Gene Therapy: A Paradigm Shift in Medicine

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Viral vectors are most prominent, especially AAV

- **Viral gene therapy could treat incurable diseases**
- **One-time injection could treat chronic diseases**

Key company players include small biotechs and Big Pharma

- **The gene therapy pipeline is growing**
- **Rapid increase in partnerships between both the licenser and licensee**

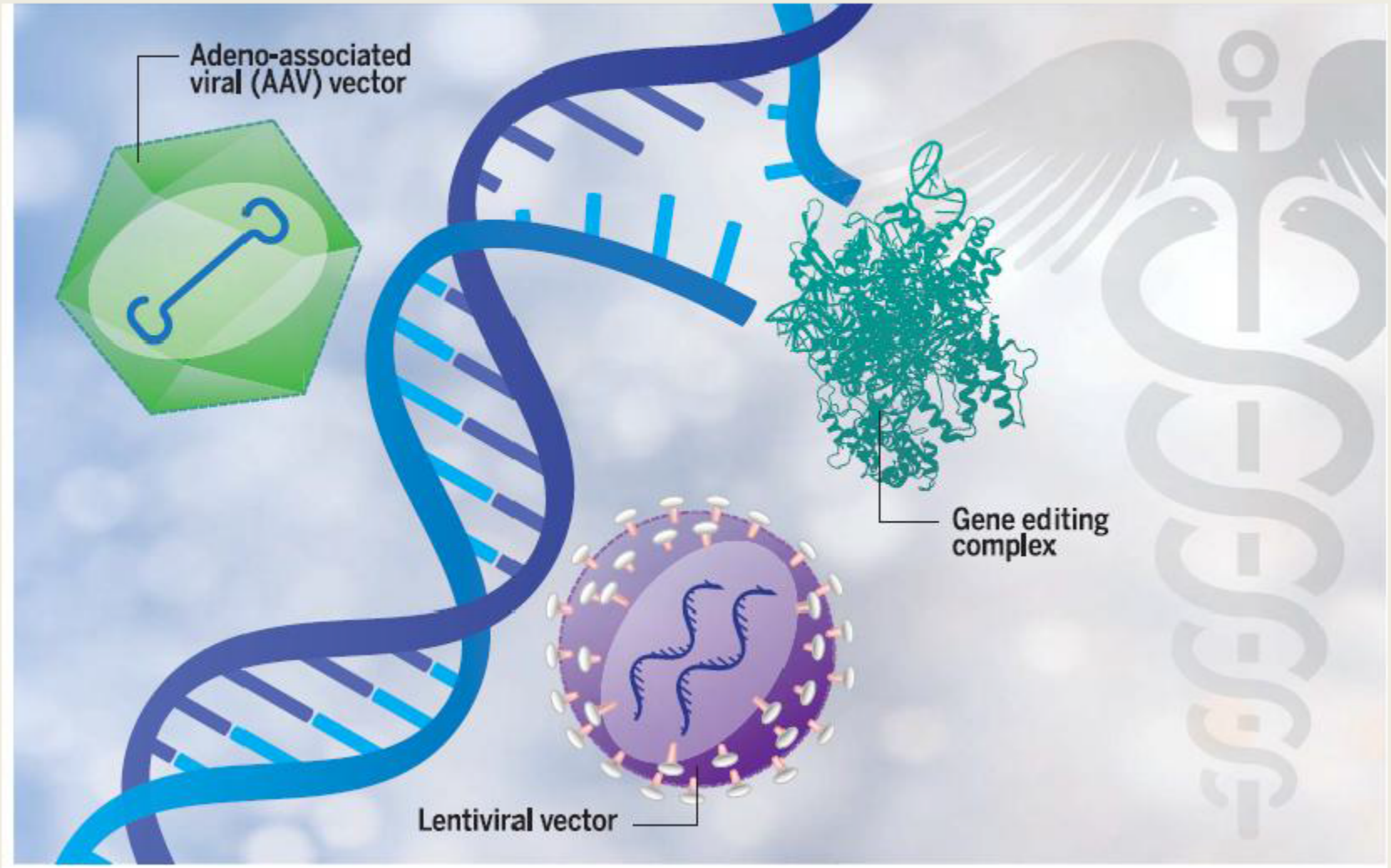
Manufacturing (CMC) is one of the main issues in gene therapy commercialization

The regulatory paradigm is being changed

Cost is the biggest concern

Challenges _ Long-term benefits, off-target effects…

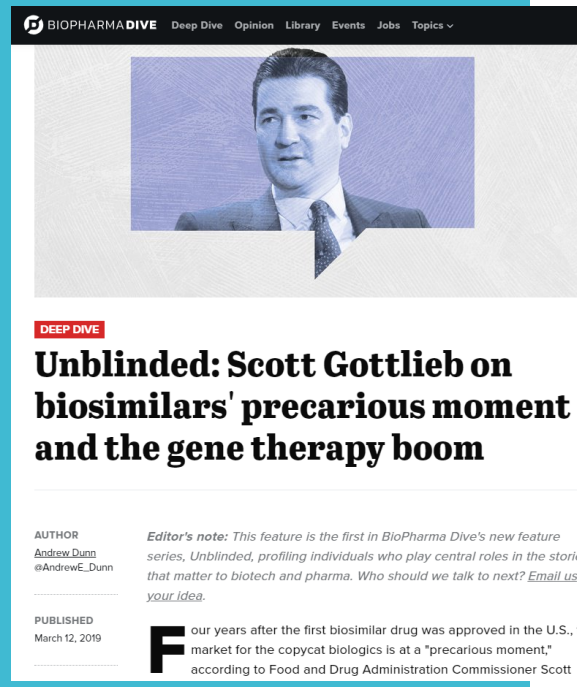
Three essential tools for human gene therapy



Dunbar et al., Science 359, 175(2018)

품목허가 받은 유전자 치료제 (미국 & EU)

제품명	회사명	분 류	벡 터	적 응 증	치료 약가	승인일	국가
Zynteglo	Bluebird Bio	유전질환	LentiVirus	β0/β0 유전자형이 아닌 베타글로빈 유전자 결함 12세 이상 수혈 의존형 베타 지중해성 빈혈(TDT)	미 정	2019.06	유럽
Zolgensma	Novartis/AveXis	유전질환	AAV9	SMN1 변이 척수성 근위축증(SMA)	$2,125,000 (약 25억원)	2019.05	미국
Luxturna	Spark Therapeutics	유전질환	AAV2	PRE65 변이 관련 망막 형성 장애	$850,000 (약 9억원)	2017.12	미국
Yescarta	Gilead/ Kite Pharma	혈액암	RetroVirus	재발성 또는 불응성 DLBCL, PMBCL 성인 환자	$373,000 (약 4억2천만원)	2017.10	미국
						2018.08	유럽
Kymriah	Novartis	혈액함	LentiVirus	소아, 25세 이하 ALL, 재발성 또는 불응성 DLBCL	$475,000 (약 5억3천만원)	2017.08	미국
						2018.08	유럽
Invossa-K	Kolon Life Science	만성질환	RetroVirus	퇴행성 골관절염	약 5백만원	2017.07	대한민국
Strimvelis	GSK	유전질환	γ-RetroVirus	아데노신 탈아미노효소 결핍(ADA-SCID)	€600,000 (약 8억원)	2016.05	유럽
Imlygic	Amgen	흑색종	Oncolytic Virus(HSV-1)	절제 불가능한 악성흑색종	$65,000 (약 7,000만원)	2015.10.	미국
						2015.12	유럽
Glybera	UniQure	유전질환	AAV	지질단백 분해효소 결핍증(LPLD)	€1,100,000 (약 15억원)	2012.10.	유럽



In a joint Jan. 15 statement, Gottlieb and Peter Marks, director of the agency's Center for Biologics Evaluation and Research, set out ambitious expectations: a near future with 200 Investigational New Drug Applications a year by 2020, leading to approvals of between 10 and 20 cell and gene therapies each year starting in 2025.

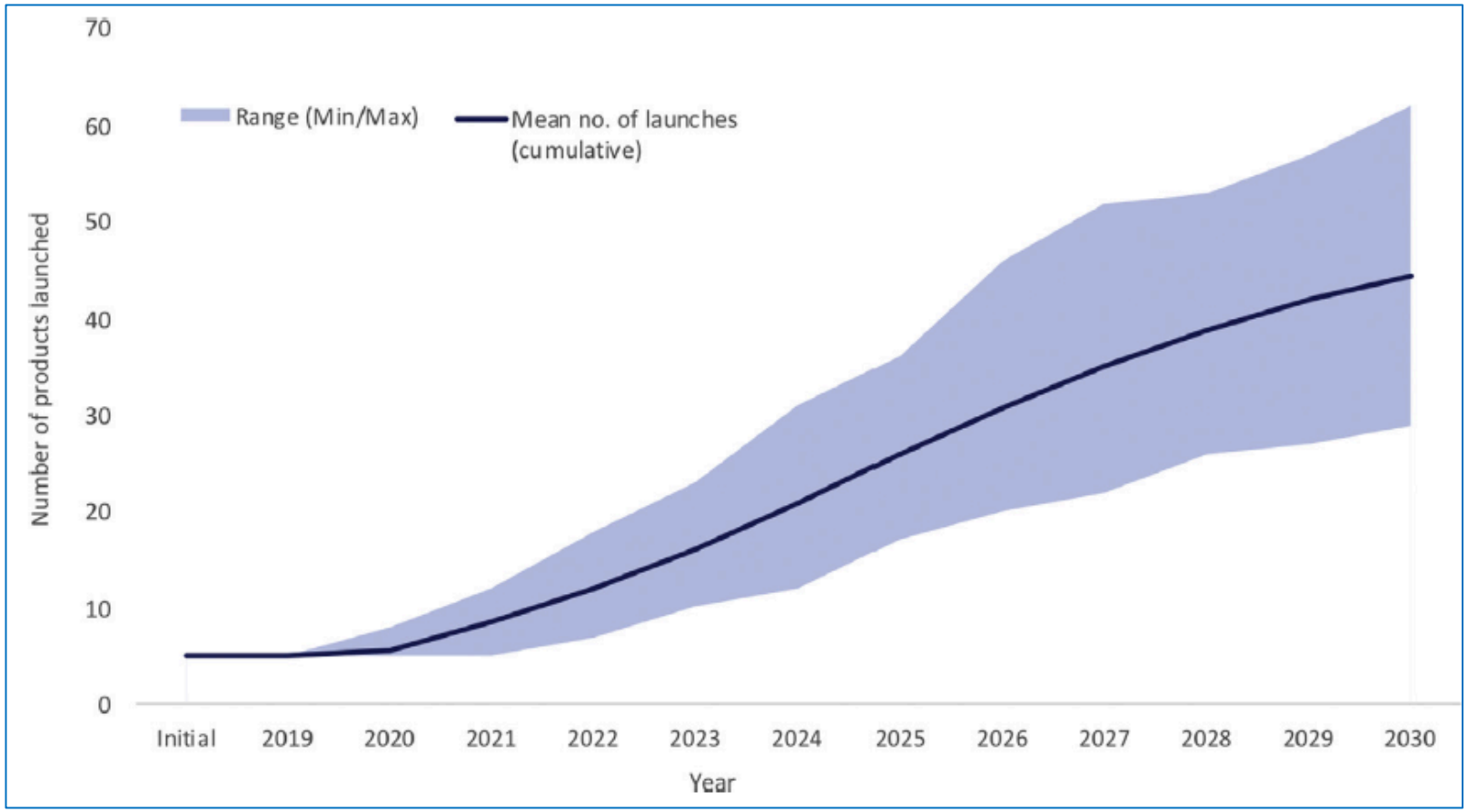
To prepare, the two leaders outlined a plan to add 50 clinical reviewers while issuing a slate of guidance documents to shepherd drugmakers. The drug review process for gene therapies will be fundamentally different, however. Typically, about 80% of an FDA review is on the clinical portion of a company's application and about 20% on chemistry, manufacturing and controls, or CMC, Gottlieb said. "With gene therapies, it's almost inverted," he added, with the most challenging questions on CMC. "We do need to think of a different regulatory paradigm."

Spark CEO Jeff Marrazzo, for instance, recently told BioPharma Dive that its application with the FDA ran to roughly 60,000 pages, the vast majority of which was dedicated to CMC.

And with response to gene therapy potentially so much clearer, clinical questions may no longer be as paramount in the FDA's initial review.

Estimating the Clinical Pipeline of Gene Therapies

Predicted cumulative product launches, 2018-2030



VALUE HEALTH. 2019; 22(6):621–626

Technology

Biotech Investors Zero In on Gene Therapy as Next Big Frontier

By Tatiana Darie
2019년 3월 16일 오전 1:48 GMT+9

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Biotech investors are bullish on the market for gene therapies, even though actual sales of a few existing drugs have so far failed to impress some Wall Street analysts.

Fund managers and venture capitalists discussed their outlook for the technology in interviews in Boston, where investors gathered for the Cowen health-care conference. Investor interest in gene-therapy stocks is high, as investing has paid off this year. Roche Holding AG and Biogen Inc.

Alliance for Regenerative Medicine

Address Manufacturing and Look Beyond Cancer, Panel Advises Cell and Gene Therapy Companies

By **Alex Philippidis** - March 22, 2019

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[L-R] Reni Benjamin, PhD, of Raymond James; Elona Baum of DEFTA Partners; Dennis Purcell of Aisling Capital; Patrick Rivers of Aquilo Capital Management; and Matthew Gline of Roivant Sciences discuss the investment outlook for the cell and gene therapy sector at the Alliance for Regenerative Medicine's Cell & Gene Therapy Investor Day, held in New York [Alliance for Regenerative Medicine]

"Manufacturing becomes question numbers one, two, and three when we're beginning to know a gene therapy company for the first time," Rivers said. "To a much bigger extent than with generally any other type of company, the first thing that we're going to interrogate is, what is your manufacturing setup? How scalable is it? What can you do yourself? What do you have to have a source do? What are you doing in process development today vs. what you plan to accomplish tomorrow?"

"It's a pretty opaque area. Very few companies are really willing to talk about manufacturing at a granular level, because there's a lot of secret sauce that's attached to it," as in proprietary processes. "They don't really want to talk about it. I find myself asking the same question over and over and over again, to try and glean a small amount of information."

Reni Benjamin, PhD, managing director and senior biotechnology analyst at Raymond James, said many investors he speaks with prefer cell and gene therapy startups to develop their own manufacturing solutions rather than rely on contract manufacturers.

Key Considerations for Gene Therapy Clinical trial

- ✓ Gene Therapy Market & Industry
- ✓ Target Diseases
- ✓ Mode-of-Action & Proof-of-Concept
- ✓ Product Efficacy & Safety
- ✓ Manufacturing of Gene Therapy Product
- ✓ Regulatory Approval

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Draft Guidance for Industry

JULY 2018

Download the Draft Guidance Document | Read the Federal Register Notice

Draft

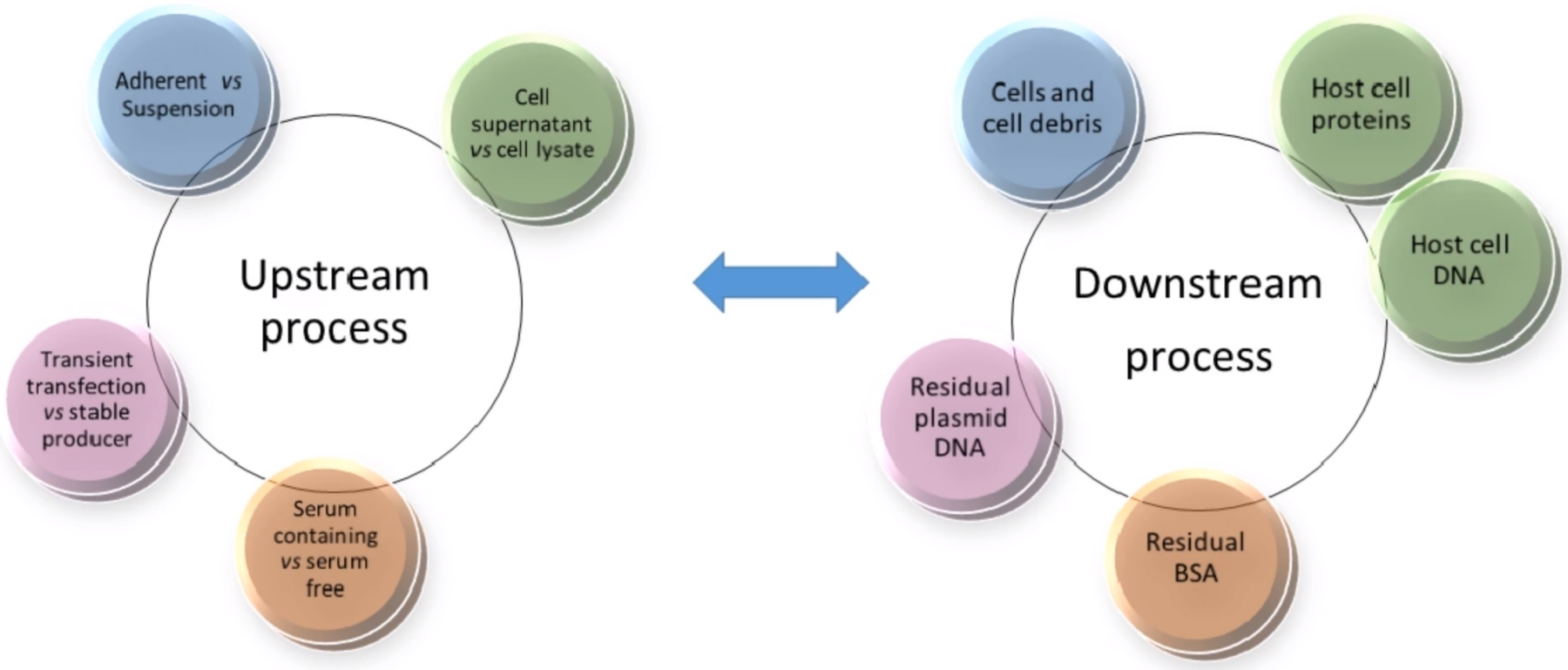
Not for implementation. Contains non-binding recommendations.

This guidance is being distributed for comment purposes only.

Transient Transfection	Producer Cell Line
Limited yield • Cell line, medium	Cell line development • Time, stability, cytotoxicity
Control of transfection process • Variability, operational constraints	Low specific productivity
Raw materials • Sourcing, quality, infrastructure	Technology and infrastructure
Limited scalability	

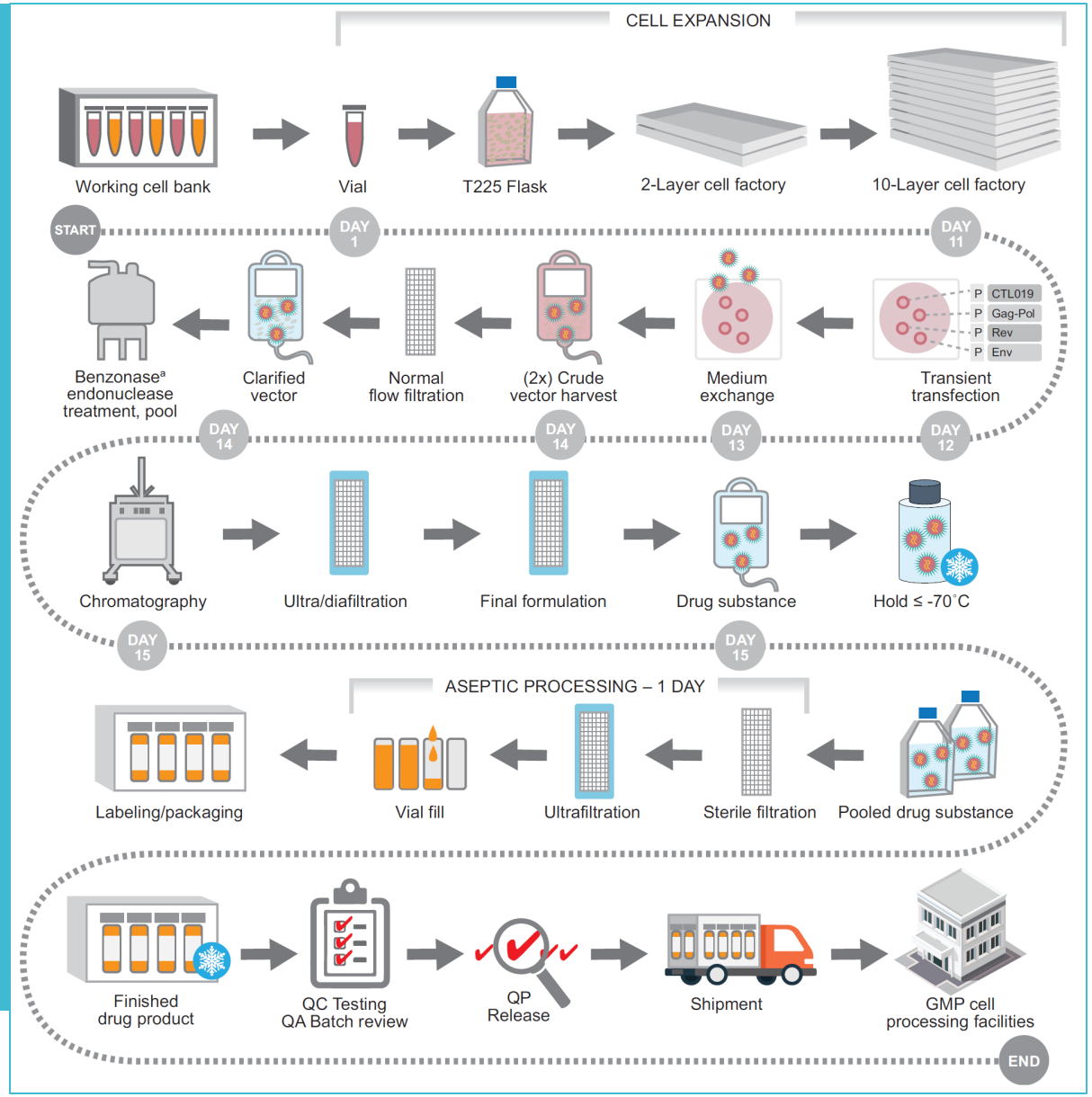
https://insights.bio/cell-and-gene-therapy-insights/optimizing-the-workflow-for-therapeutic-viral-vectors-upstream-and-downstream-2/

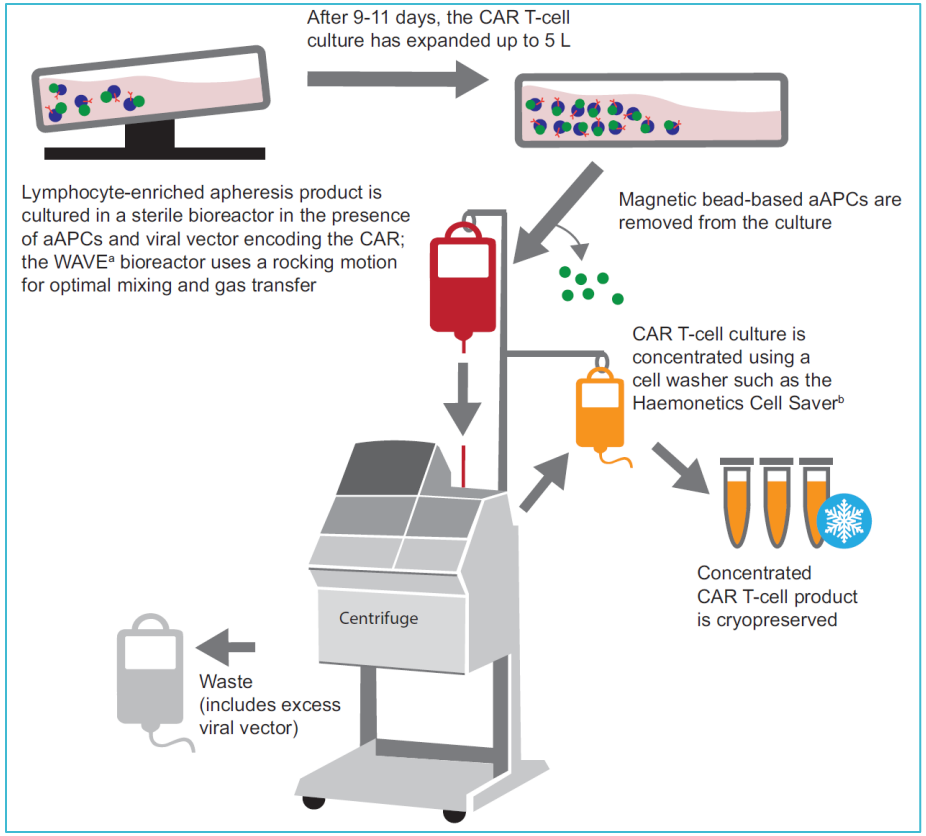
Upstream process (USP) parameters can influence Downstream processing (DSP)



https://insights.bio/cell-and-gene-therapy-insights/optimizing-the-workflow-for-therapeutic-viral-vectors-upstream-and-downstream-2/

Manufacturing of CAR T Cell Therapy





Molecular Therapy: Methods & Clinical Development Vol. 4, 92-101, 2017

In-House

vs.

Outsourcing to CDMO

Process Development _ Tech. Transfer

Engineering Run

GMP Run

QC/Validation

- **Safety:** The product does not elicit unexpected side effects when used appropriately in the patient.
- **Identity:** The product is exactly what is described on the label.
- **Strength/Potency**: The product delivers the correct dosage over the shelf-life of the product.
- **Purity:** The product is free from physical, biological and chemical contamination.
- **Quality**: The product is manufactured using established quality systems to ensure product consistency and quality specifications are met.

Overview of Analytical Methods used in Viral Vector Manufacturing

Quality	Attribute	Technique
Identity	Confirm presence and identity of viral vector	SDS-PAGE, Mass spectrometry (MS), Western blot (immunoblot), Genome sequencing (NGS), PCR
Potency	Physical viral titer	DNA hybridization, Real-time PCR (qPCR, ddPCR), Optical density ($A_{260/280}$), NanoSight, HPLC
	Functional viral titer	Plaque-forming assay, Fluorescence foci assay, $TCID_{50}$ (end point dilution assay)
Purity	Process-related impurities	MS, Chromatography, TEM
	Host cell-related Impurities	Host cell DNA/RNA: Picogreen, DNA Threshold assay, qPCR, Host cell proteins: ELISA,TEM
	Capsid content (empty: full capsids)	TEM, AUC
Safety	Sterility	Standard sterility tests (EP 2.6.1, USP71)
	Endotoxin	LAL method (EP 2.6.14, USP85), Rabbit pyrogen assay
	Mycoplasma	PCR, Cell cultured based-assays
	Replication Competent Virus (presence of *rep* or *cap* sequences)	Southern blotting, qPCR
	Adventitious Agents	*In vivo* and *in vitro* assays
Stability	pH	Potentiometry
	Osmolality	Osmometry
	Aggregate formation	Light microscopy, DLS, SEC-MALS, TEM, AUC, FFF-MALS

Components used to manufacture the product

- Vector
- Cells
- Banking system
  - Master cell bank (MCB)
  - Master viral bank (MVB)
- Reagents

Gene therapy products must meet rigorous safety guidelines highlighting the importance of well-characterized analytics.

Vectors

plasmid
lentivirus
AAV
retrovirus
adenovirus
herpesvirus
vaccinia virus
sendaivirus
…

- Description, history and details on derivation of construct
- Vector diagram
- Sequence analysis
  - Full sequence for vectors <40 kb
  - Vectors >40 kb: sequence inserts, flanking regions, modified regions
  - Description of unexpected sequences
    - Raw sequence data is not sufficient

Vector Design

Use of non-state-of-the-art vector and packaging cells should be avoided,

- **to allow manufacture of consistent and safe product.**

  Sponsor Statement: "There are molecular strategies by which the generation of RCVs during manufacture can be reduced or potentially eliminated, for example the use of cell lines and vectors which lack overlapping […] nucleotides, thus preventing homologous recombination. However, such a system is not currently employed by the Sponsor."

- **to avoid later changes in vector design and subsequent `comparability´ exercises**

  Use of non-SIN retroviral vectors, use of WPRE with destroyed X-reading frame

Information needed on

- history
- genetic manipulation
- establishment and
- characterisation and control of viral vector seed
  - (sequencing data)

Cells

packaging
virus producing
ex vivo targeting

- Cell substrate for production of vector
  - History, source, general characteristics
- Cells used as cell therapies
  - Source
    - tissue and cell type
  - Collection procedure
    - mobilization, surgery, leukapheresis, devices used
  - Donor Eligibility
    - infectious disease screening & testing, 21 CFR 1271

MCB and MVB safety testing

- Sterility
- Mycoplasma
- Adventitious Virus
  - *in vitro* and *in vivo* adventitious virus assays
  - Bovine and porcine viruses
    - Not needed if reagents tested
  - For human cell lines:
    - Typically EBV, HBV, HCV, CMV, HIV 1&2, HTLV 1 & 2, Parvovirus B19
  - For murine cell lines:
    - Typically mouse antibody production test, retroviruses
  - Replication-competent virus

✓ Master cell bank characterization

- Identity
  - Examples:
    - Isoenzyme
    - Karyotype
    - Short tandem repeat (STR) profiling
- Viability
- Stability

✓ Reagents used in manufacturing

- Tabulation of reagents
  - Final concentration
  - Vendor
  - Source (human, bovine, etc.)
  - Grade
    - e.g. licensed product, clinical grade, reagent grade
- May need to provide details on reagent manufacturing
- Certificates of Analysis
- Cross reference letters
- Qualification program
  - Safety testing and quality assessment

✓ Product Manufacturing

- Vector production / purification
  - Describe all steps
    - e.g. cell growth, infection, harvest, purification, formulation, vialing, storage
  - Flowchart
- Describe the formulation
  - Buffer components
  - Excipients
  - Product concentration
  - Storage

✓ Final Product Testing

- Goals:
  - Safety
  - Product characterization
  - Product lot consistency
- List all of your:
  - Release tests
  - Test methods
  - Acceptance criteria (specifications)

✓ Final product testing: safety

- Sterility
- Mycoplasma
- Endotoxin
- Adventitious Virus
  - *in vitro* virus assays
  - Replication competent virus

✓ Final product testing: characterization

- Final product lot release testing
  - Concentration
  - Purity
    - e.g. residual cellular DNA, empty viral particles
  - Identity
    - e.g. restriction digest
  - Activity
    - e.g. infectious titer
  - Potency
    - e.g. transgene-specific protein expression
  - Cell viability *(ex vivo gene therapy product)*
- Stability
  - Storage
  - Shipping
  - Compatibility with delivery devices

Summary

- For a phase I submission, *product safety* is the focus of the CMC assessment
  - Freedom from microbes and adventitious agents
  - Safety-related characterization
  - Appropriate GMPs
- Gene therapies and other complex biologics can be a challenge to characterize, and often require unique assays
- Product control and process control should increase with clinical development

Company Details

창의거점지원사업
스마트유전자의약플랫폼기반기술구축사업

ICGM
INNOVATION CENTER FOR GENE MEDICINE

유전자의약 오픈 이노베이션센터
충남대

운영위원회

장비위원회

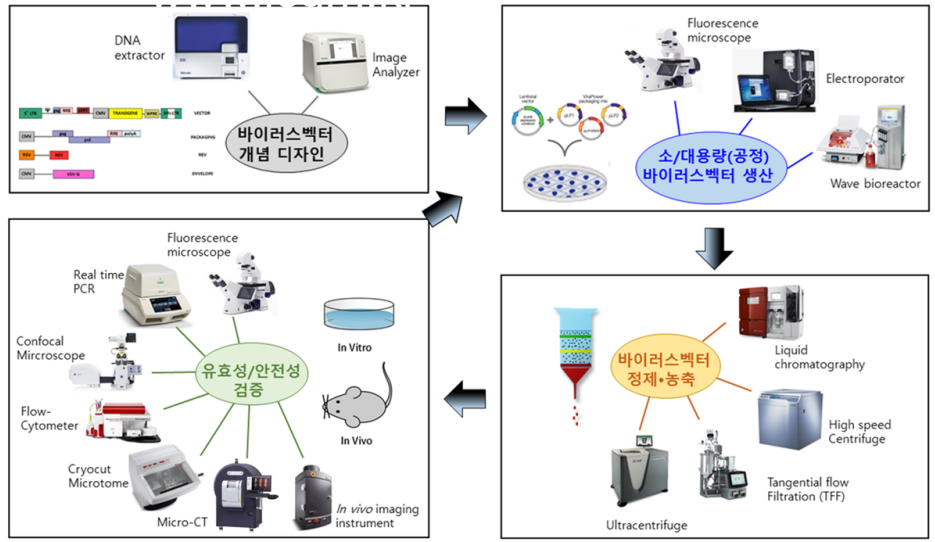
공정개발 Core
충남대

유효성·안전성 평가 Core
충남대, 안전성평가연구원
충남대병원

GMP Core
충남대(바이러스벡터 생산)
대전테크노파크(시설장비 관리)

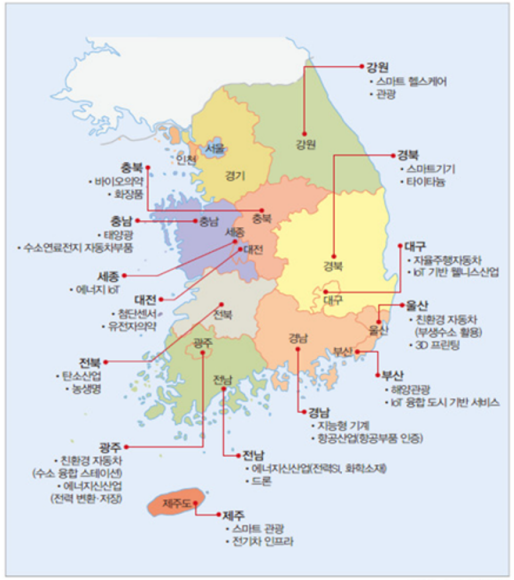
산업통상자원부 | KIAT 한국산업기술진흥원 | 대전광역시 DAEJEON METROPOLITAN CITY | 신약전문대학원

바이러스벡터 개발 및 생산 모식도



ㅇ 2016년 3월 기획재정부 전국 시도별 전략산업 지원전략 발표에서 대전시는 전략지원 육성산업으로 유전자 의약을 선정함

전국 14개 시·도별 27개 전략산업



자료 : 기획재정부

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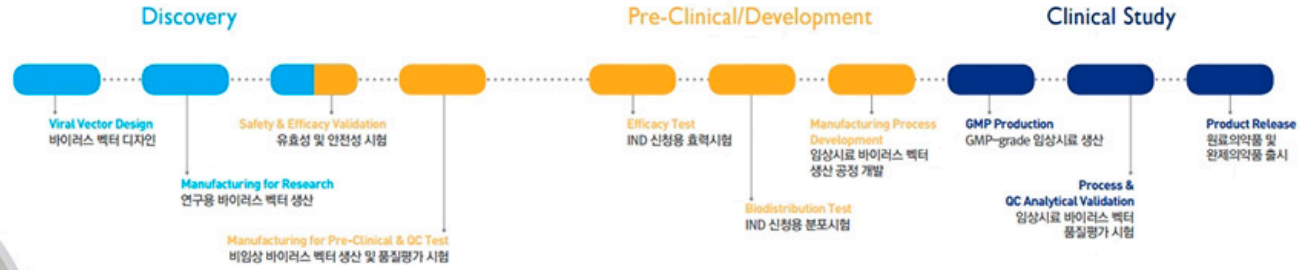
SERVICE FOR GENE THERAPHY

Discovery Study

바이러스 벡터 디자인
연구용 바이러스 벡터 생산
CRISPR/Cas9 라이브러리 스크리닝 서비스
CAR 신규 scFv 발굴



GMP 기반 CDMO

수요자 맞춤형 AAV, Lentivirus, Retrovirus 기반 벡터
GMP Grade 공정개발 및 생산

Development
임상 공정 최적화 및 대량생산 공정 개발
분석시험법 개발 및 검증

GMP Manufacturing
GMP 임상용 원료의약품 및 완제의약품 제조
공인 전문가 생산, IND의 CMC 부분 지원

Quality Assurance
MFDS의 품질보증 시스템 구축, 공인 전문가

Regulatory
Pre-IND, IND를 위한 문서화, 인허가 컨설팅

CRO

임상용 원료의약품 및 완제의약품
품질평가 시험

미생물학적 시험
무균시험, 마이코플라즈마 부정시험
외래성바이러스 부정시험

확인시험 및 특성 분석
Sequencing, Restriction Enzyme Digestion, Expression
물리화학적 & 생물학적 특성 분석, RCL & RCA Assay 등

순도시험
Endotoxin 시험, Host Cell DNA & Protein
Residual BSA & Plasmids

역가시험
Physical & Genomic & Infectious Titer

IND 신청을 위한 약리(효력 및 분포) 시험

효력시험
시험관 내(*in vitro*), 생체 내(*in vivo*) 시험 수행
Proof of Concept 및 후보물질 도출
IND 제출용 잠재적 임상효과 및 관련 생물학적 효과
작용기전 비임상 근거 제공

분포시험
유전자치료제의 특성에 따라 분포시험(qPCR, BLI Analysis)
바이러스 배출(Shedding) 평가

국내 유전자치료 임상시험 현황

제품명	개발사	Vector	대상 질환	임상단계
VMDA-3601	㈜바이로메드/ 동아제약(주)	Naked DNA	허혈성족부궤양	2상 완료
GX-12	포스텍/ 동아제약(주)	Naked DNA	AIDS치료백신	1상 완료
VM202	㈜바이로메드/ 이연제약	Naked DNA	허혈성 심혈관질환	1상 완료
			중증하지허혈질환	2상 완료
			당뇨병성 신경병증	2상 완료
인보사	코오롱생명과학(주)	Retrovirus/ Allogeneic Chondrocyte	퇴행성관절염	3상 완료
VM106	㈜바이로메드	Retrovirus + Stem cell	만성육아종	1/2상 완료
HB-110	제넥신	Naked DNA + Electroporation	만성 B형 간염	2a상
쎄라젠	㈜뉴젠팜	Adenovirus	전립선암	2상 완료
			췌장암	1상
DWP-418	㈜대웅제약	Adenovirus	불응성고형암1	1상 완료
펙사벡	신라젠	Vaccinia Virus	간암	3상
XRP0038	㈜사노피- 아벤티스코리아	Naked DNA	급박하지하혈증	3상 중단
JX-594	삼성의료원	Vaccinia Virus	대장암	1상
	부산대병원		간암	1상
DA-3607	동아제약(주)	Adenovirus	뇌종양	1상
VGX-3400	진원생명과학(주) (구VGX인터네셔널)	Naked DNA + Electroporation	조류독감예방백신	1상 완료
VM206	㈜바이로메드/ 이연제약	Naked DNA	유방암	1/2상 완료
VGX-3100	이노비오	Naked DNA + Electroporation	자궁경부전암CIN2/3	3상
GX-188E	제넥신	Naked DNA + Electroporation	자궁경부전암CIN2/3	2상
VGX-6150	진원생명과학	Naked DNA + Electroporation	만성C형간염치료백신	1상

<표> 국내기업의 글로벌 임상 현황

개발기업	유전자치료제	개발 단계
코오롱생명과학	인보사케이주	~~시판허가(2017. 7)~~
티슈진		미국 임상 3상 filing
바이로메드	VM202-PAD	미국 임상 3상 진행
	VM202-DPN	미국 임상 3상 완료
	VM202-ALS	미국 임상 1/2상 완료
신라젠	펙사벡(JX-594)	미국 글로벌 임상 3상 중단
제넥신	GX-188E	유럽 임상 2상 진행

출처 : 한국보건산업진흥원, 글로벌 진출을 위한 유전자 치료제 현황과 과제, 2016.05
생명공학정책센터, 줄기세포 및 유전자치료제 3P(논문, 특허, 산업)분석, 2018.09.20.

ICGM
INNOVATION CENTER FOR GENE MEDICINE

국내 45개 기업이 유전자치료제 개발 중

Gene Therapy Prices

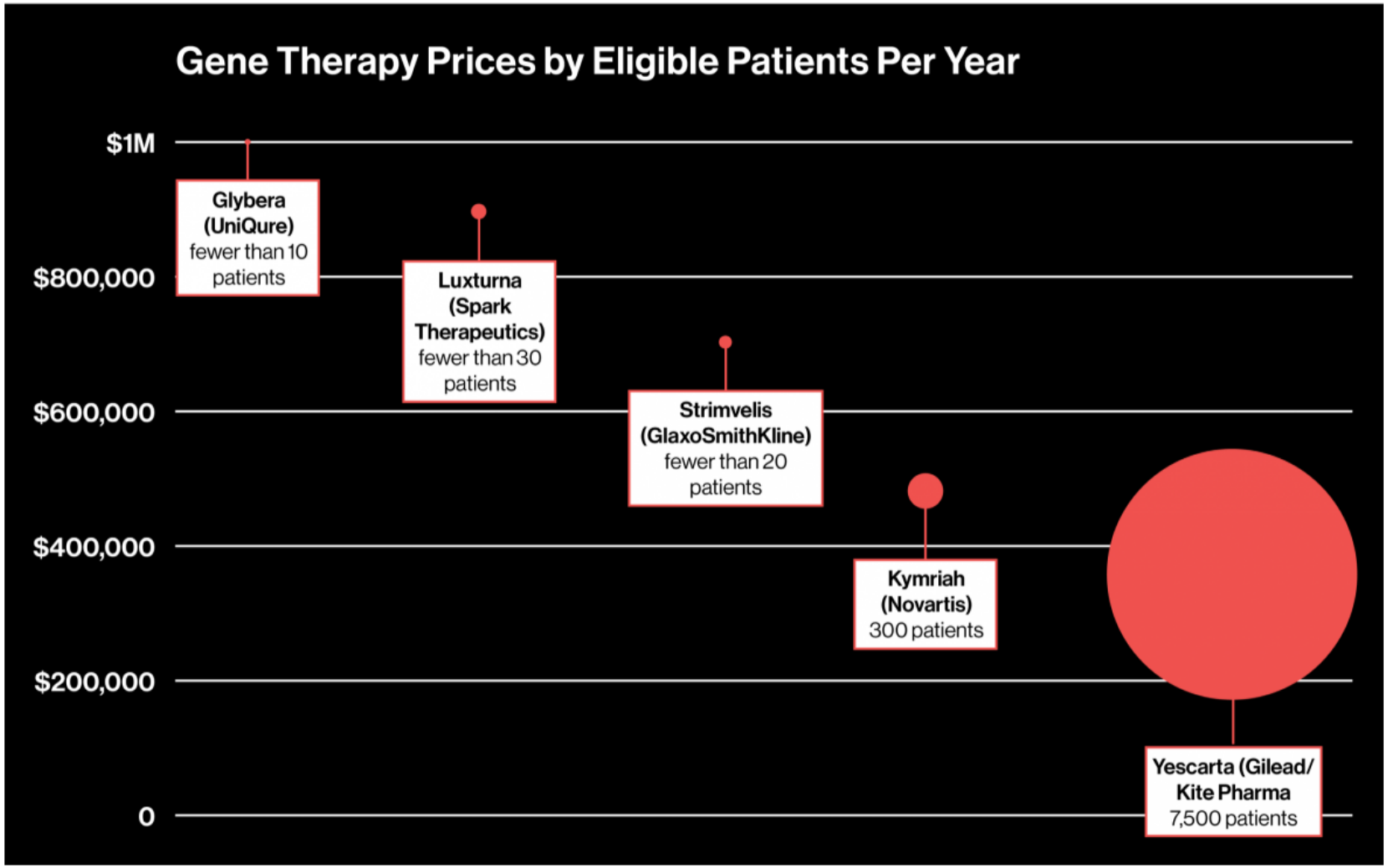
MIT Technology Review

Rewriting Life

Tracking the Cost of Gene Therapy

Though expensive now, prices could get cheaper for more common diseases.

by Emily Mullin October 24, 2017



Gene Therapy Prices

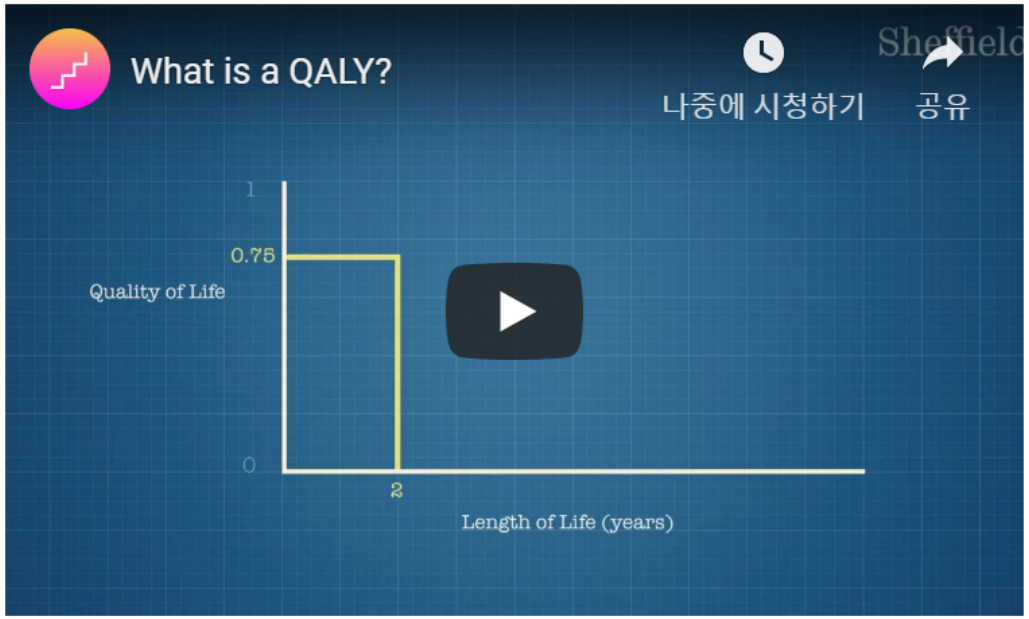
QALY calculation

We first assume that health is a function of length of life and quality of life. A QALY score combines these values into a single number.

To determine QALYs, you multiply the value associated with a given state of health by the years lived in that state.

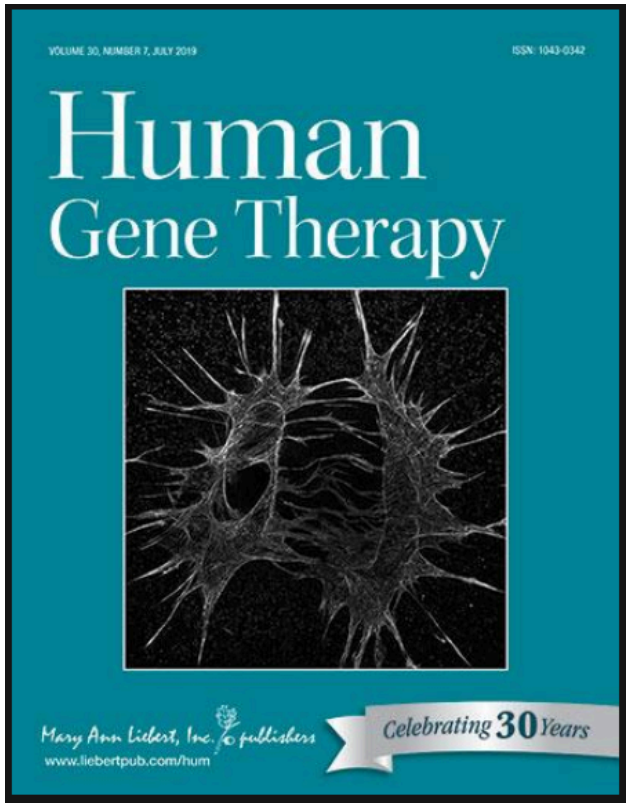
A year of life lived in perfect health is worth 1 QALY. (1.0 year of life × 1.0 health value = 1 QALY)

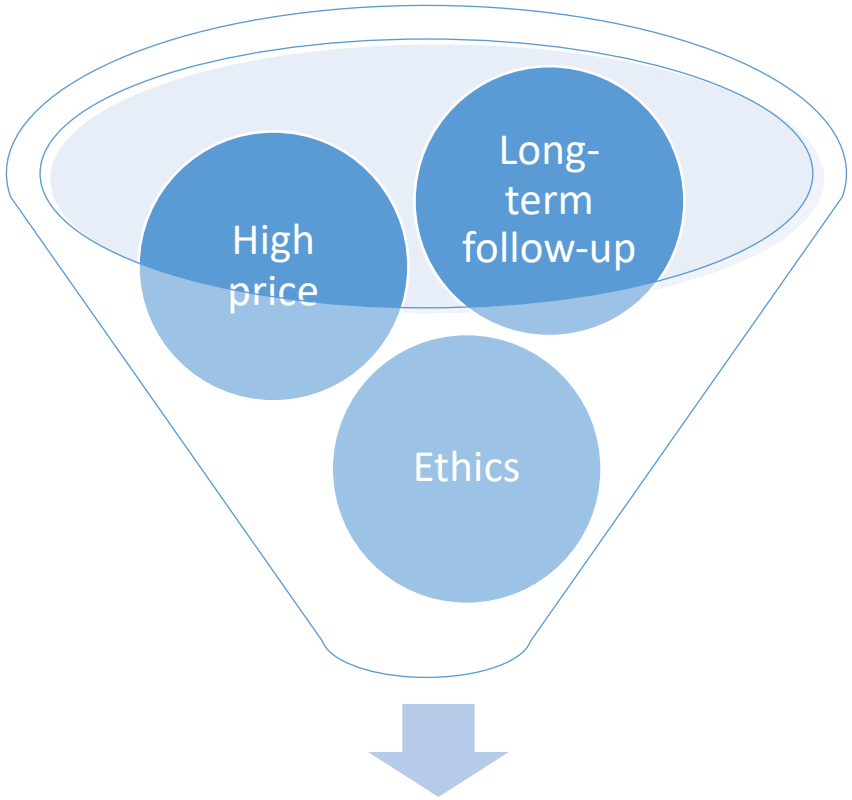
Now, let's imagine you have a genetic disorder and you want to compare the QALY of 2 different treatments for that disorder.



This short and sweet video does a great job describing QALYs.

Is it possible to place a dollar value on one year of being alive? In reality, the answer is no. Life is a personal, spiritual and abstract concept. Life can't be reduced to a column on an excel spreadsheet. But, for the sake of this discussion, yes life can reduce down to a value on a spreadsheet. **The average value of one human life year is worth $50,000.**





Benefits to patients