Recent Advances in Gene Therapy

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Topics for Discussion

- What are Rare & Common Diseases
- Approaches Prevention & Treatment
- Current Gene Therapy approaches
- Looking ahead

Definition of 'Rare' Disorders

- USA Orphan Drug Act as
  those affecting less than 200,000 people throughout the country

- Swedish National Board of Health and Welfare
  a maximum of one hundred people per one million inhabitants

- EU defines
  5 or less in every 10000

- Taiwan Rare Disorders and Orphan Drugs Act
  an incidence below a level defined and announced by the competent central authority

Definition of Orphan Disease

- One which has not been "adopted" by the pharmaceutical industry because it provides little financial incentive for the private sector to make and market new medications to treat or prevent it
- An Orphan Disease may be a Rare Disease, or a Common Disease which has been ignored because it is far more prevalent in developing countries than the developed

Languages: Français | English | Español | Deutsch | Italiano | Português

Homepage
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orphanet

Inserm

The portal for rare diseases and orphan drugs

Rare diseases | Orphan drugs | Expert centres | Diagnostic tests | Research and trials | Patient organisation | Professional and institutions | Other information

SIMPLE SEARCH

Search a disease → OK

> Alphabetical list of rare diseases

OTHER SEARCH OPTION(S)

- > Orphan drugs
- > Research and trials
- > Diagnostic tests
- > Patient organisations
- > Expert centres
- > Professionals and institutions

ORPHANET DATA

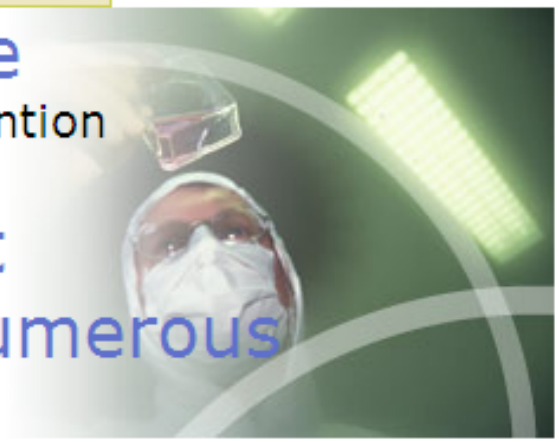
Diseases	:	5954
Expert centres	:	4942
Laboratories	:	5424
Professionals	:	15019
Daily visitors	:	12810

RARE DISEASES

- > Information about a disease
- > Alphabetical list
- > Search by clinical sign
- > Search by gene
- > Emergency guidelines
- > Encyclopaedia for patients
- > Encyclopaedia for professionals

There is no disease so rare that it does not deserve attention

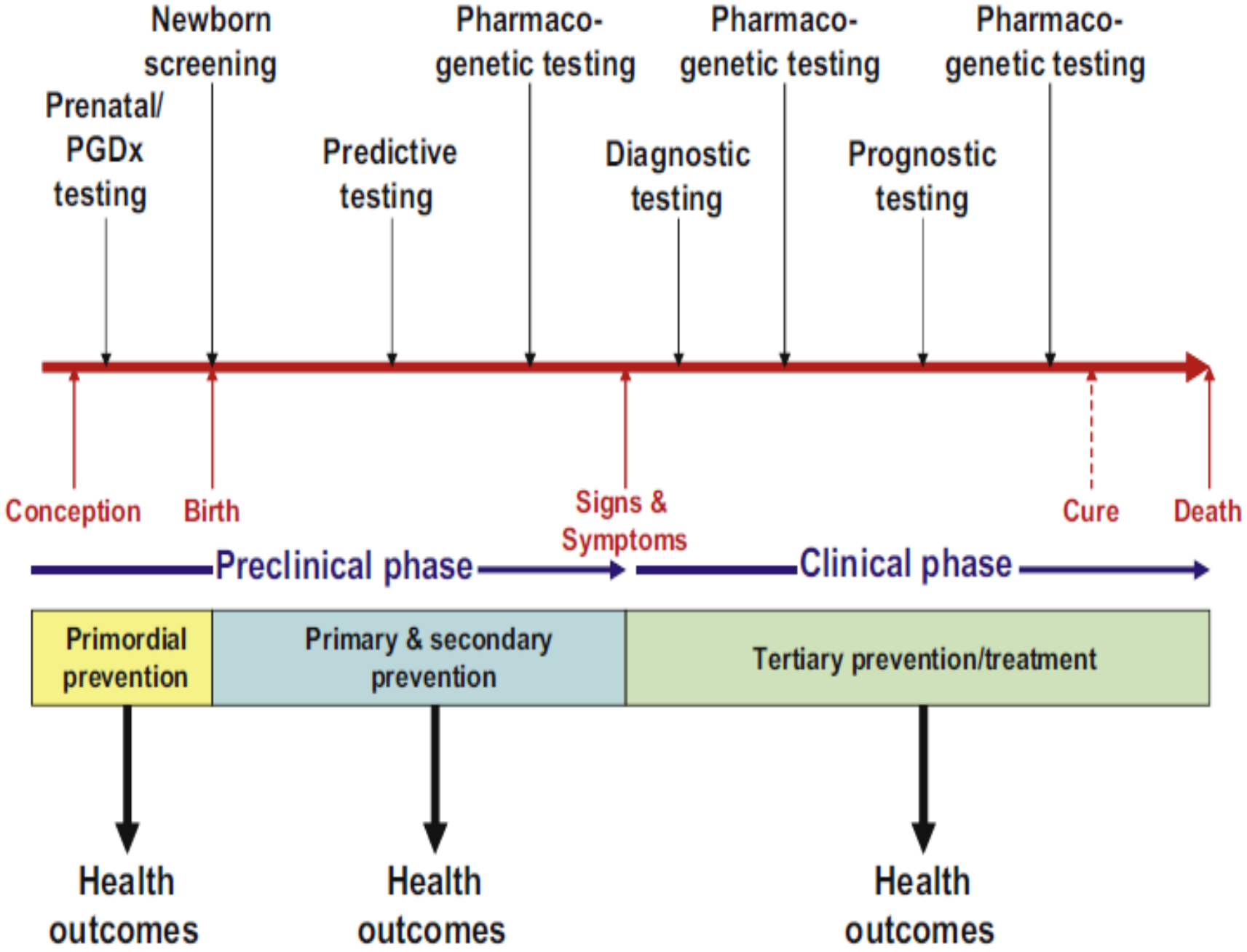
Rare diseases are rare, but rare disease patients are numerous



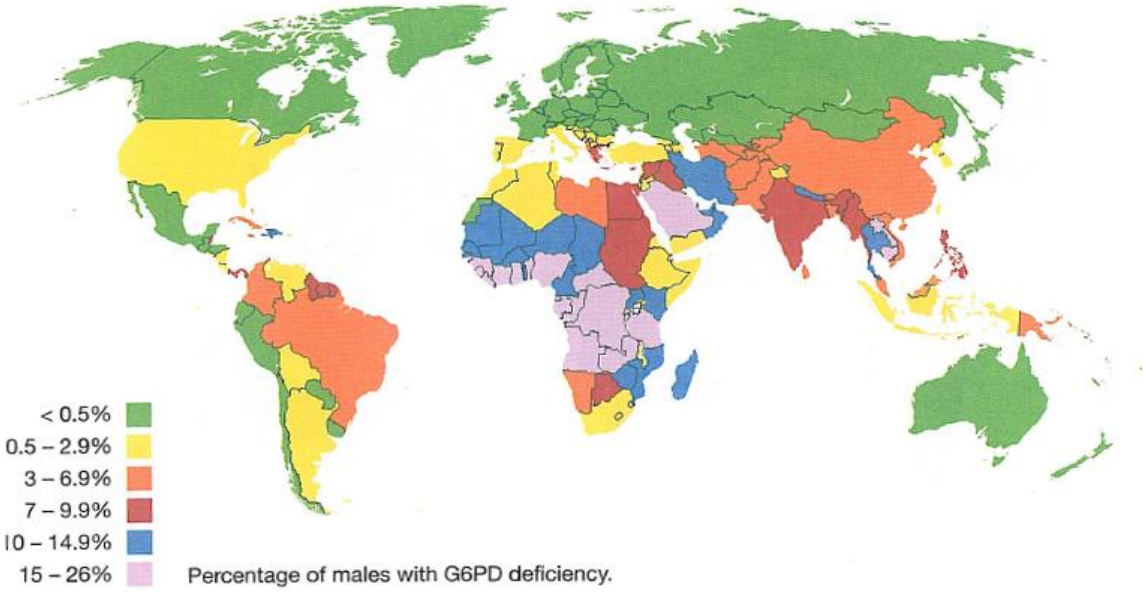
About Orphanet | Quality charter
Register your activity

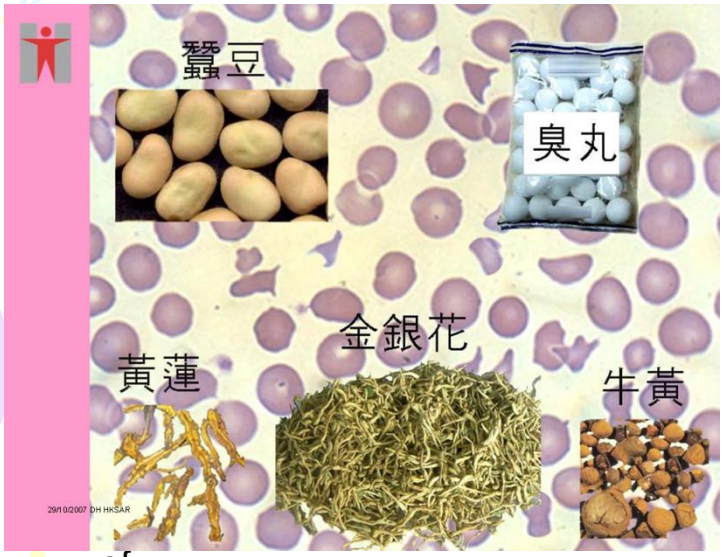
International Efforts in Management Rare Diseases

- France – information, screening, diagnostics, treatment
- Italy – National Network Centers of Excellence for Rare Diseases, National Registry
- European Commission – consultation
- USA – NORD, legislation, advocacy, policies
- Taiwan - TRDF


Prenatal/ PGDx testing
Newborn screening
Predictive testing
Pharmaco-genetic testing
Diagnostic testing
Pharmaco-genetic testing
Prognostic testing
Pharmaco-genetic testing
Conception
Birth
Signs & Symptoms
Cure
Death
Preclinical phase
Clinical phase
Primordial prevention
Primary & secondary prevention
Tertiary prevention/treatment
Health outcomes
Health outcomes
Health outcomes

Global Distribution of Males with Glucose- 6-Phosphate Dehydrogenase (G6PD) Deficiency, 1996*





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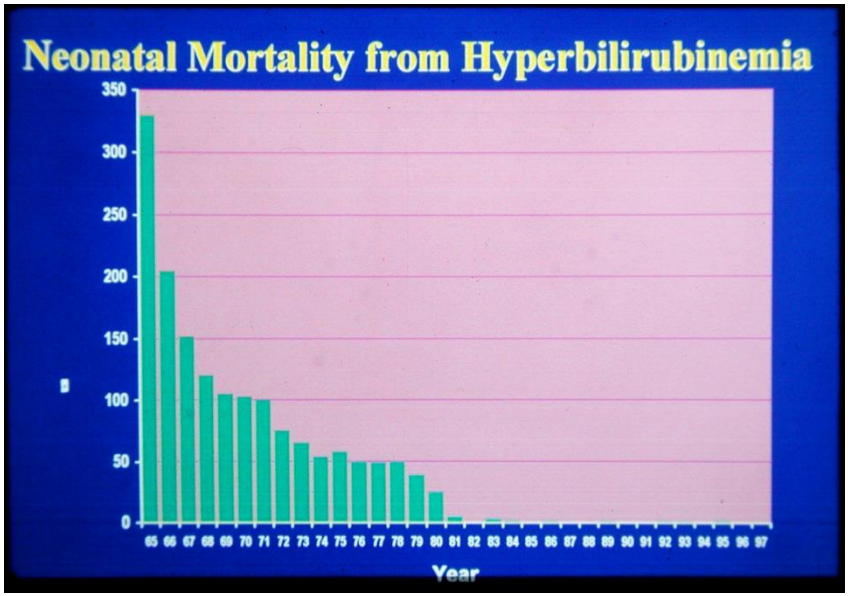


Treatment of Genetic Diseases

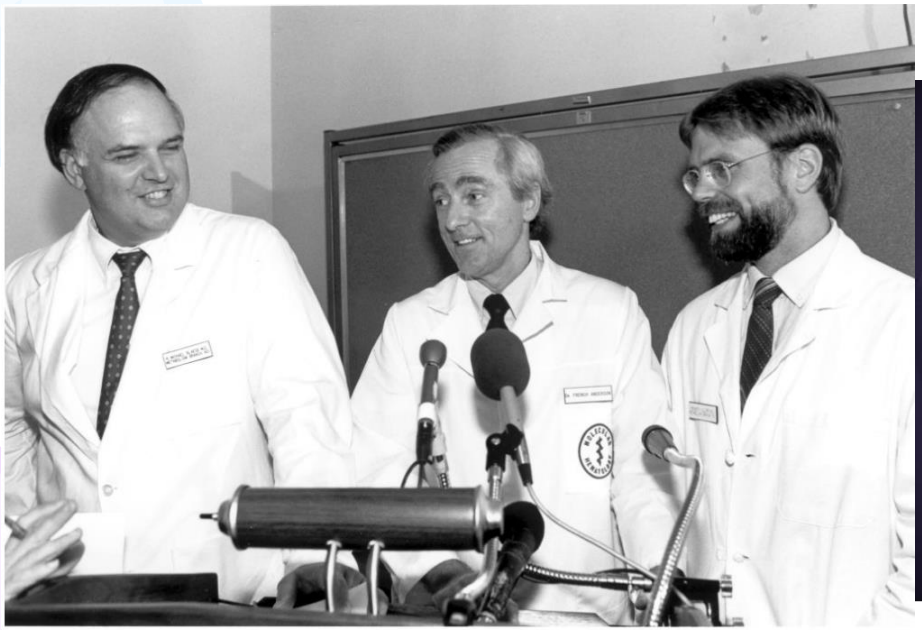
- Environmental Manipulation
- Physical Therapy
- Provision of Gene Products
- Provision of ‘Normal’ Genes

Developments in Orphan Drugs

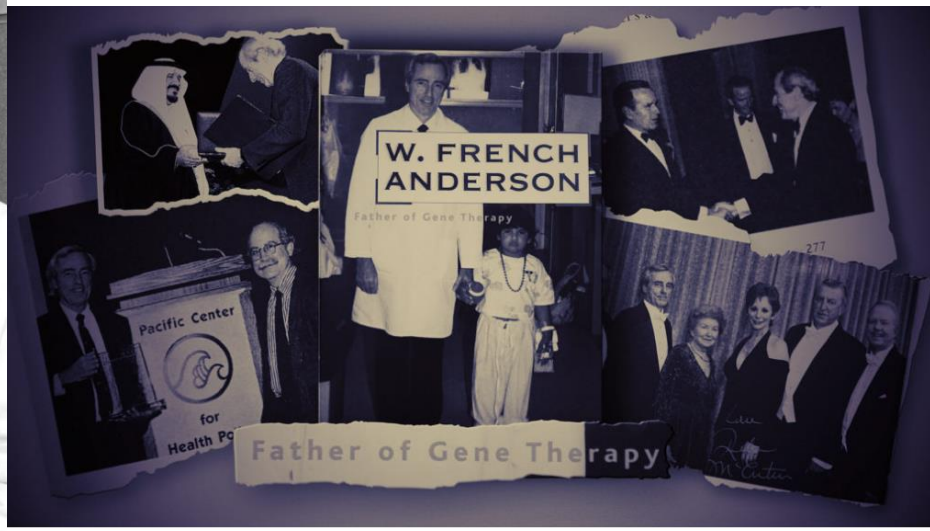
- USA – 1800 drug candidates, 325 approved, benefitting 25 M Americans
- European Commission – Register of designated Orphan Medicinal Products (total 571)
- Taiwan – 171 official rare diseases, 86 orphan drugs & 40 special nutrients approved
- Hong Kong – Hospital Authority has 'Rare Disease' branch under Chief Pharmacist's Office

Gene Therapy

- Historical
  - Anderson 1987 proposed
  - implemented 1990 ADA deficiency



Anderson (center) with Dr. R. Michael Blaese (left) and Dr. Kenneth Culver at a press conference in 1990, before their first patient received gene therapy.
NATIONAL CANCER INSTITUTE



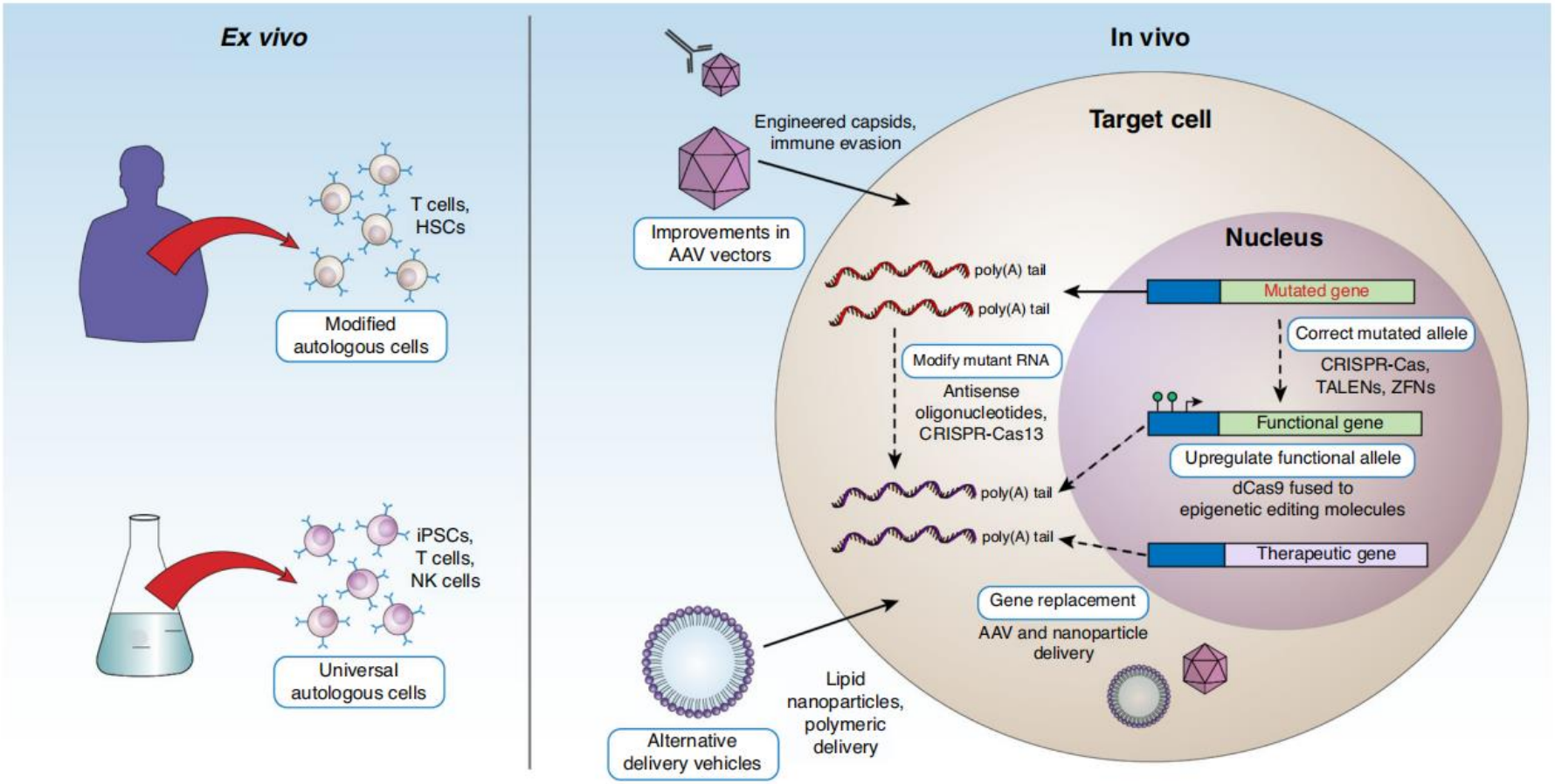


Fig. 2 Schematic of ex vivo and in vivo strategies (shown in blue boxes) for treating genetic diseases. For ex vivo approaches (left panel), autologous cells can be isolated directly from the patient and genetically modified to elicit a therapeutic effect, while allogeneic cells can be produced and readily available "off the shelf." In vivo strategies require targeting of specific cells in order to overexpress a therapeutic gene or correct pathological mechanisms to allow functional gene expression (dashed arrows).

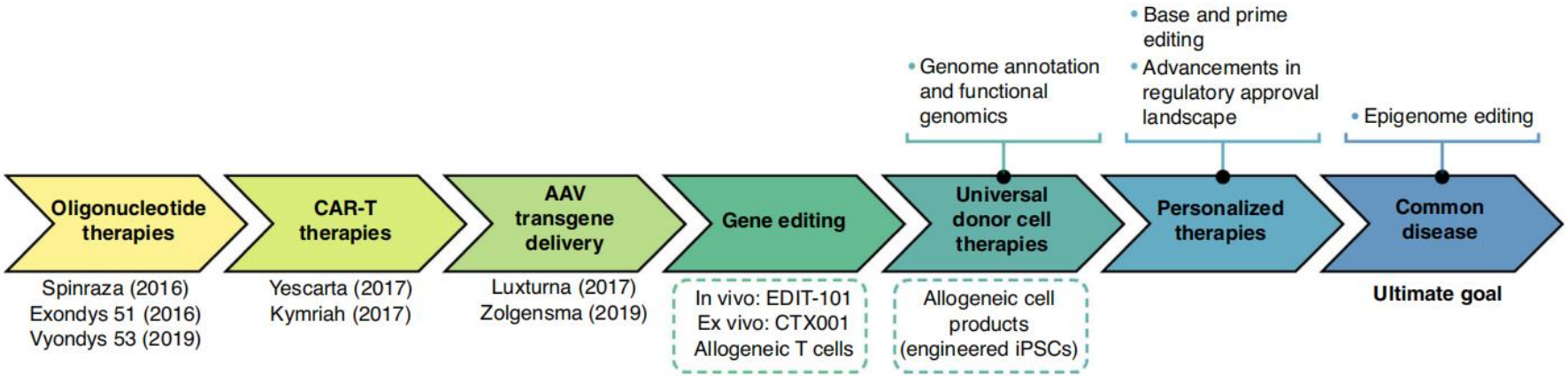
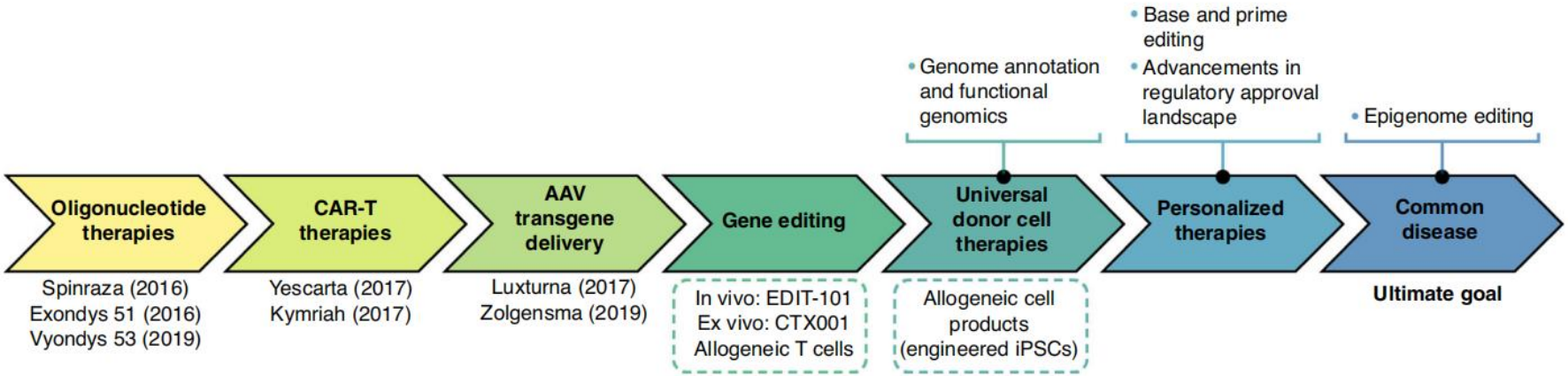


Fig. 1 Timeline depicting milestones (in colored arrows) towards gene therapies for common disease. Approved treatments and year of their approval as well as investigational therapies (in dashed boxes) are shown below each milestone. Further exploration of alternative therapeutic approaches and fundamental scientific questions is still needed to accomplish later milestones (shown in bullets).

Antisense Therapy

- Use Single strand synthetic nucleotide
- Induce SMN2
- 2010 clinical trial
- 2016 FDA approval
- Nusinersen (Spinraza)
- once 4 monthy, US$ 750,000 each



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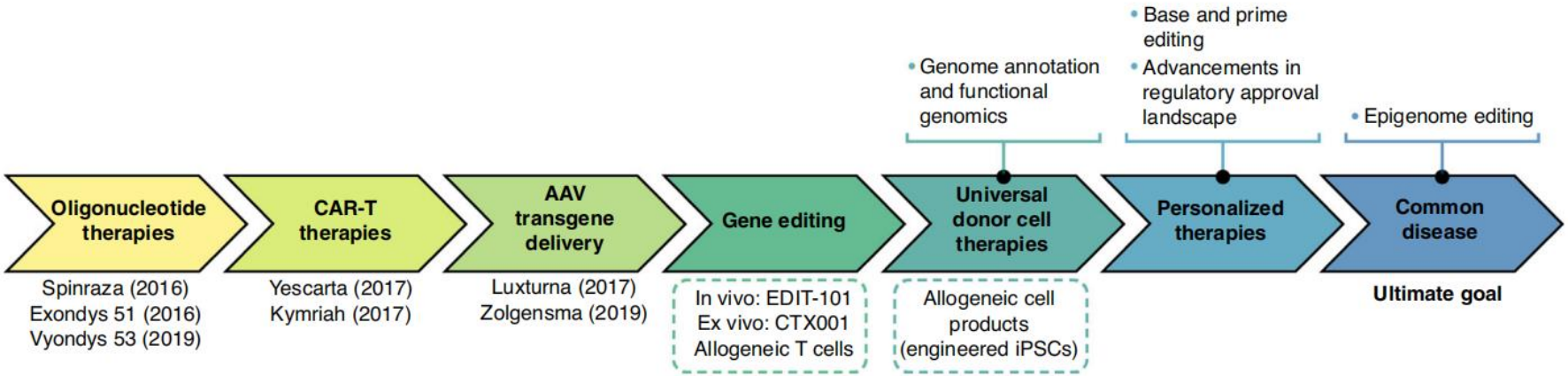
(CAR) T Cell Therapy

- Chimeric antigen receptor (CAR) therapy studied 2010
- for lymphoma treatment
- Autologous T cells> altered genes> infuse back
- 2016 Tisagenlecleucel (Kymriah) by Novartis approaved by FDA for ALL
- also large B cell lymphoma therapy
- US$ 475,000 once



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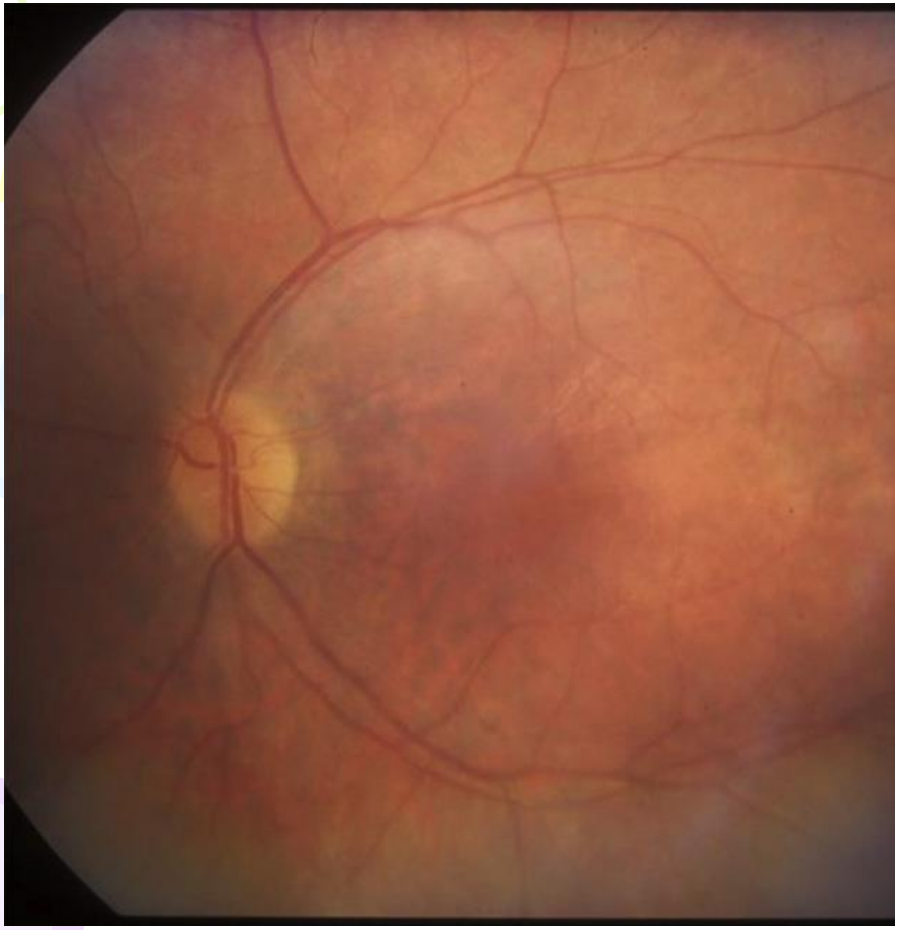
Leber Congenital Amaurosis



Present at birth
or infancy
Poor vision,
night blindness
Pigmentary retinopathy
Heterogeneous
Gene therapy RPE65

AAV transgene therapy

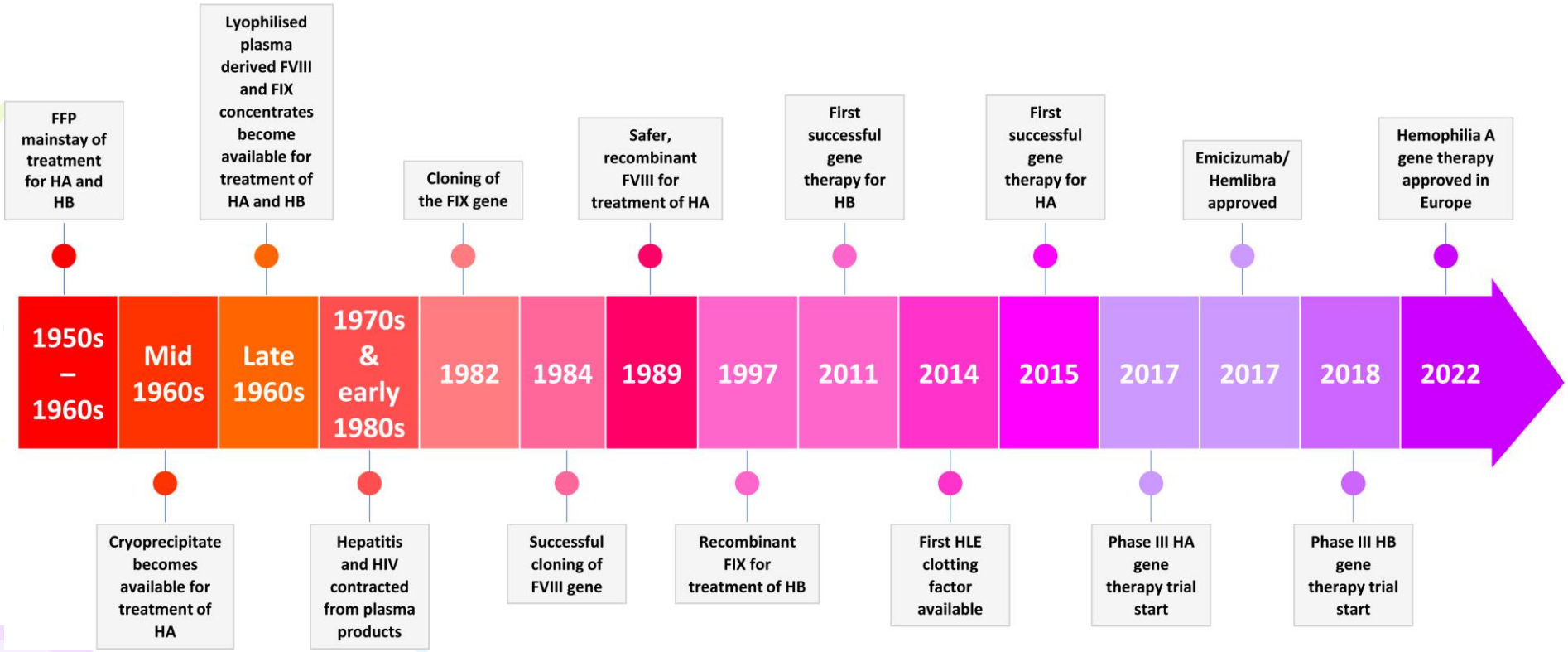
- Leber Congenital Amaurosis II/RP
- 2017 Luxterna
- 6000 worldwide
- US$ 425,000 per eye
- vision retained upon follow up

AAV Gene transfer

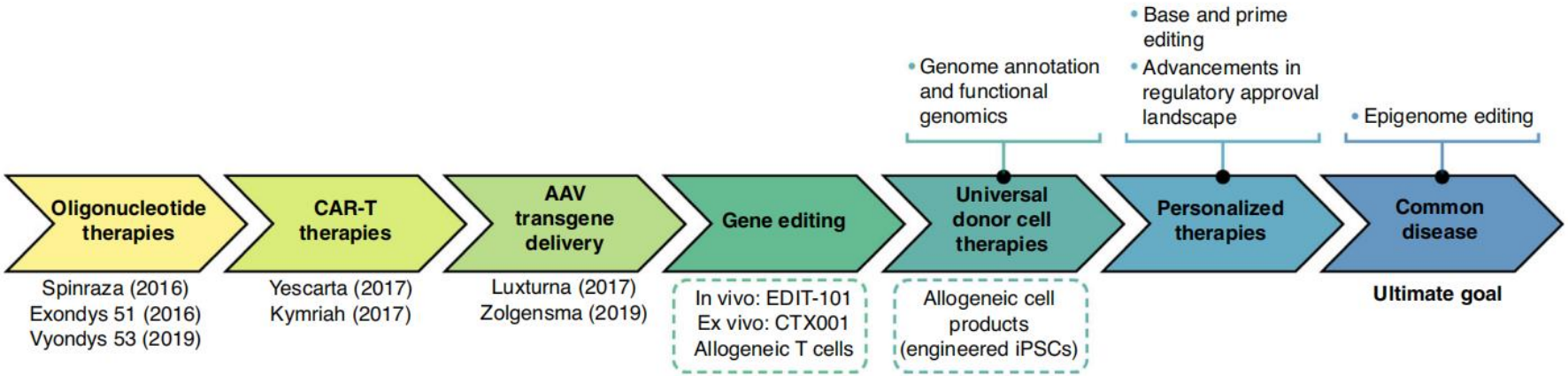
- Spinal Muscular Atrophy
  - Zolgensma
- other conditions
  - hemophilia
  - Duchenne Muscular Dystrophy

Gene therapy for hemophilia

Timelines for hemophilia gene therapy



Amit C. Nathwani, Gene therapy for hemophilia, Hematology Am Soc Hematol Educ Program, 2022,



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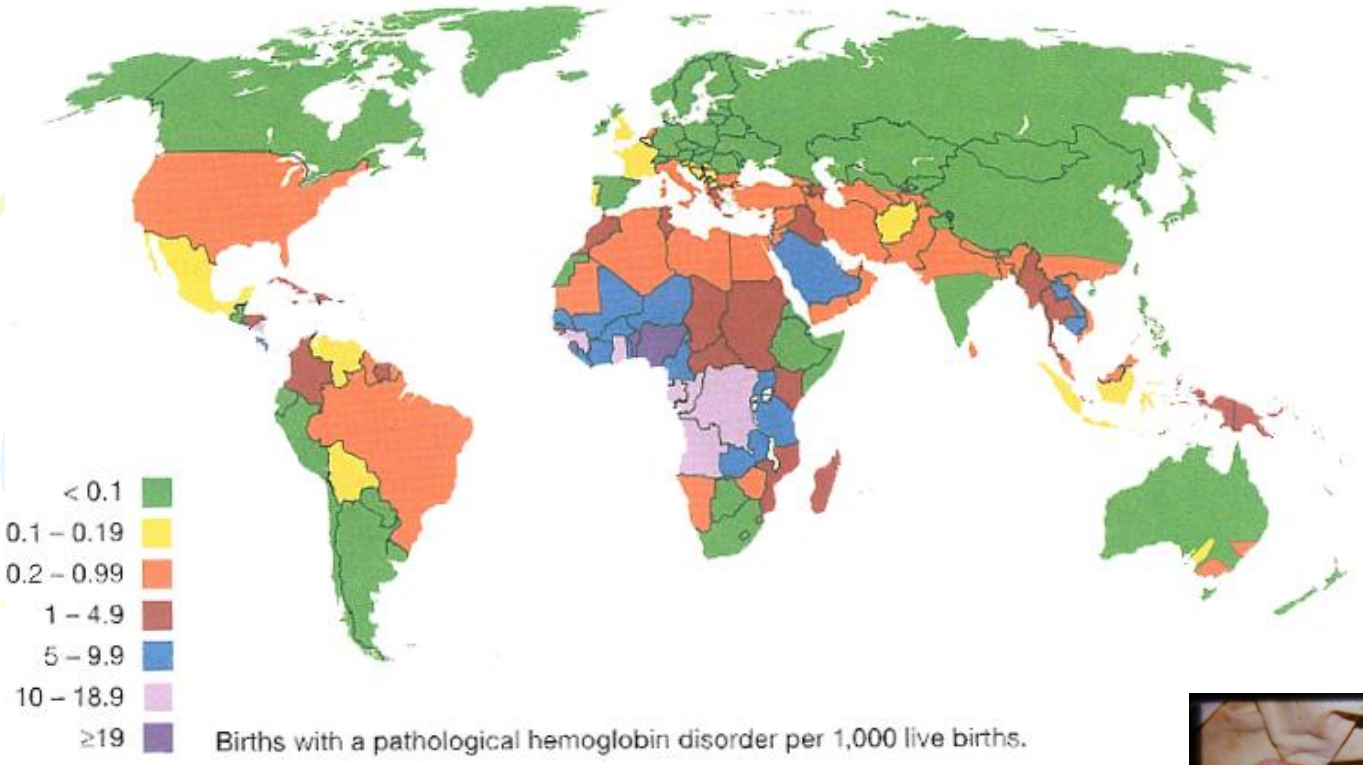
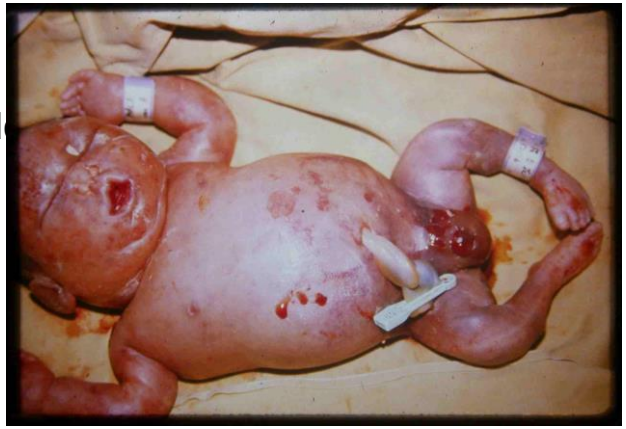
Global Distribution of Pathological Hemoglobin Disorders, 1996



Births with a pathological hemoglobin disord



Genome Editing

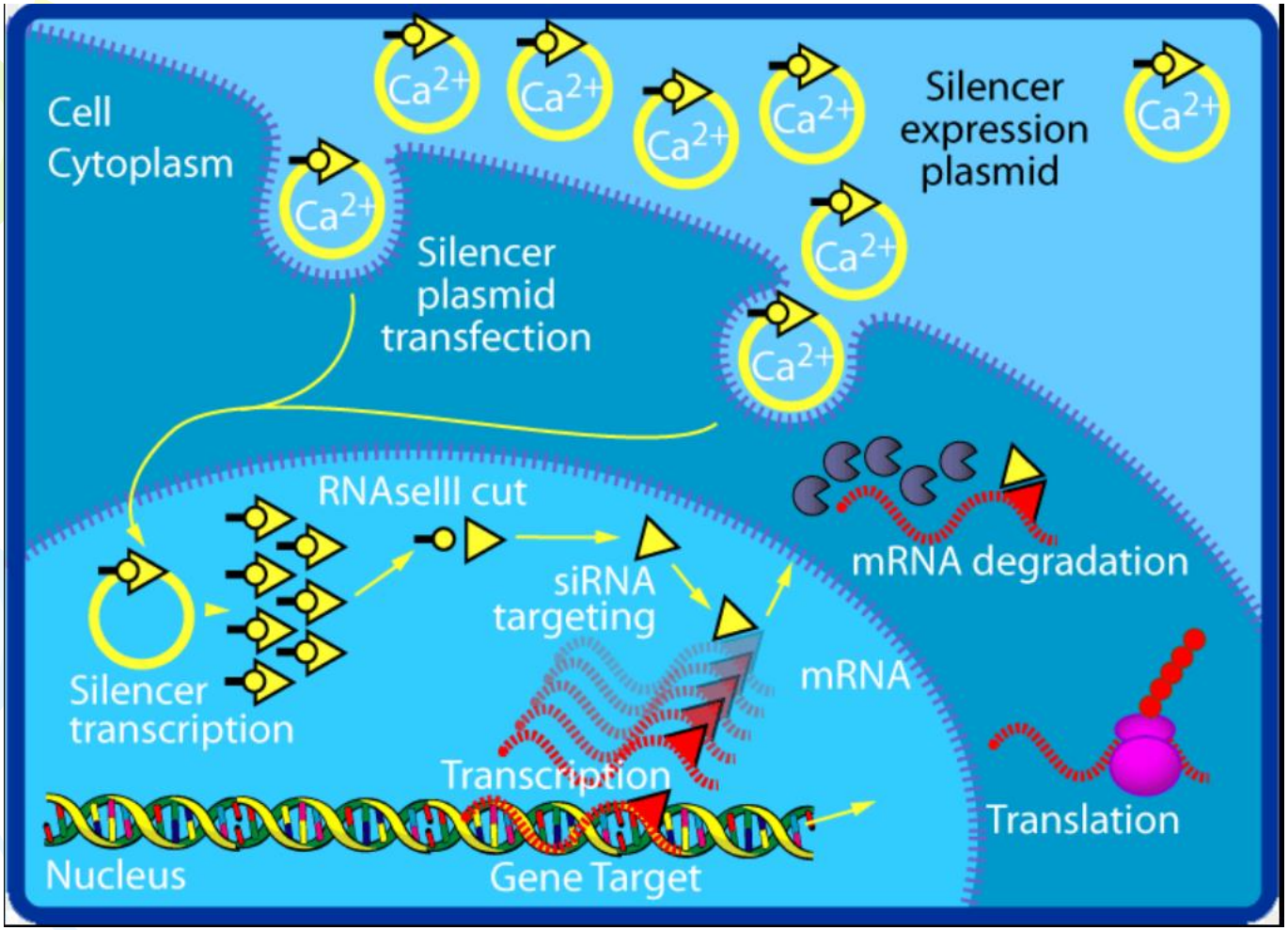
- CRISPR-Cas9 since 2012
- 2021 clinical trial for
  - sickle cell anemia
  - thalassemia
- by Vertex Pharmaceuticals

Further Gene Editing trials

- 2019
- clinical trials
  - AAV gene editing Retina (EDIT-101)
  - non-viral (NTLA-2001)
    - nanoparticle based delivery of CRISPR to liver

siRNA-based

- Hereditary ATTR amyloidosis
- 2018
- Onpattro



Small interfering RNA (siRNA), sometimes known as short interfering RNA or silencing RNA, is a class of double-stranded RNA at first non-coding RNA molecules, typically 20–24 (normally 21) base pairs in length, similar to miRNA, and operating within the RNA interference (RNAi) pathway. It interferes with the expression of specific genes with complementary nucleotide sequences by degrading mRNA after transcription, preventing translation.[

Recent Advances

- Base editing
- Prime editing
- RNA targetted editing
- Epigenome editing
- CRISPR edit gene regulatory element
- Universal cell therapy

Thank You!