罕藥給付對於遺傳罕病的積極意義與罕病基因治療重要性

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一個治療罕見疾病的醫生

缺藥的年代

The Triumph of Death is a painting by Pieter Bruegel the Elder, painted c. 1562 it was inspired by the waves of the Black Death plaguing the 14th century. Image in public domain. BRUEGEL

Incentive

Table 1: Policies that Support Orphan Drugs

Policies/Programs	
Longer market exclusivity	7 years of market exclusivity for approved orphan indications
Tax credits for expenditures incurred in conducting clinical trials	25% federal tax credit for expenditures incurred in conducting clinical research within the U.S.
User fee waiver	Waiver of Prescription Drug User Fee Act (PDUFA) fees
Research grants	Ability to compete for research grants from the Office of Orphan Products Development (OOPD) to support clinical studies for orphan drugs

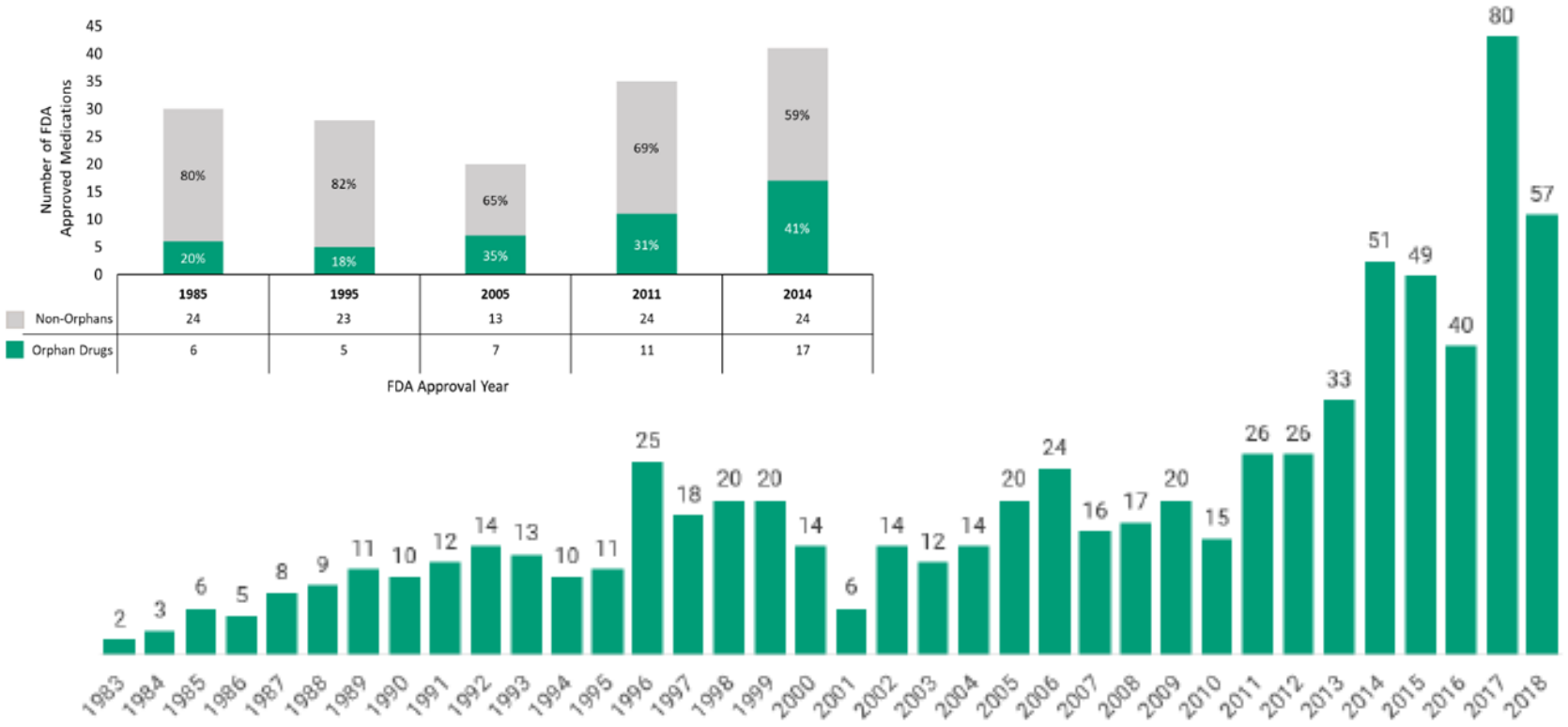
- **Market Exclusivity**: Seven years of market exclusivity to sponsors of approved orphan indications. The market exclusivity in the U.S. is typically five years for a new chemical entity. ODA market exclusivity begins on the day of FDA approval of an orphan indication and differs from patents that usually start early in the development process. The ODA exclusivity allows manufacturers a guaranteed period without head-to-head generic competition for the indication, though it does not prevent generic drugs from launching for other non-orphan indications of the product and thereafter being used off-label to compete with the brand drug.

Institute for Clinical and Economic Review 2022

The Next Generation of
Rare Disease Drug Policy:
Ensuring Both Innovation and Affordability

Figure 3: Number of Orphan Indications Approved in the United States, 1983 - 2018[29]

Figure 4. Percent of Novel New Orphan and Non-Orphan Drugs Approved by FDA[64]



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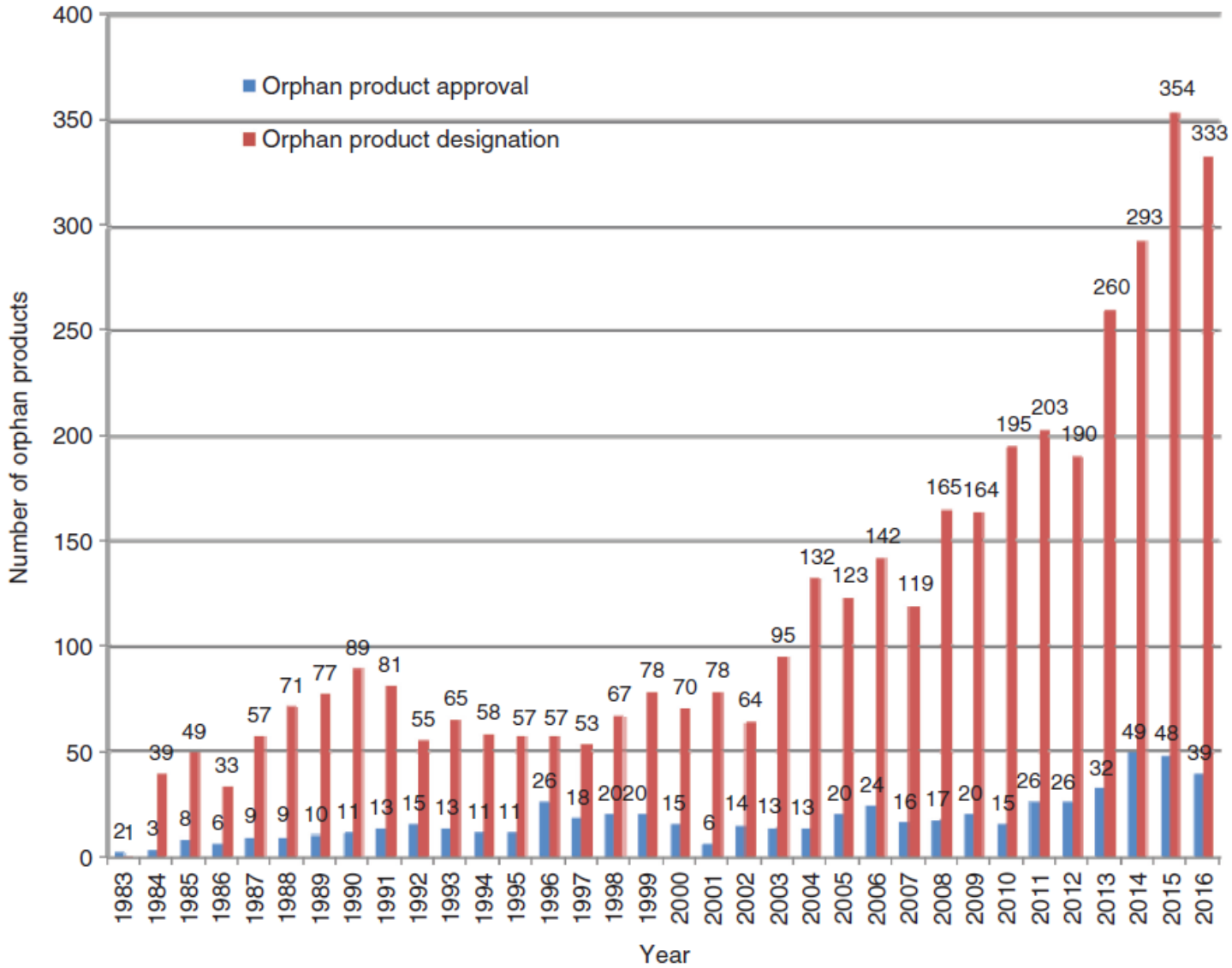


Figure 1: Number of orphan product designations and approvals by FDA until 2016 [24, 25].

Process

「一個性命垂危的孩子坐在這裡，社會大眾決定要不要救他。」為了搶救蕭仁豪，罕媽陳莉茵與罕爸曾敏傑持續動員媒體關注，一邊全力奔走，從醫生、立委、衛生主管機關著手，爭取救命藥物。擔心改變制度緩不濟急，伊甸基金會率先紓困，捐助260萬的買藥錢。

在社會催促下，政府火速一個月通過健保給付支付藥費。蕭仁豪是台灣第一個因凝聚社會、官方共識救起來的罕病孩子，成為第一個接受酵素療法的患者，也開啟罕病基金會成立的前奏曲。

……

罕病基金會創辦人陳莉茵知道，同情是短暫的，不能給罕病患者長久保障，唯有建立制度才是解決之道。「我們不可能照顧孩子一輩子，但制度可以」她永遠不會忘記，罕病立法的那一天，「罕見疾病防治及藥物法」從一讀到三讀僅42天，2000年1月14日，當槌子敲下的那一刻，台灣是全世界第五個立法保障罕病用藥和生存權的國家。

https://health.udn.com/health/story/5960/4116499

罕見疾病物流中心

宗旨

確保及協助各診療醫院及罕見疾病病人取得維持生命所需之特殊營養食品及緊急需用之罕見疾病適用藥物。

願景

成為全國唯一且最專業維護罕見疾病病人醫療營養補給及緊急用藥之物流中心。

價值

以罕病病人特殊營養補充及緊急需用藥物需求為基礎，提供必要、快捷、安全與正確的服務。

The orphan drugs in the lock

€40million per year

€50,000 or more/patient/year

目前仍排隊等待健保給付的罕病新藥[1]

Table 1. ZIN horizon scanning data for orphan drugs in the lock

Drug	Indication	Annual patient numbers	Annual per patient cost	Annual total cost
Atidarsagene autotemcel (Libmeldy®)	Metachromatic leukodystrophy	1-5	€2,500,000-€3,000,000	€8,250,000
Avalglucosidase alfa (Nexviadyme®)	Pompe disease	130	>€467,000	€60,710,000
Brexucabtagene autoleucel (Tecartus®)	Follow-up treatment of mantle cell lymphoma	20-30	€327,000	€8,175,000
Carfilzomib (Kyprolis®)	Multiple myeloma	250	€18,280-€146,060	€20,542,500
Crizanlizumab (Adakveo®)	Sickle cell disease	<150	€45,500-€49,000	€7,087,500
Glasdegib (Daurismo®)	Acute myeloid leukemia	<386	<€41,000	€15,826,000
Idecabtagene vicleucel (Abecma®)	Multiple myeloma	<50	€320,000-€330,000	€16,250,000
Pegcetacoplan (Aspaveli®)	Paroxysmal nocturnal hemoglobinuria (rare blood disease)	<80	€340,000-€400,000	€29,600,000
Ripretinib (Qinlock®)	Advanced gastrointestinal tumors	<50	€40,000	€2,000,000
Risdiplam (Evrysdi®)	Hereditary muscle disease (spinal muscular atrophy)	190-327	<€390,000	€100,815,000
Selumetinib (Koselugo®)	Neurofibromatosis in adolescents (von Recklinghausen's disease)	40-125	<€125,000	€10,312,500
Tafasitamab (Minjuvi®)	Diffuse large B-cell lymphoma	<[illegible]		

序號	成分名	病症	取得罕病認定日期
1	protein C	同基因合子蛋白質C缺乏症	94年1月28日
2	Tafamidis meglumine	FAP	102年4月19日
3	Cerliponase alfa	神經元蠟樣脂褐質儲積症	107年9月7日
4	Patisiran	FAP	108年1月19日
5	Migalastat	Fabry	108年5月30日
6	Stiripentol	SMEI, Dravet	108年7月18日
7	Onasemnogene abeparvovec	SMA	109年3月18日
8	Burosumab	佝僂症	109年8月26日
9	Givosiran	紫質症	109年9月29日
10	Chenodeoxyholic acid	先天性膽酸合成障礙	109年9月29日
11	Edaravone	ALS	109年9月29日
12	Risdiplam	SMA	109年12月30日
13	Ofatumumab	MS	109年12月30日
14	Ravulizumab	PNH	109年12月30日
15	Human C1-esterase inhibitor	HAE	109年12月30日
16	Ataluren	DMD	109年12月30日
17	Ozanimod	MS	110年10月13日
18	Luspatercept	海貧	110年10月13日
19	Ponesimod	MS	111年1月21日
20	Avalglucosidase alfa	Pompe	111年1月21日

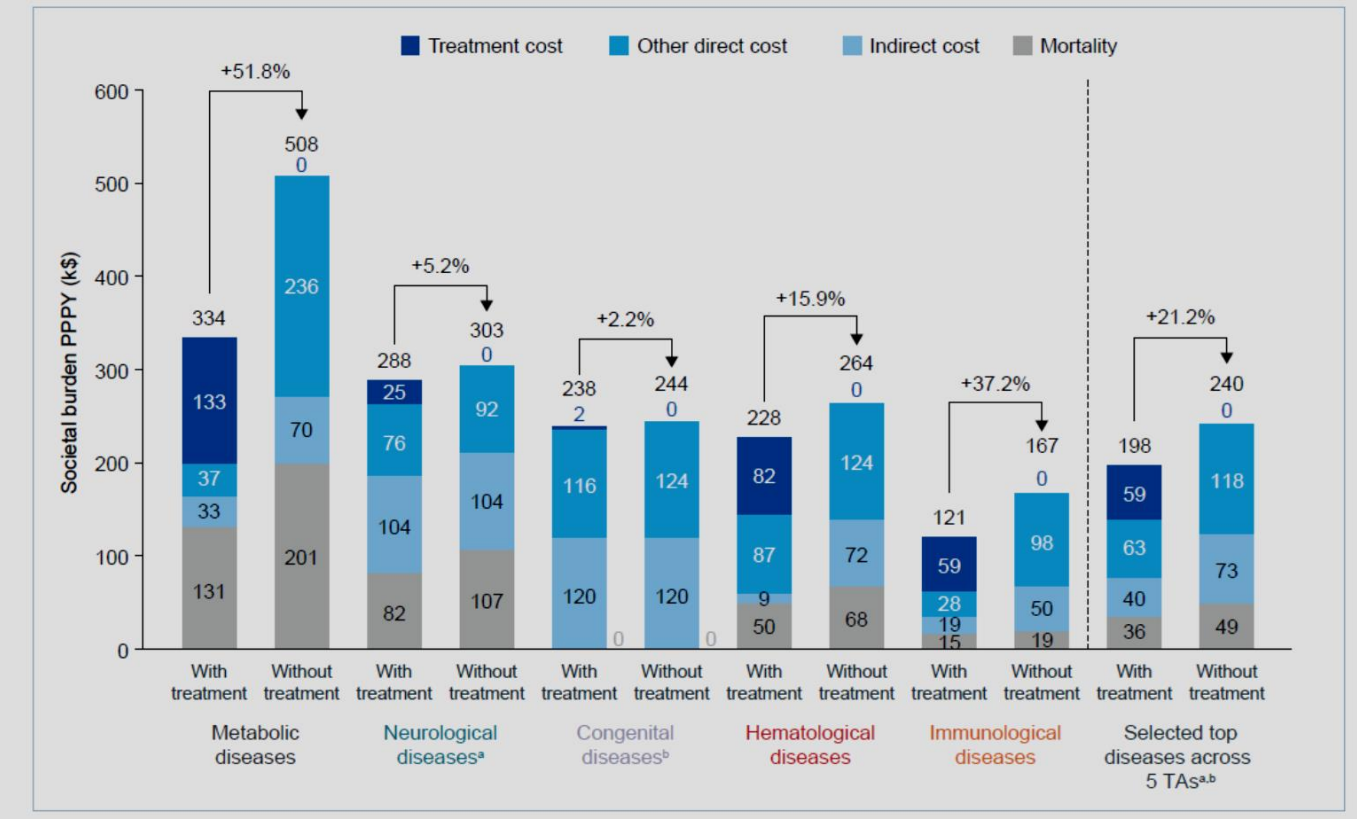
治療準則以及給付規範

Source: Zorginstituut Nederland. 2022b.

1. https://www.upmedia.mg/news_info.php?Type=2&SerialNo=146533
2. 整理歷年全民健康保險醫院總額協商議事會議資料。取自：衛生福利部中央健康保險署-醫院總額 (nhi.gov.tw)

Lack of treatment for a rare disease is associated with a 21.2% increase in total costs

Burden of disease PPPY (per patient per year) across rare diseases with and without treatment and value assessment



https://c212.net/c/link/?t=0&l=en&o=3455890-1&h=460956728&u=https%3A%2F%2Fchiesirarediseases.com%2Fassets%2Fpdf%2Fchiesiglobalrarediseases.whitepaper-feb.-2022_production-proof.pdf&a=https%3A%2F%2Fchiesirarediseases.com%2Fassets%2Fpdf%2Fchiesiglobalrarediseases.whitepaper-feb.-2022_production-proof.pdf

What is Gene Therapy?

- Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.
- Gene therapies can work by several mechanisms:
  - Replacing a disease-causing gene with a healthy copy of the gene
  - Inactivating a disease-causing gene that is not functioning properly
  - Introducing a new or modified gene into the body to help treat a disease
- Gene therapy products are being studied to treat diseases including cancer, genetic diseases, and infectious diseases.

Pros and Cons of Gene Therapy

Pros

Gene therapy can potentially cure someone of a disease.
Only has to be given one time.
Long-lasting effects.
Positive effects passed down through generations.
If you remove a faulty gene from a parent, they won't transfer this gene to their kids.
Rapidly-changing technology.

Cons

Expensive.
Experimental.
Potentially dangerous.
Ethical issues.
May cause infection.

Viral Vectors for Gene Therapy Have Evolved Over the Past 30 Years

1989 — **Retrovirus vector**
First officially approved gene transfer into humans with **advanced cancers** (Steven A Rosenberg)[1]

1990 — **Retrovirus vector**
First therapeutic gene transfer in patients with an ADA-SCID deficiency[2]

1999 — **Adenovirus vector**
The death of gene therapy clinical trial **OTCD** patient, Jesse Gelsinger[3]

2003 — **Adenovirus vector**
China is the first country to approve a gene therapy-based product for clinical use[4]

2009 — **Adenovirus vector**
First successful phase 3 gene therapy clinical trial in the EU[5]

2012 — **AAV vector**
Nov: **First gene therapy** approved in Western world to treat patients with **lipoprotein lipase deficiency**[6]

2016 — **Retrovirus vector**
Europe approves gene therapy to treat patients with **ADA-SCID**[7]

2017 — **Lentivirus vector**
US approves immunotherapy (**CAR-T**) for **leukemia** and **B-cell lymphoma**[8,9]

2017 — **AAV vector**
Dec: US approves first directly administered gene therapy for **retinal dystrophy**[10]

2019 — **AAV vector**
May: US approves systemic gene therapy for **SMA**[11]

2020–2021 — **AAV vector**
Argentina, Australia, Brazil, Canada, EU, Israel, Japan, and Taiwan all approve systemic gene therapy for **SMA**[12-18]

	Voretigene neparvovec Leber Congenital Amourosis	**Onasemnogene abeparvovec** Spinal Muscular Atrophy	**Betibeglogene autotemcel** beta-thelassemia	**Elivaldogene autotemcel** cerebral adrenoleukodystrophy	**Autologous CD34+** Adenosine Deaminase Deficiency	**Alipogene tiparvovec** Lipoprotein Lipase Deficiency
US FDA approved	**2017**	**2019**	**2022**	**-**	**-**	**-**
EMA authorized	**2018**	**2020**	**2019**	**2021**	**2016**	**2012, Withdrawn**

1
3

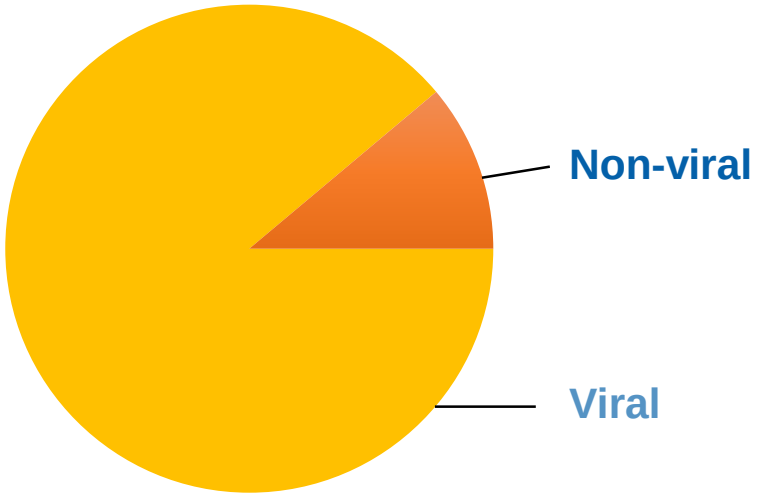
AAV, adeno-associated virus; ADA-SCID, severe combined immunodeficiency due to adenosine deaminase deficiency; CAR, chimeric antigen receptor; SMA, spinal muscular atrophy.
Timeline adapted with permission from Wirth T et al.[5]

1. Rosenberg SA et al. *N Engl J Med.* 1990;323(9):570-578. **2.** Blaese RM et al. *Science.* 1995;270(5235):475-480. **3.** Sibbald B. *Can Med Assoc J.* 2001;164(11):1612. **4.** Peng Z. *BioPharm Int.* 2004;17(5):1-3.
5. Wirth T et al. *Gene.* 2013;525(2):162-169. **6.** National Organization for Rare Disorders (NORD). Accessed August 10, 2021. https://rarediseases.org/glybera-becomes-first-ever-gene-therapy-approved-in-europe/
7. Hoggatt J. *Cell.* 2016;166(2):263. **8.** FDA (September 7, 2017). Accessed August 10, 2021. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm574154.htm **9.** Maude SL et al. *N Engl J Med.* 2018;378(5):439-448. **10.** FDA (December 18, 2017). Accessed August 10, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss **11.** FDA (May 24, 2019). Accessed August 10, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease **12.** Novartis (March 19, 2020). Accessed August 10, 2021. https://www.novartis.com/news/media-releases/novartis-receives-approval-from-japanese-ministry-health-labour-and-welfare-Onasemnogene abeparvovec-only-gene-therapy-patients-spinal-muscular-atrophy-sma **13.** Novartis (May 19, 2020). Accessed August 10, 2021. https://www.novartis.com/news/media-releases/avexis-receives-ec-approval-and-activates-%22day-one%22-access-program-zolgensma-only-gene-therapy-spinal-muscular-atrophy-sma **14.** Novartis Pharmaceuticals Canada (June 9, 2021). Accessed August 10, 2021. http://www.ask.novartispharma.ca/download.htm?res=zolgensma_scrip_e.pdf&resTitleId=1747 **15.** Ministry of Health Israel. The Israeli Drug Registry. Accessed August 10, 2021. https://data.health.gov.il/drugs/index.html#!/medDetails/165%2075%2036125%2000 **16.** Chand D et al. *J Hepatol.* 2021;74(3):560-566. **17.** Onasemnogene abeparvovec package insert. Novartis Argentina S.A. 2020. **18.** Onasemnogene abeparvovec. Product information. Macquarie Park, NSW, Australia: Novartis Pharmaceuticals Australia Pty Limited. 2021.

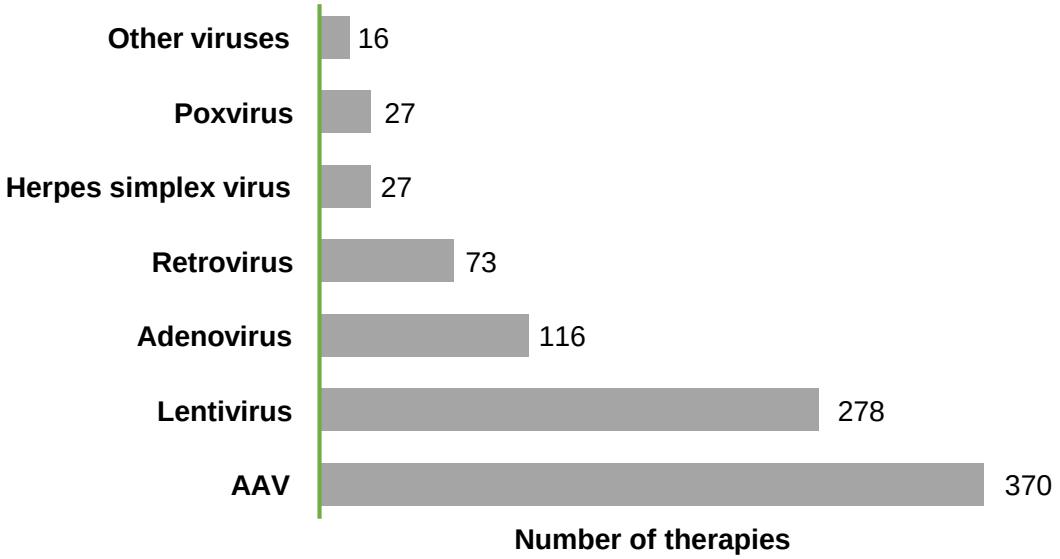
The Majority of Gene Therapies in Development Use AAV Vectors

88% of gene therapies in development use viral vectors, with AAV vectors being the most common

Viral vs Non-viral Gene Delivery



Viral Vectors Used in Pipeline Therapies



AAV, adeno-associated virus.

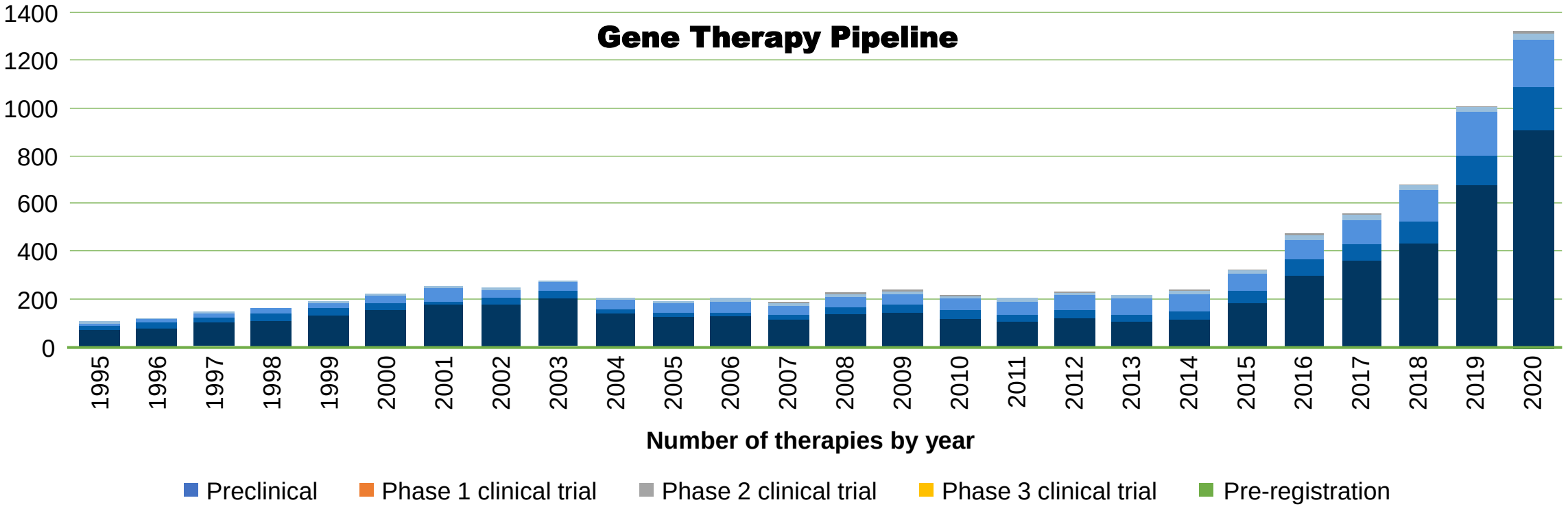
Figure adapted with permission from American Society of Gene and Cell Therapy. American Society of Gene and Cell Therapy (April 2021). Accessed September 9, 2021. https://asgct.org/global/documents/asgct-pharma-intelligence-quarterly-report-q1-2021.aspx

Gene Therapy Booming Development

- US FDA predicts that by 2025 it will be approving **10~20** cell and gene therapies every year.
- There are **1,745 gene therapies** in development around the world. A large fraction of this research focuses on rare genetic diseases, which affect **400 million people** worldwide.

https://theconversation.com/new-gene-therapies-may-soon-treat-dozens-of-rare-diseases-but-million-dollar-price-tags-will-put-them-out-of-reach-for-many-164990

There Has Been a Rapid Growth in the Gene Therapy Landscape in Recent Years[1]

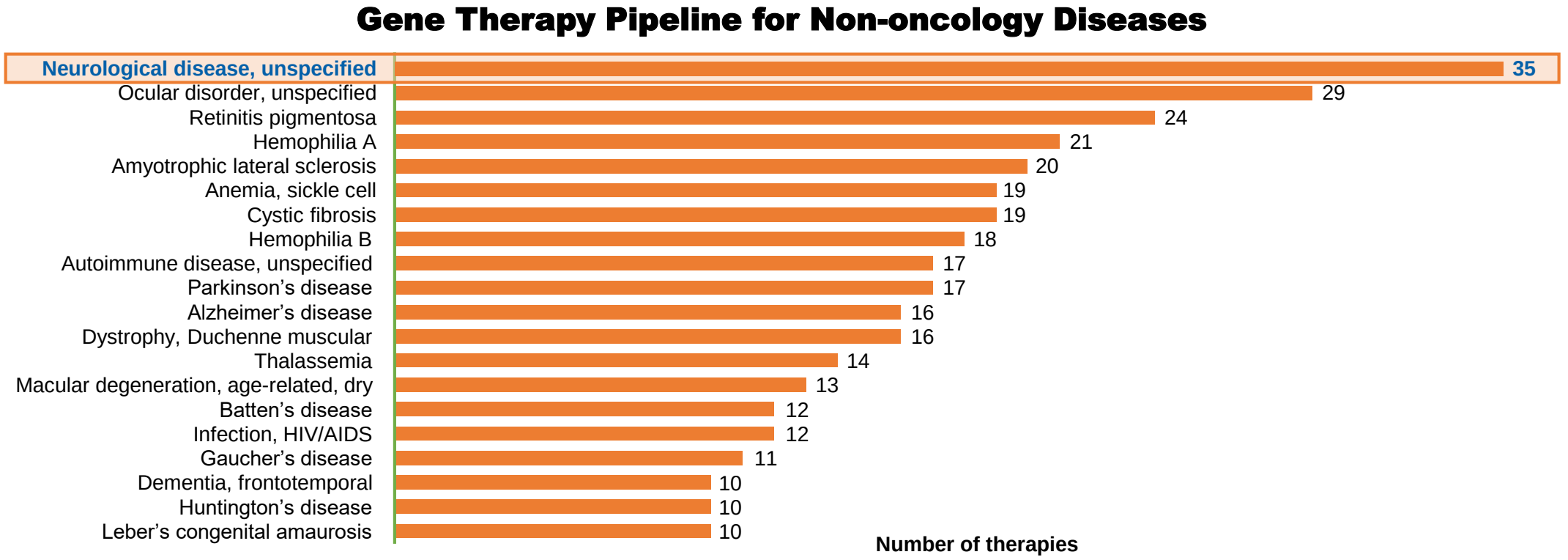


The number of gene therapy clinical trials has significantly increased over the last 30 years, with an increasing number of investigational new drug (IND) applications[2,3]

IND, investigational new drug.
Figure adapted with permission from American Society of Gene and Cell Therapy.[1]

1. American Society of Gene and Cell Therapy (April 2021). Accessed August 11, 2021. https://asgct.org/global/documents/asgct-pharma-intelligence-quarterly-report-q1-2021.aspx
2. Ginn SL et al. *J Gene Med.* 2018;20:e3015. **3.** Eisenman D. *Applied Biosafety: J ABSA International.* 2019;24(3):147-152.

Neurological Diseases Are the Most Common Non-oncology Disease States Targeted by Gene Therapies



35 gene therapies for neurological disorders are in development, from preclinical to pre-registration stages

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.
American Society of Gene and Cell Therapy (April 2021). Accessed August 11, 2021. https://asgct.org/global/documents/asgct-pharma-intelligence-quarterly-report-q1-2021.aspx.

Finding **NEW** ways to pay

- **Outcomes-based model**
  - Upfront + pay rest only if the patient improves
  - Cover the entire cost upfront and receive a reimbursement if the patient doesn't get better
  - Share financial risk with the drug developers
  - Example: implemented in gene therapy reimbursement in Korea, Australia, Italy

- **"Netflix" model**
  - HepC drug in Louisiana, US
  - Subscription-based service
  - Louisiana's program will cap gross expenditures at a fixed amount while retaining unlimited access to the needed antiviral hepatitis C treatment for both Medicaid managed care beneficiaries and those covered under fee-for-service.
  - Pay a pharmaceutical company a flat fee for access to unlimited treatments. This would allow a state to provide the treatment to residents who qualify, helping governments balance their budget books while giving drugmakers money upfront

https://theconversation.com/new-gene-therapies-may-soon-treat-dozens-of-rare-diseases-but-million-dollar-price-tags-will-put-them-out-of-reach-for-many-164990

台大醫院成功開發「芳香族L-胺基酸脫羧基酶AADC缺乏症」療法，成功幫助30位病童，成為全球第1個取得藥品管理單位批准的AADC缺乏症治療方式，日前獲歐洲藥品管理局（EMA）同意授予這項基因治療藥物Upstaza的上市許可。

https://cc.tvbs.com.tw/img/program/upload/2022/07/22/20220722135947-c861346d.jpg