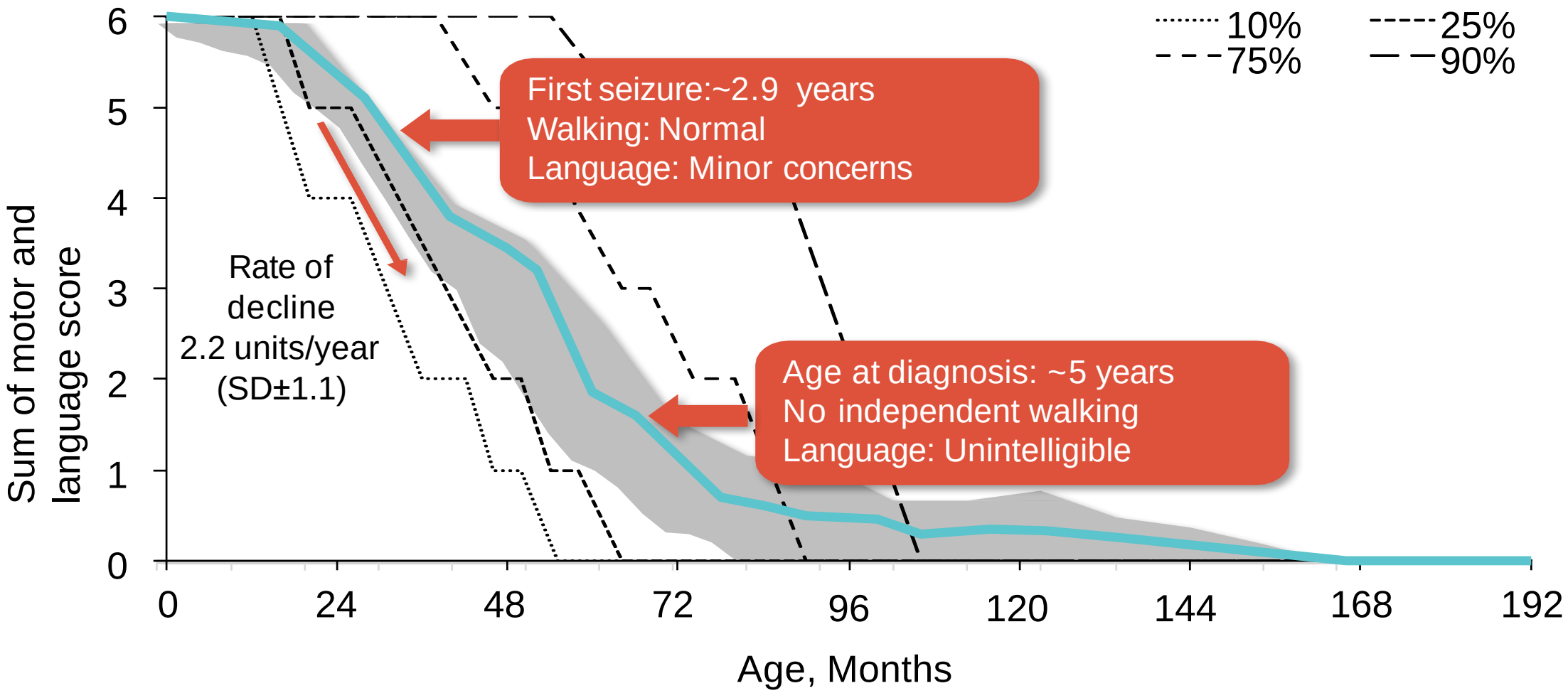
Adapted from: Kohlschütter A. *Pediatr Endocrinol Rev* 2016

Motor & language function scoring (CLN2)

Score	Functional Description	
	Motor Domain	Language Domain
3	Has grossly normal gait; no prominent ataxia, no pathologic falls	Has apparently normal language that is intelligible and grossly age-appropriate, with no decline noted
2	Has independent gait as defined by ability to walk without support for 10 steps; obvious instability and possibly intermittent falls	Has language that has recognizable abnormalities but includes some intelligible words; may form short sentences to convey concepts, requests, or needs
1	Requires external assistance to walk or can only crawl	Has language that is hard to understand with few intelligible words
0	Can no longer walk or crawl	Has no intelligible words or vocalizations

Schulz et al., 2018

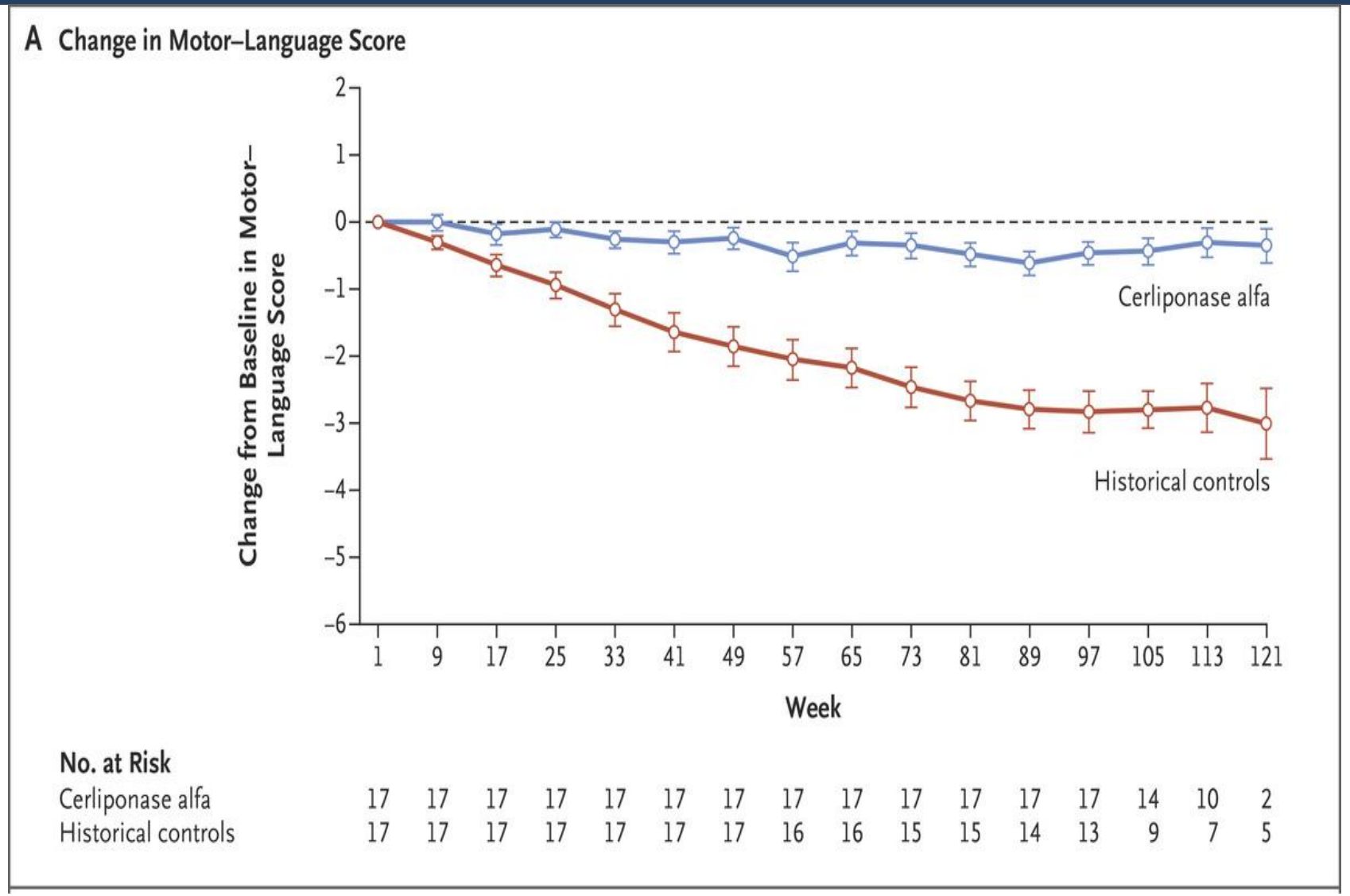
CLN2 Natural History

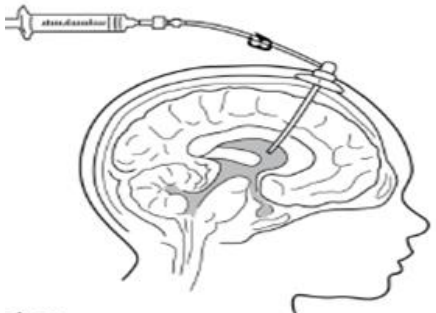


N=58 subjects with CLN2 disease in the DEM-CHILD registry, a multinational NCL patient database.

Nickel M, et al. *Europ J Paed Neuro* 2015 PP03.8 – 2898.

Cerliponase alfa – approved for prevention of loss of ambulation in CLN2 disease (2017)





A Schulz, et al. NEJM 2018.

Spinal Muscular Atrophy (SMA)
Leading Genetic Cause of Infant Mortality

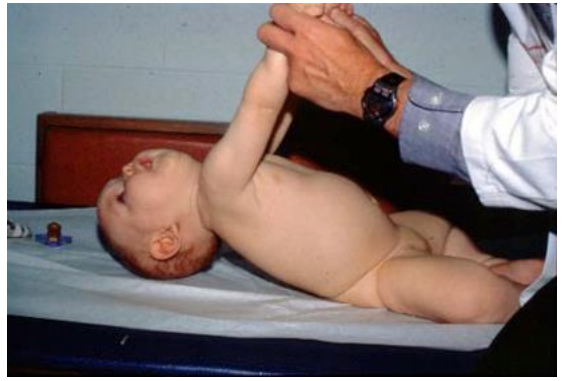
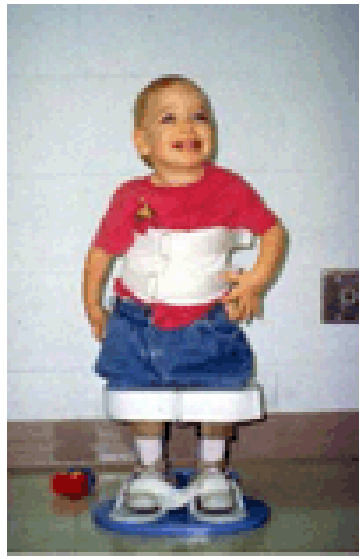


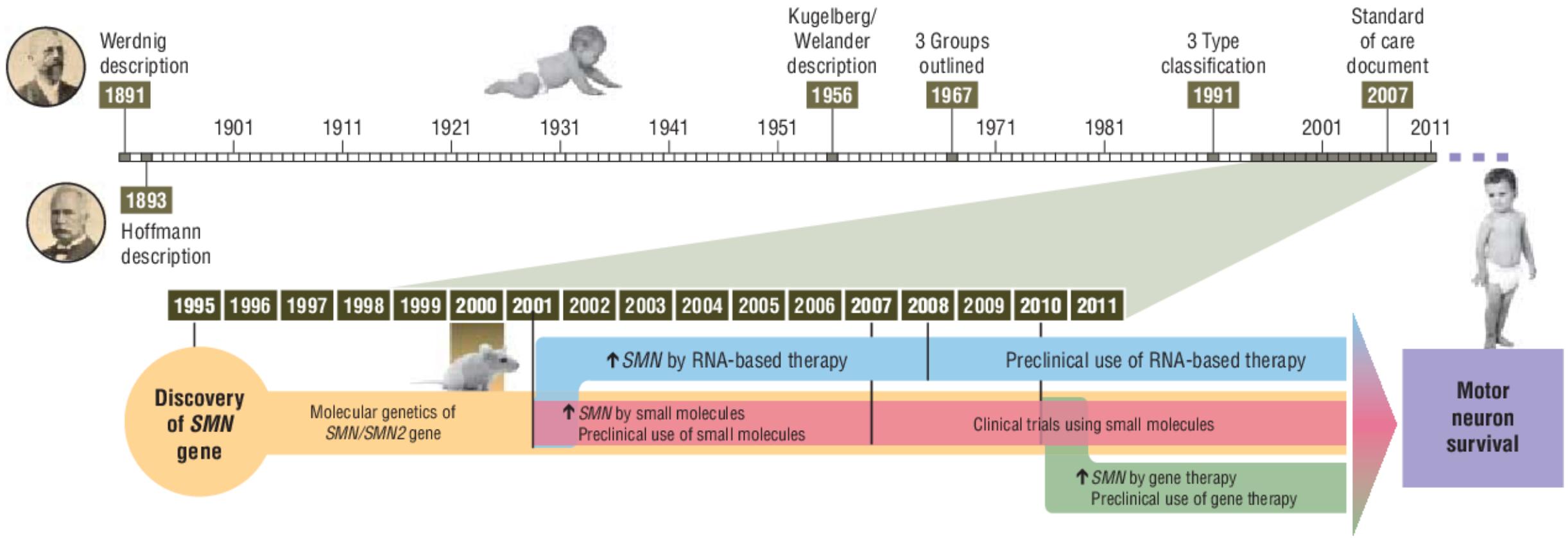
Table 1
Spinal muscular atrophy classification

Type	Age of Onset	Highest Function	Natural Age of Death
0	Prenatal	Respiratory support	<1 mo
1	0–6 mo	Never sit	<2 y
2	<18 mo	Never stand	>2 y
3	>18 mo	Stand alone	Adult
3a	18 mo–3 y	Stand alone	Adult
3b	>3 y	Stand alone	Adult
4	>21 y	Stand alone	Adult



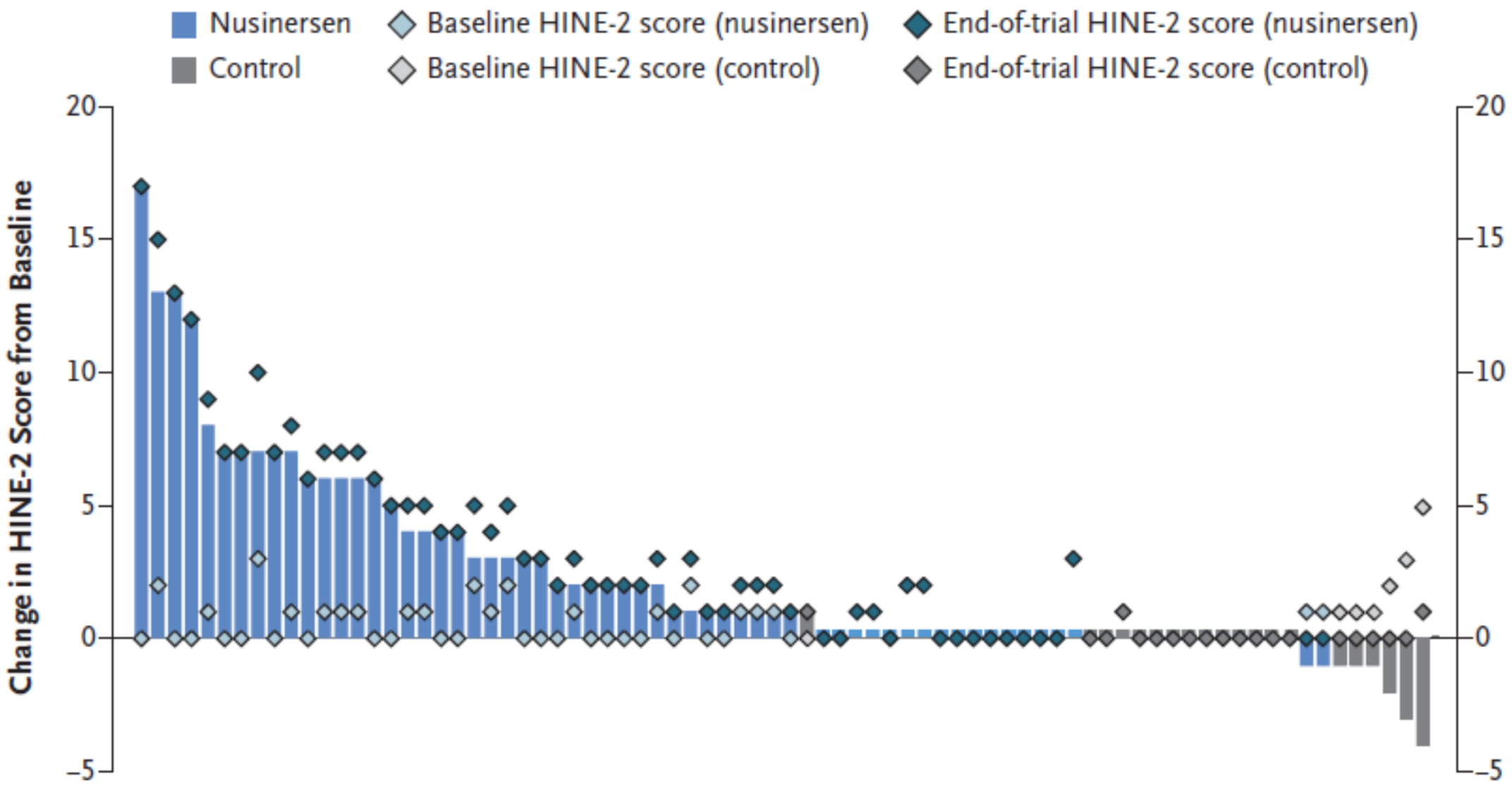
Neurol Clin 33 (2015) 831–846

Spinal Muscular Atrophy Timeline



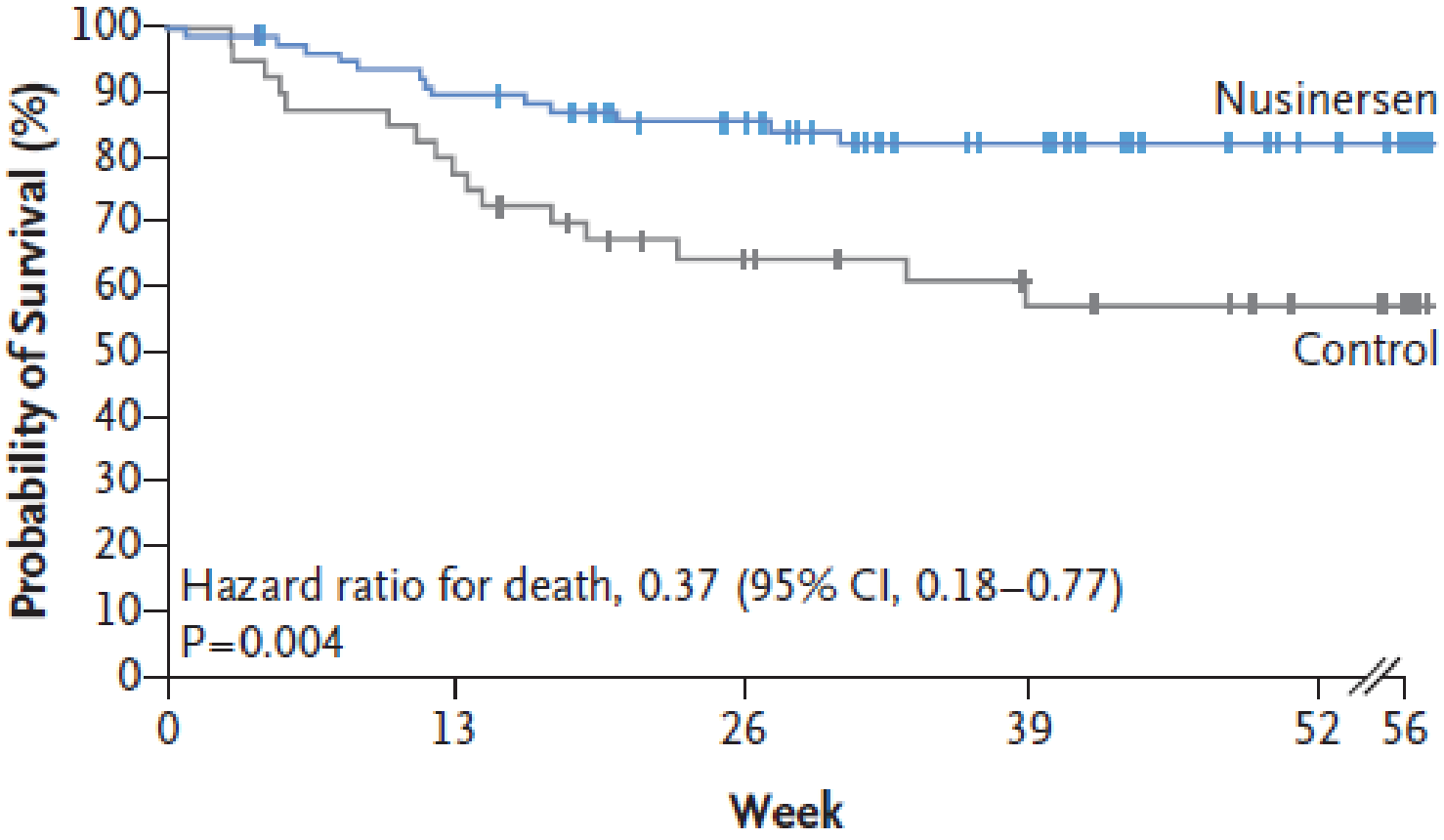
SJ Kolb and JT Kissel. Archives of neurology 68 8 (2011): 979-84 .

2017: 1st treatment for Spinal Muscular Atrophy



N Engl J Med 2017;377:1723-32.

Nusinersen impacts survival for patients with SMA

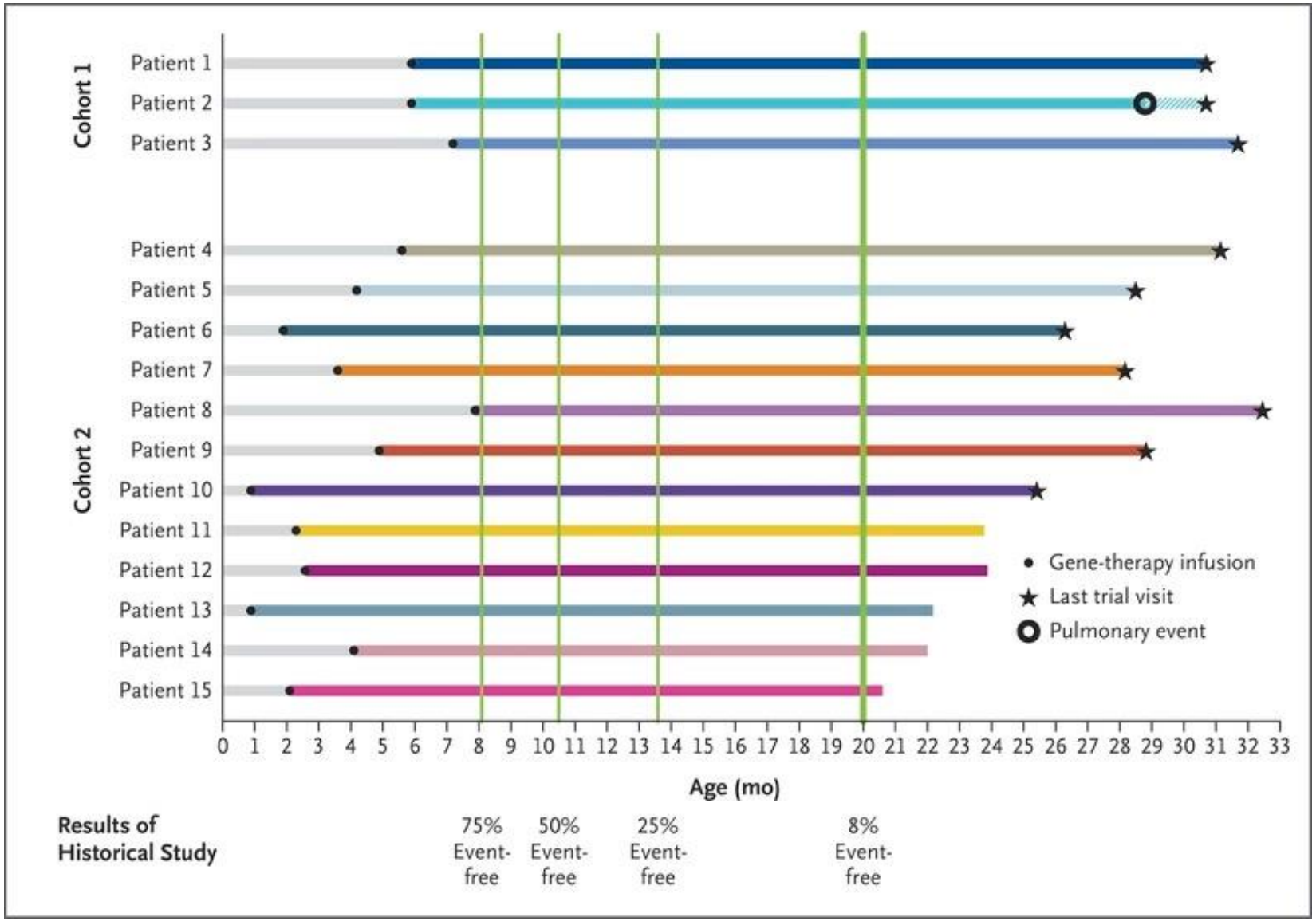


No. at Risk

Nusinersen	80	71	58	41	28	23
Control	41	33	23	17	12	10

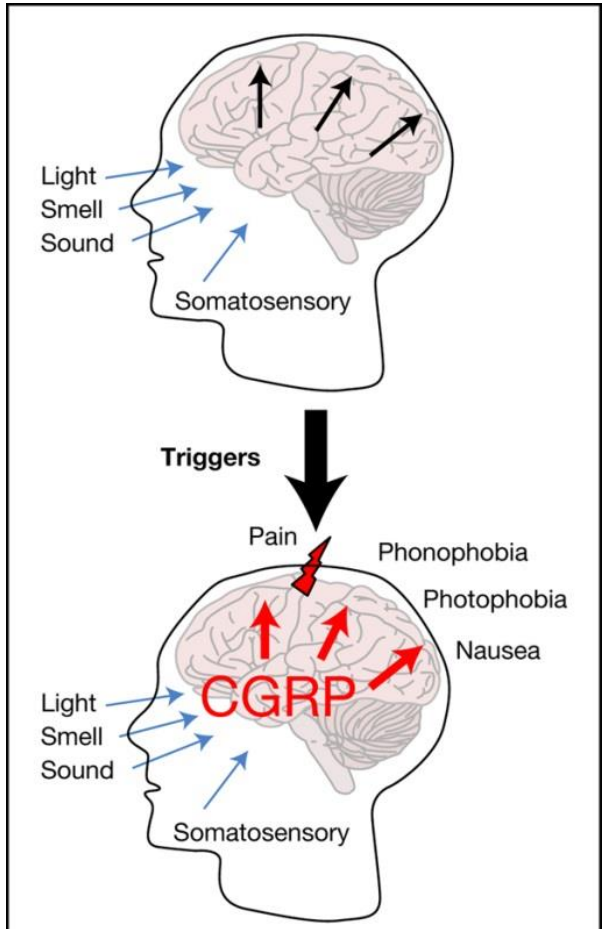
N Engl J Med 2017;377:1723-32.

Gene replacement therapy for SMA (2019)

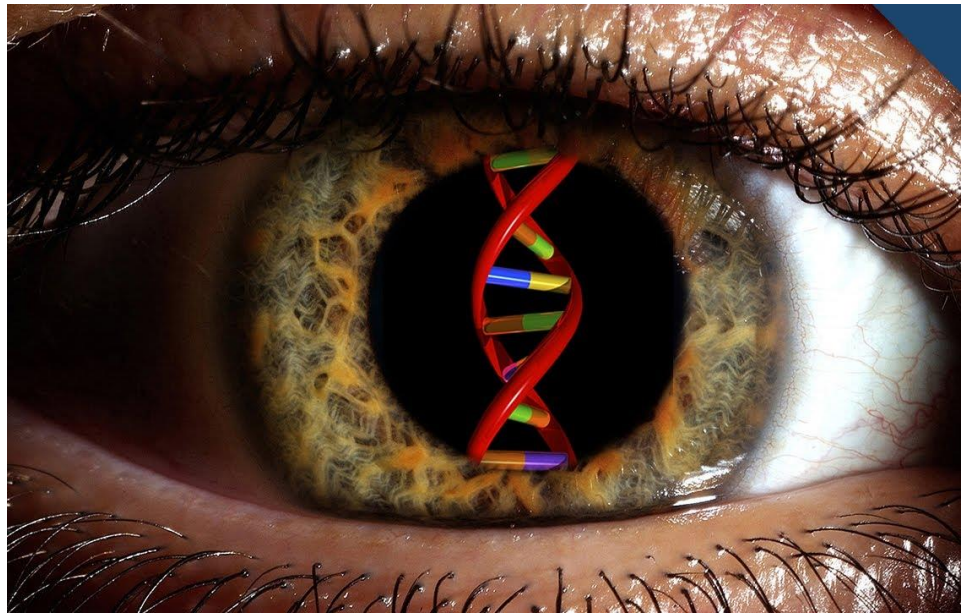


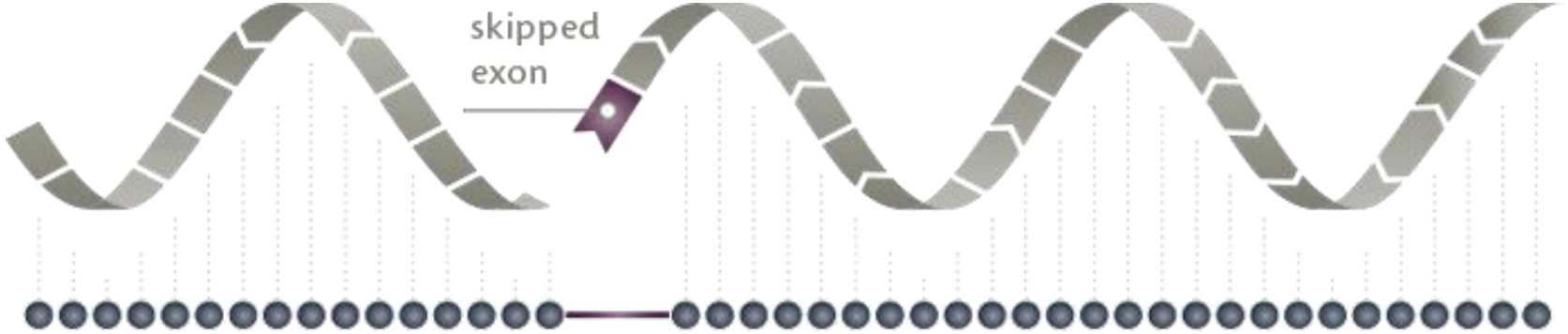
N Engl J Med 2017;377:1713-22.

PRESENT: Translating knowledge to treatment



Model of CGRP-induced hypersensitivity
Expert Reviews in Molecular Medicine © 2011
Cambridge University Press



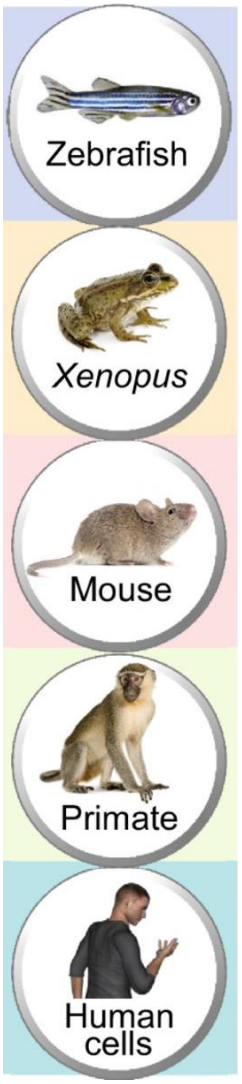


PRESENT

Describing phenomenology, grouping characteristics, linking to genetic diagnosis, accelerating development of new therapies

FUTURE

Rising Interest in Therapy Development for NCLs



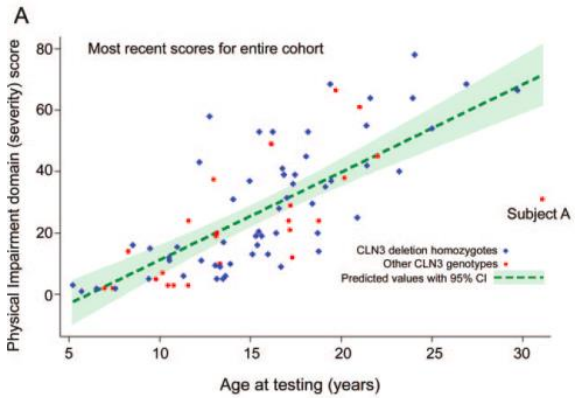
Pre-clinical models

Regulatory incentives

BATTEN DISEASE Support and Research Association

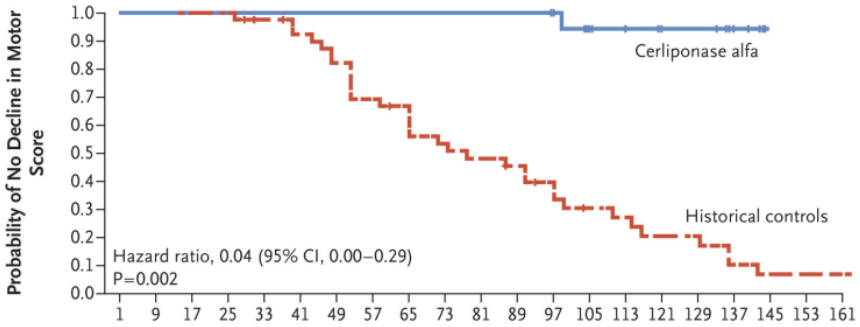
BEYOND BATTEN DISEASE FOUNDATION

Engaged families & foundations

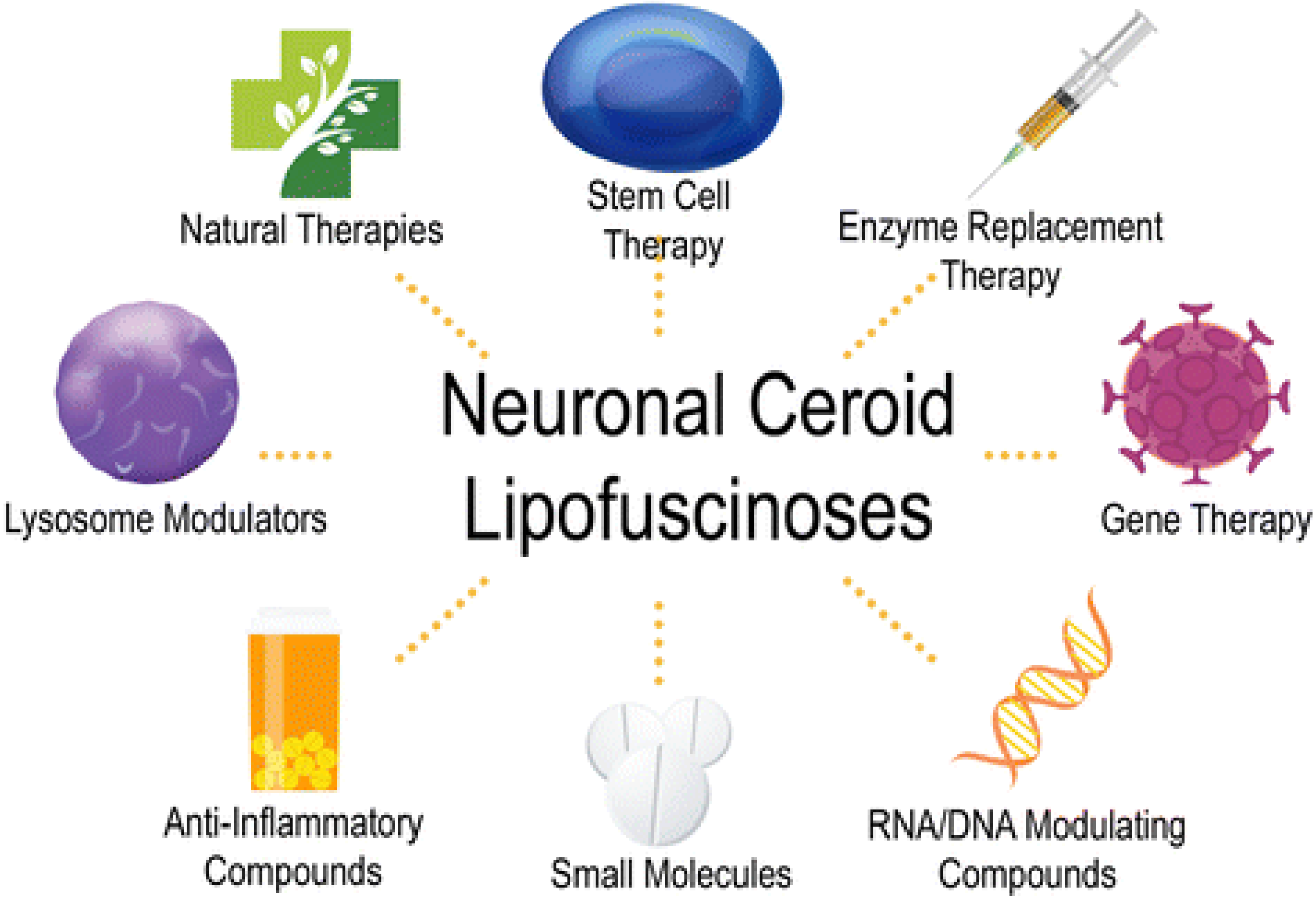


Natural history knowledge

Clinician-Investigators



Successful product approval



RD Geraets, et al. Orphanet Journal of Rare Diseasesvolume 11, Article number: 40 (2016)

NCL Therapeutic Pipeline

Small molecule approaches

CLN1, CLN3

Gene replacement therapies (AAV9, various routes of administration)

CLN1, CLN2, CLN3, CLN5, CLN6, CLN7

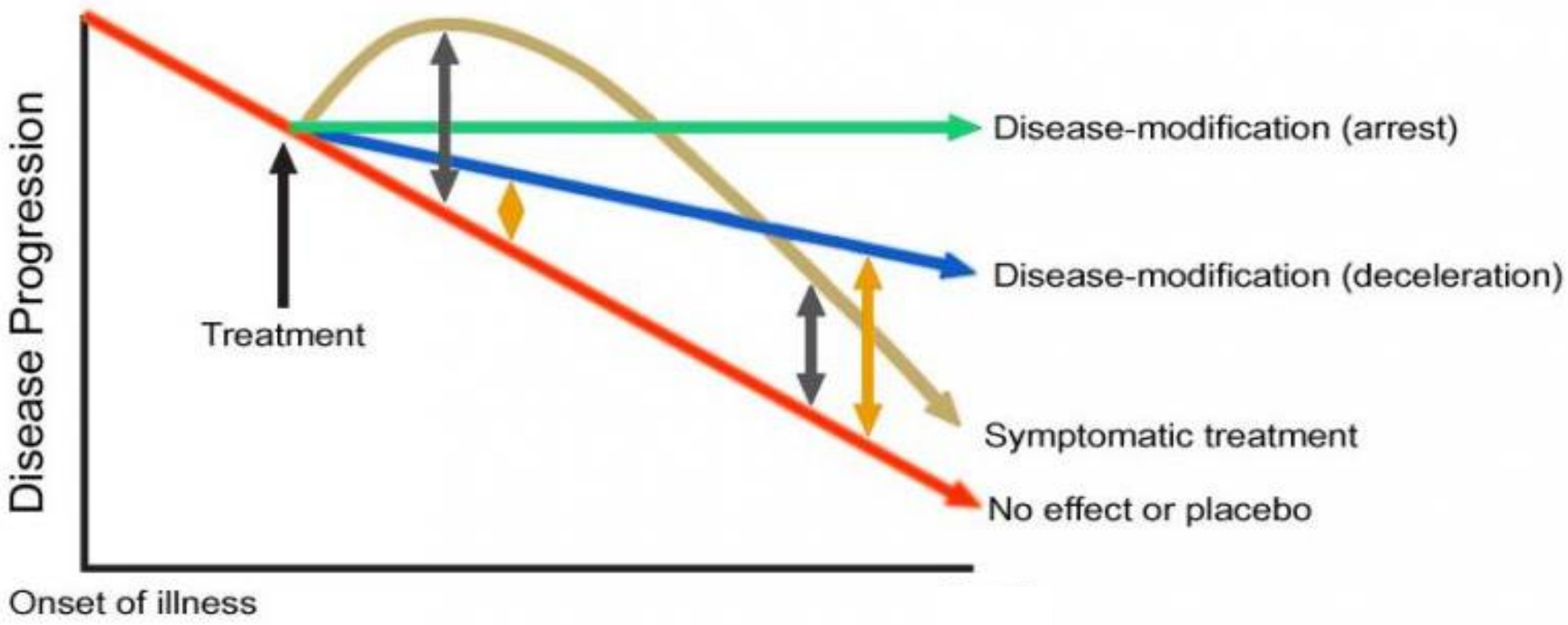
Enzyme replacement

CLN1

Anti-sense oligonucleotide therapy

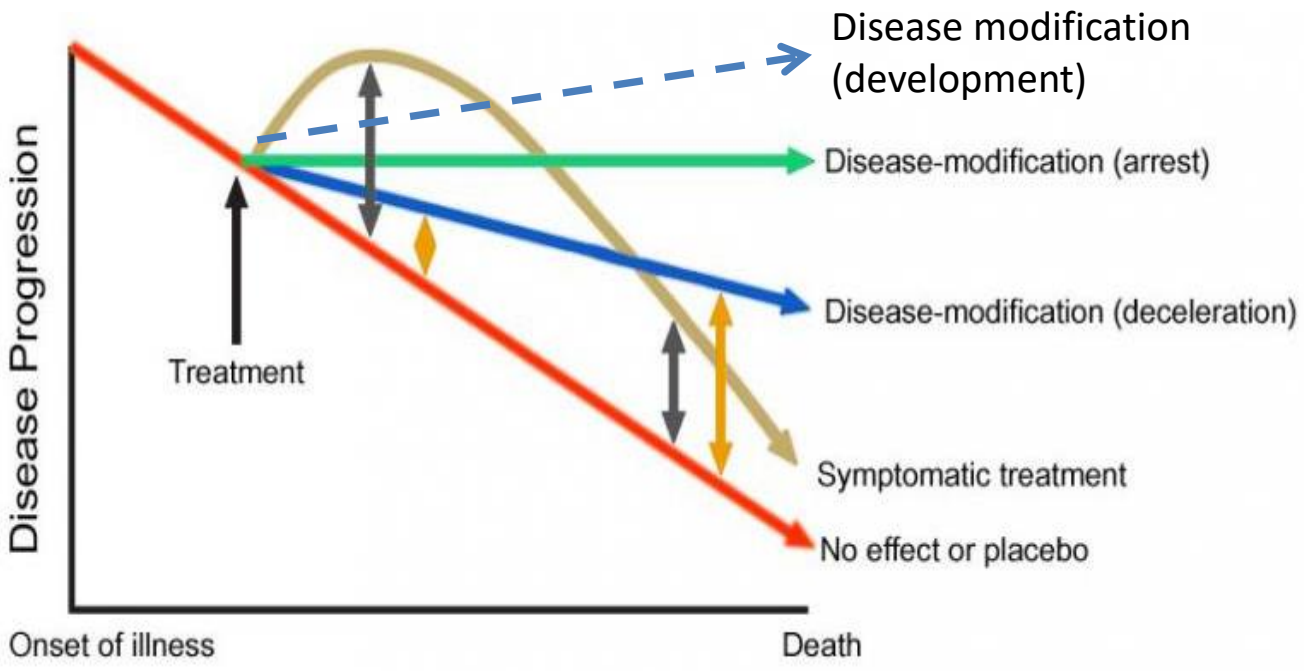
CLN7

Emerging Therapeutic Strategies



http://www.sens.org

Emerging Therapeutic Strategies



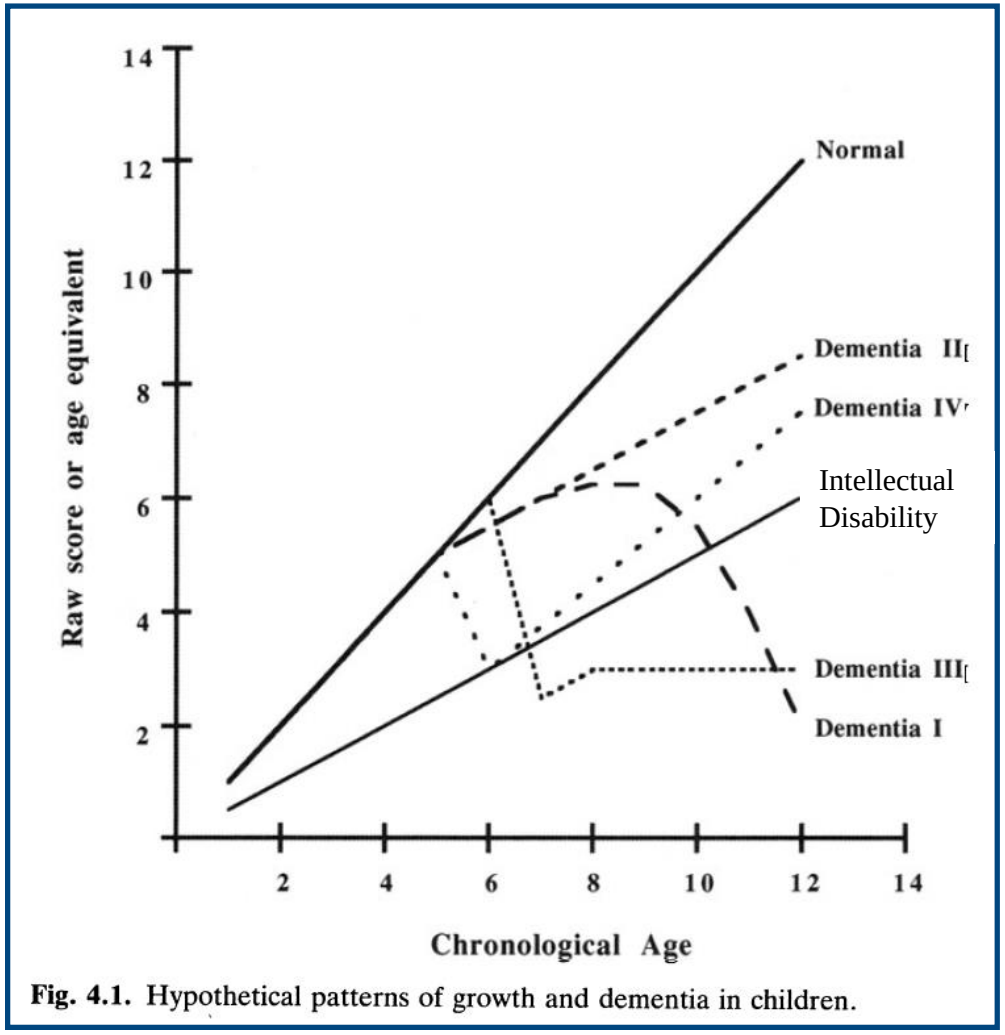


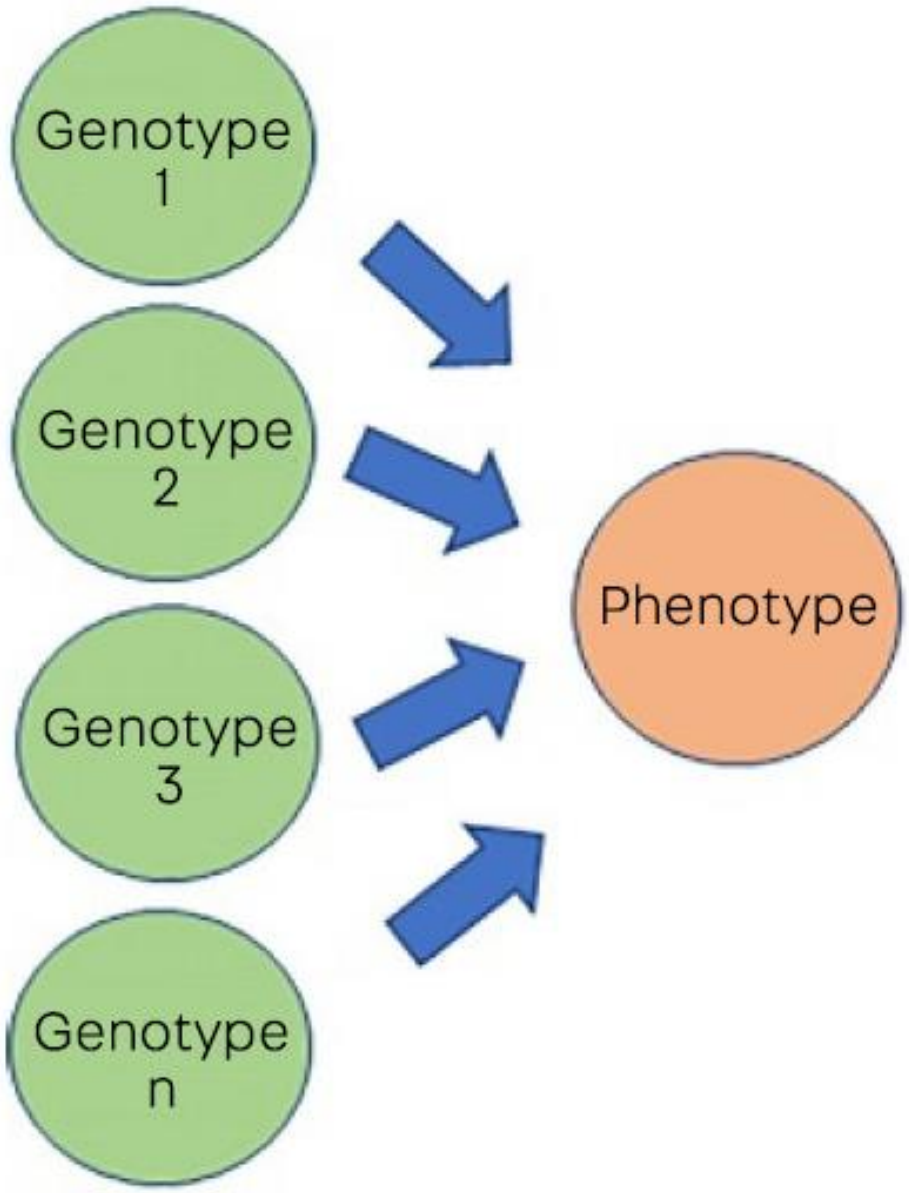
Fig. 4.1. Hypothetical patterns of growth and dementia in children.

EG Shapiro, et al 1994; http://www.sens.org

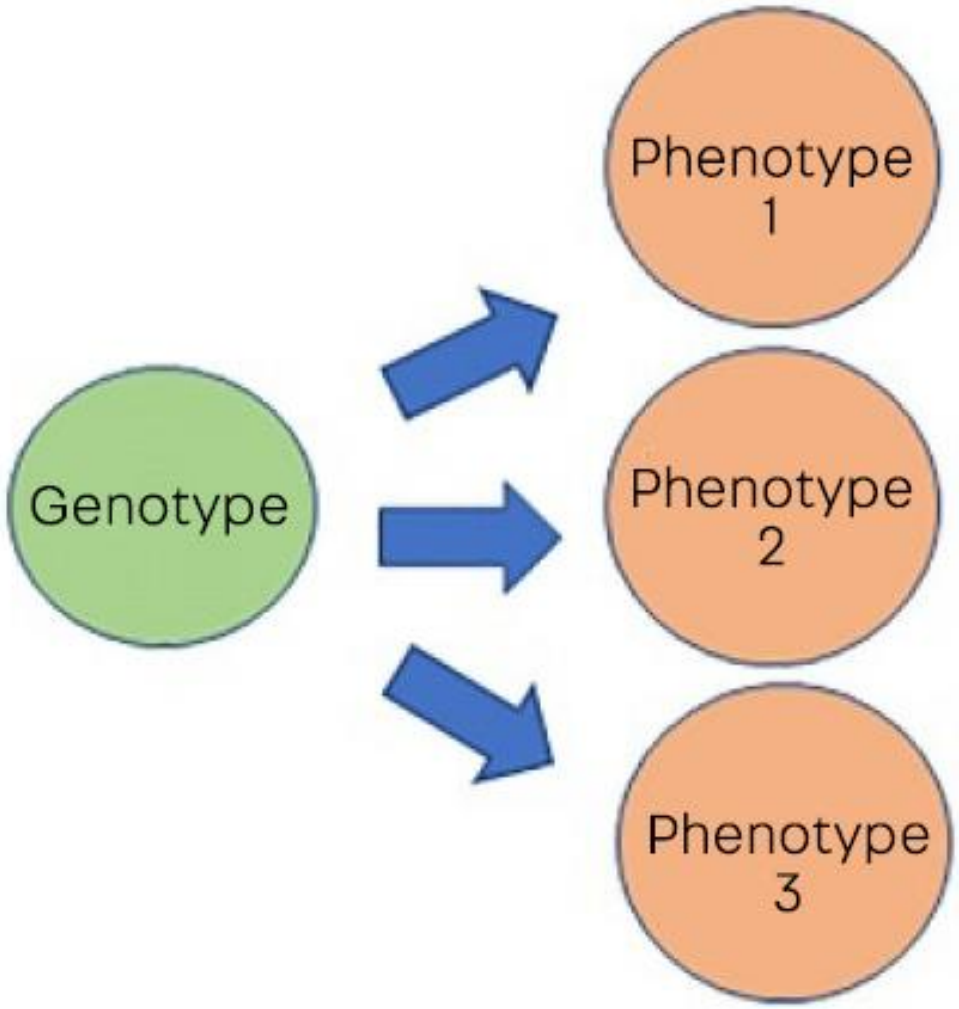
Classic Genotype-Phenotype Concordance

Paciorkowski, et al. CONTINUUM. 2018;24(1):18–36.

Genetic Heterogeneity

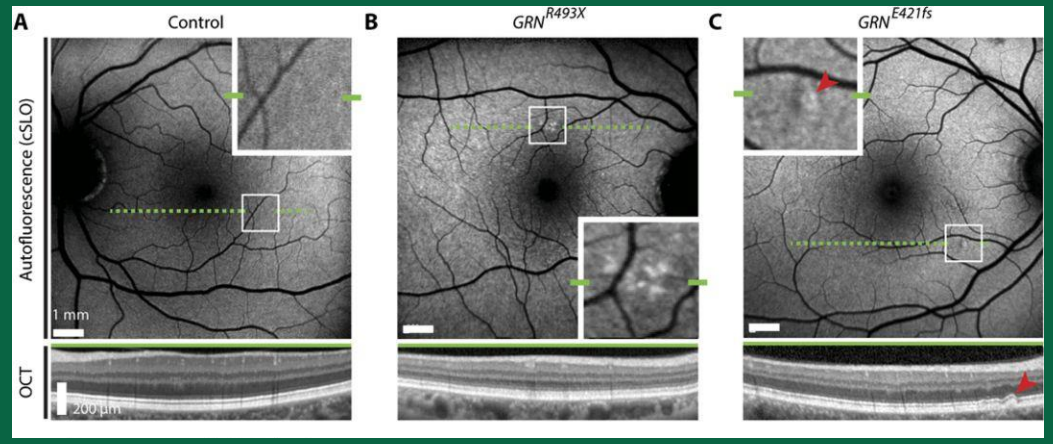


Phenotypic Pleiotropy



Paciorkowski, et al. CONTINUUM. 2018;24(1):18–36.

Increasing recognition of links between rare and common disorders



Ward, et al. *Science Translational Med*. 2017; 9(385): eaah5642

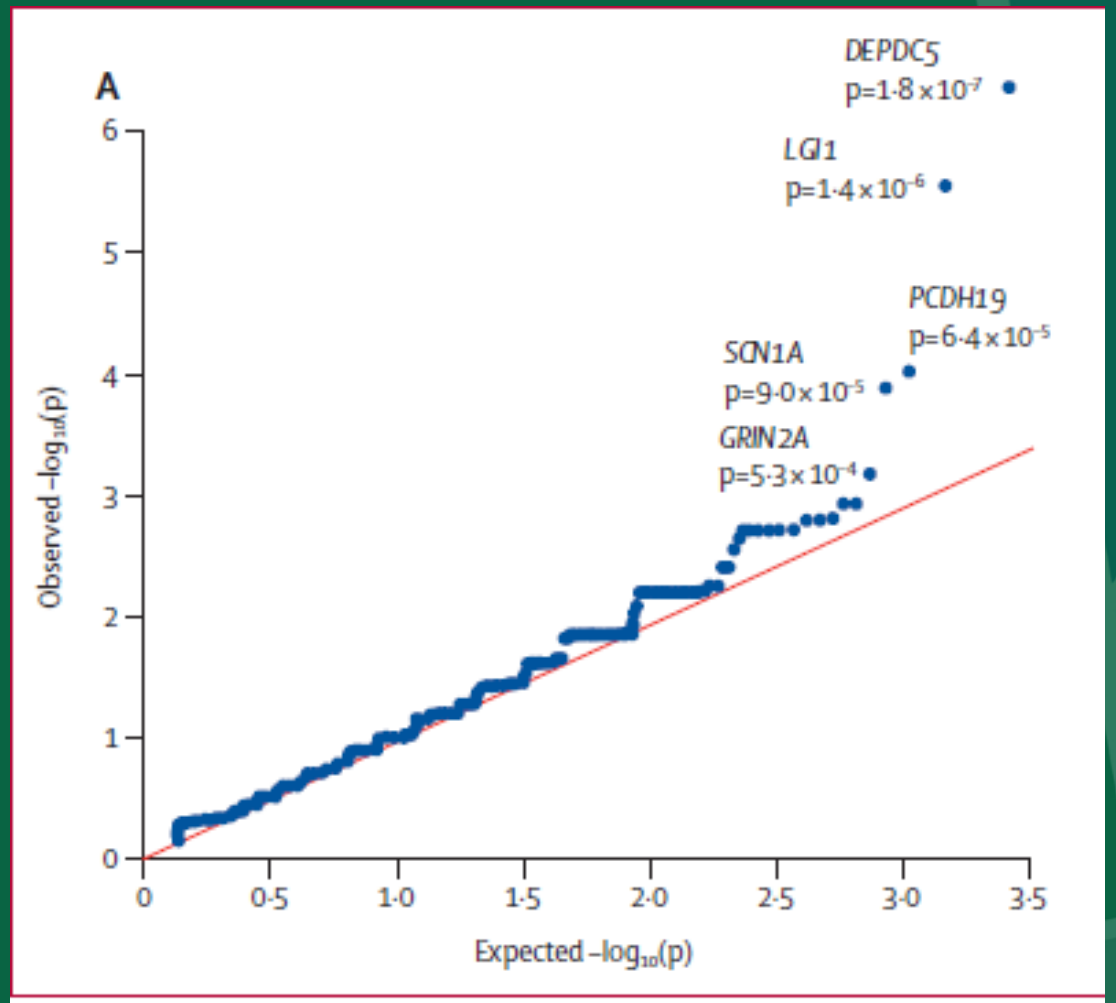
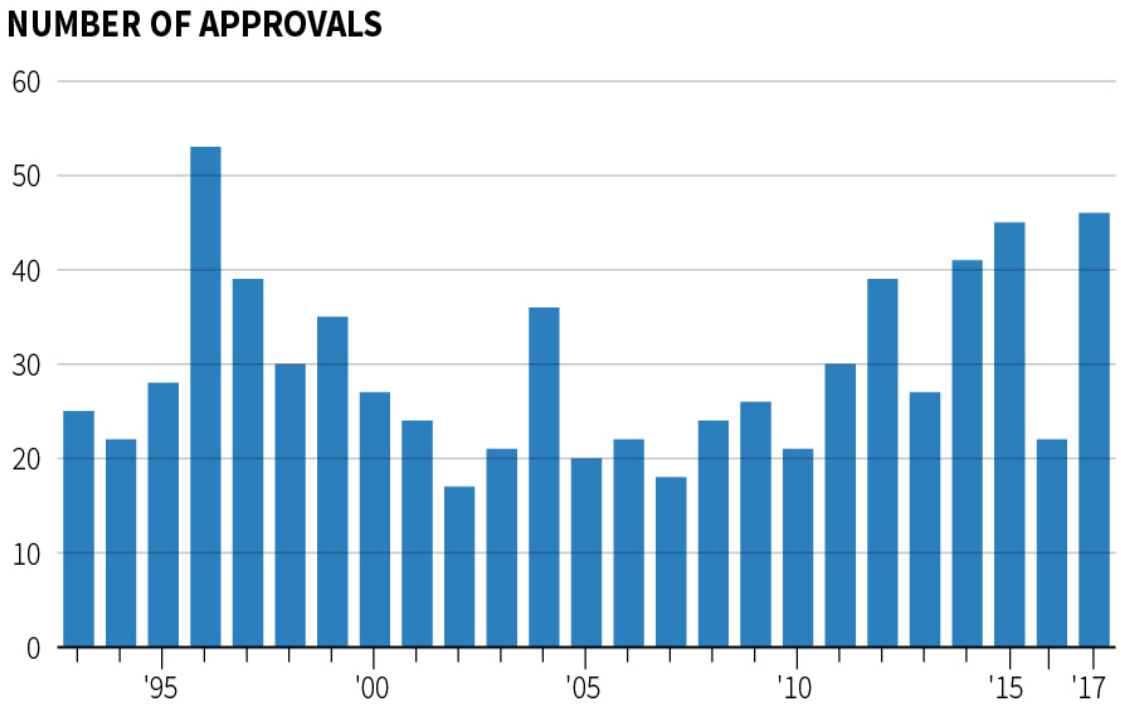


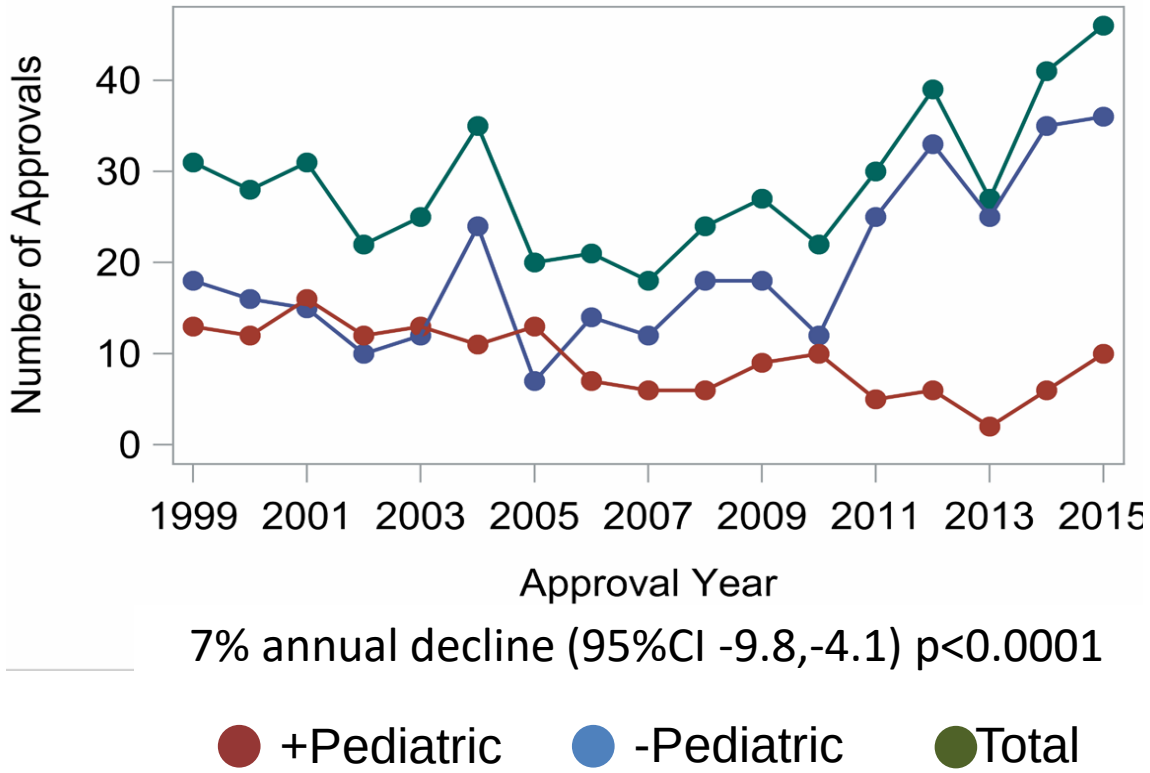
Figure 2: Primary model analysis of familial non-acquired focal epilepsy

- NCL and frontotemporal dementia
- Rare and common epilepsies
- Lysosomal storage disease and Parkinson Disease

Lancet Neurol. 2017; 16: 135–143

Pediatric approvals may be on the decline





Source: FDA Law Blog; Vermillion et al 2018

Rare Disease Barriers to Therapy Development

- Efficient diagnosis and recognition of disease
- Incomplete understanding of natural history
- Lack of robust, patient-relevant outcome measures
- Low statistical power for small sample sizes
- Challenges in recruitment
- Late phase compound failures

Augustine, et al. *J Child Neurol* 2013
deBlieck, Augustine, et al. *Contemp Clin Trials* 2013

Emerging Questions – CLN2 disease

- Impact on lifespan, other key disease domains
- Emergence of systemic pathology
- Long-term tolerability and device duration
- Delivery optimization
- Need for combination approaches
- ***Development of robust global disease endpoints***

Translational and trial design considerations

- Relative importance of gene expression level versus cell specificity
- Adequacy of preclinical model translation to human benefit
- Threshold age of intervention
- Add-on therapy considerations
- Competing trials in a small population

Challenges ahead

- Timely diagnosis for known disorders
- Defining unsolved diseases
- Approved treatments with quality data
- Treatment access
- Increasing total # of treatments
- Increasing rate of first treatments
- Future of the Orphan Drug Act

Clin Transl Sci. 2018 Jan; 11(1): 21–27

Cost and equity

FDA News Release

FDA approves first treatment for a form of Batten disease

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

For Immediate Release April 27, 2017

Cost and equity

European Commission Approves Brineura™ (cerliponase alfa), the First Treatment for CLN2 Disease, a Form of Batten Disease and Ultra-Rare Brain Disorder in Children

Dosing includes all ages from birth for this fatal and rapid pediatric neurodegenerative condition

Brineura is among first therapies to go through European Medicine Agency's new accelerated assessment process

Jun 1, 2017

Cost and equity

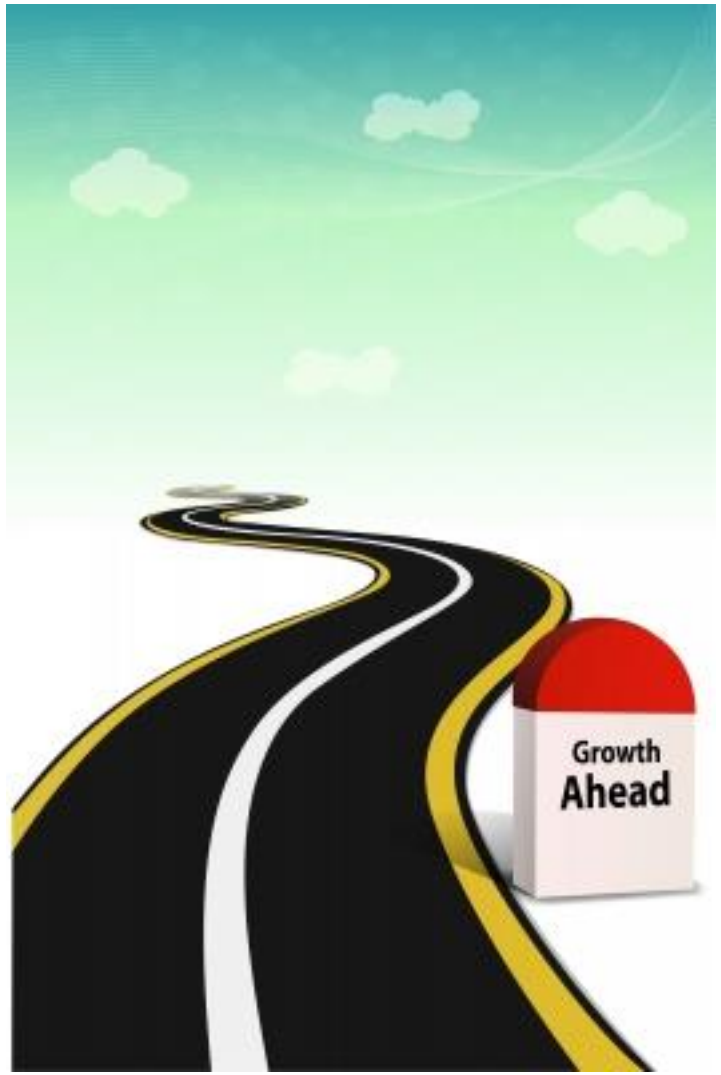
NICE deems Batten disease therapy too costly for NHS use

13th February 2018

FUTURE

Accelerating development of new therapies, defining precise and meaningful diagnosis, changing our concept of therapeutic treatment groups, early and multi-modal intervention

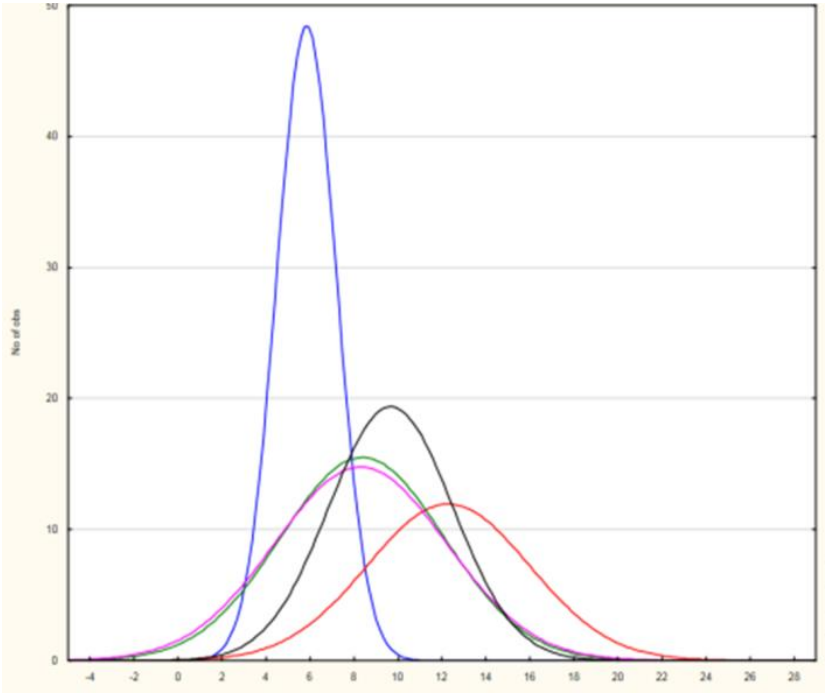
The Road Ahead



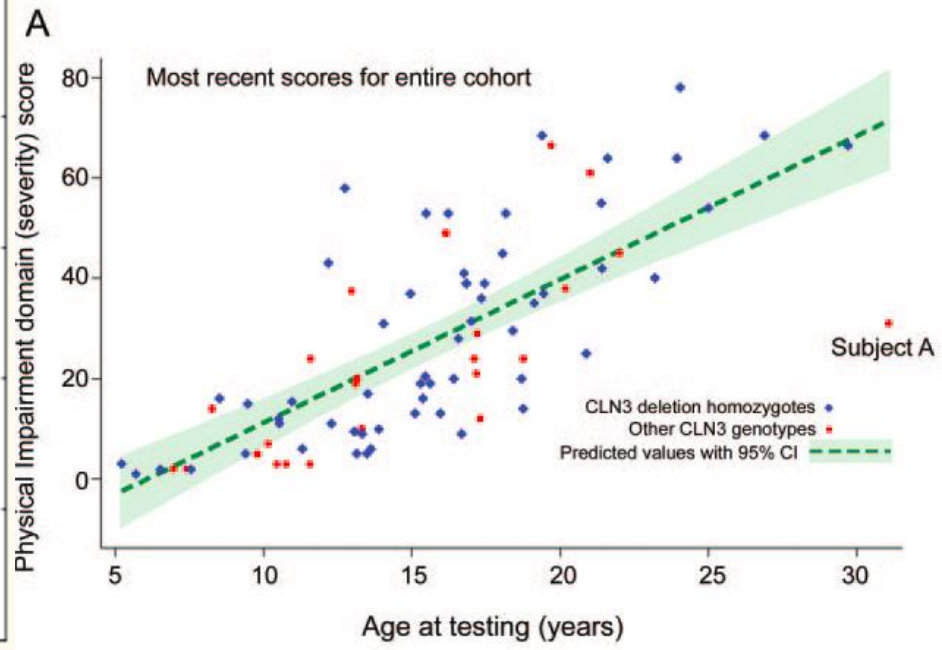
Systematically building clinical knowledge about rare diseases

Neuronal Ceroid Lipofuscinoses (Batten diseases)

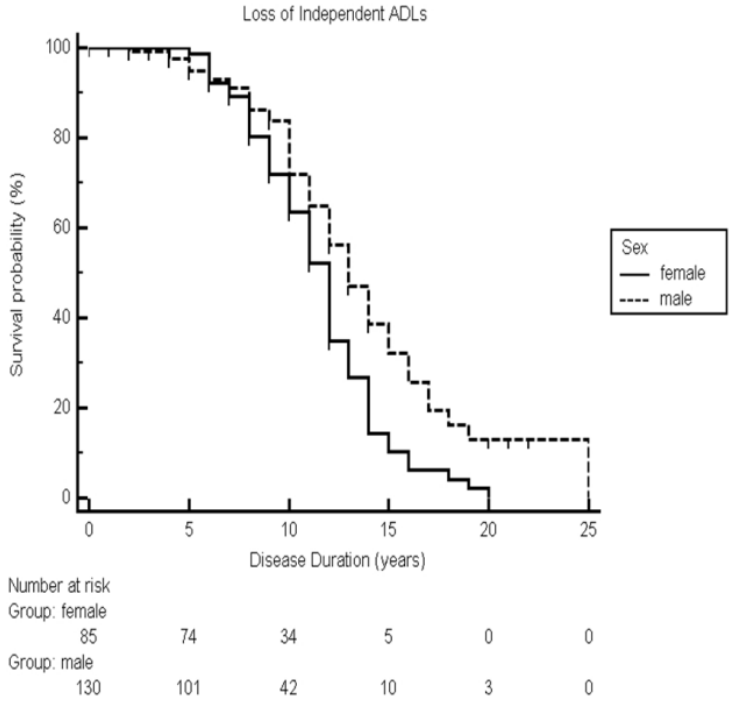
Sequencing Symptom Onset



Quantifying Progression



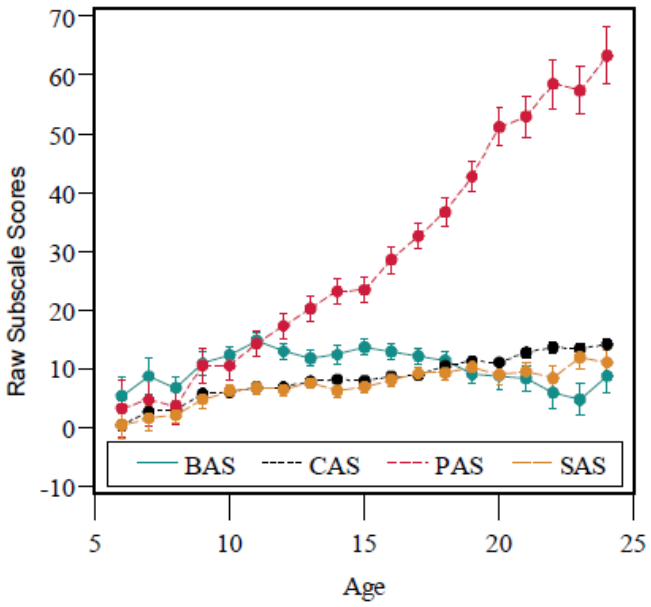
Examining Sex Differences



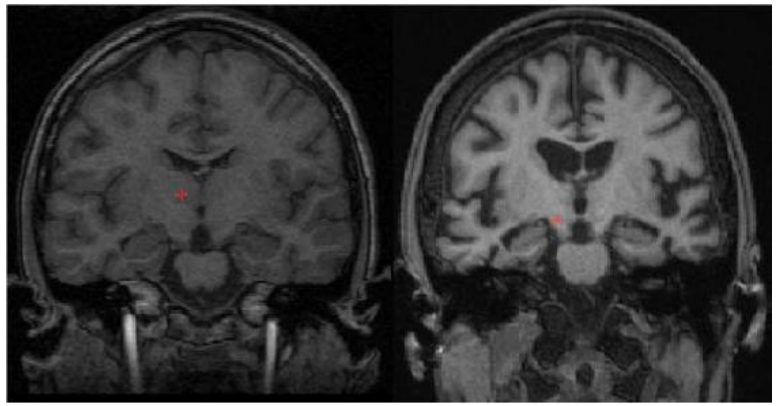
https://www.urmc.rochester.edu/neurology/batten-disease-center.aspx

Next Steps – Batten Diseases

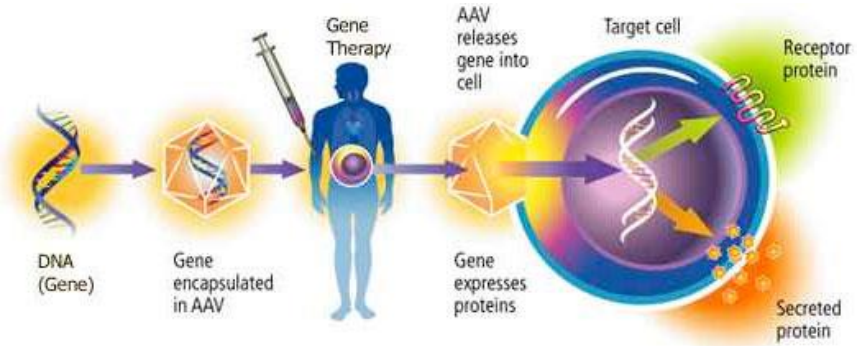
Modeling Disease Trajectory



Clinical Endpoint & Biomarker Qualification



Testing Novel Interventions



Brain image courtesy A.Schulz

www.trnds.org – September 19, 2019

TRNDS

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