University of Zurich[UZH]

Cardiovascular Gene Therapies: Ethical Considerations

ESC-CRT Workshop: “The Revolution in Pharmacotherapy”

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Disclosure

No conflict of interest to declare.

Outline

- The Importance of Ethics in Gene Therapies
- Reimbursement and Access
- Research Ethics
- Early Access Programs

The Importance of Ethics in Gene Therapies

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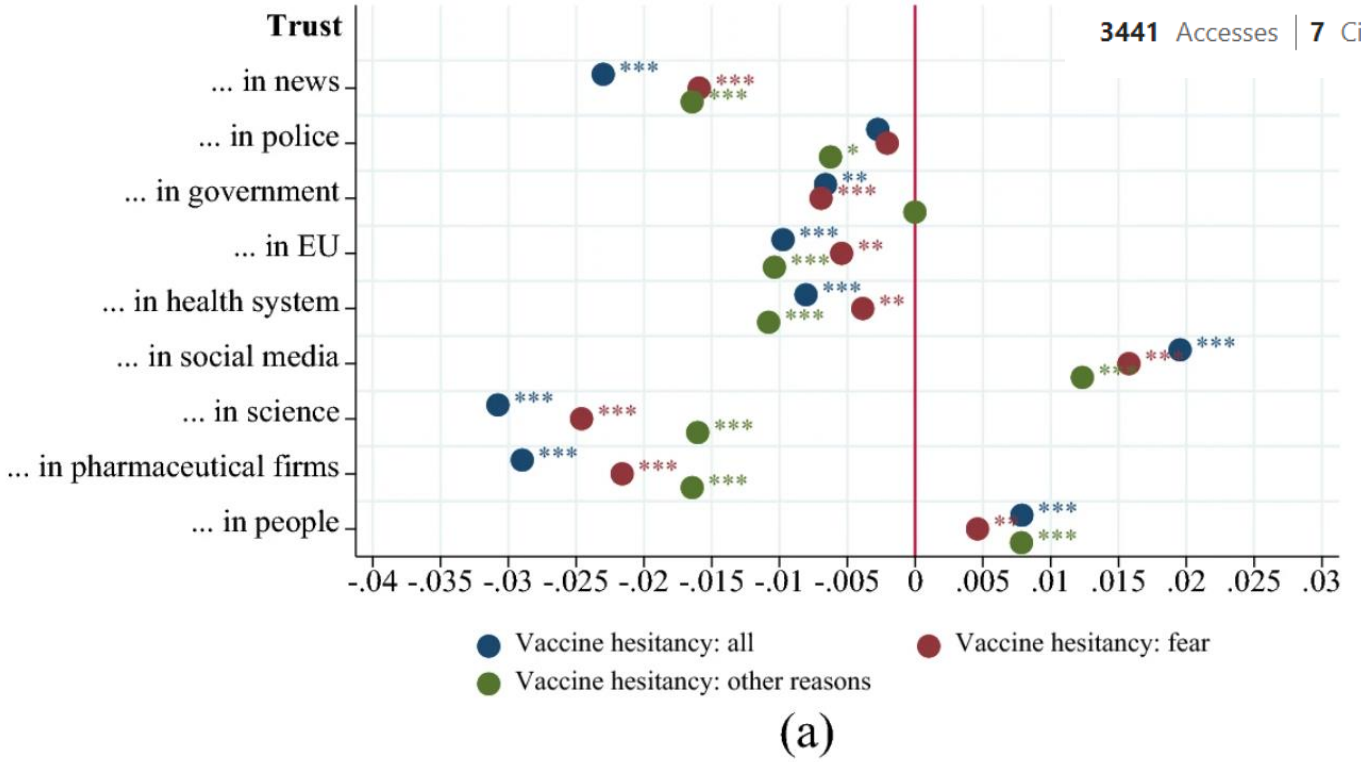
Trust and COVID-19 vaccine hesitancy

Vincenzo Carrieri, Sophie Guthmuller & Ansgar Wübker

Scientific Reports **13**, Article number: 9245 (2023) | Cite this article

Figure 1

From: Trust and COVID-19 vaccine hesitancy



(a)

The Importance of Ethics in Gene Therapies (2)

- Promote **trust** – in products, processes and prices;
- Protect and promote the **well-being of patients and their families**;
- Enhance the **acceptability and explainability** of decisions (e.g., discontinuation of a clinical trial, definition of groups to receive certain therapies first);
- Protecting the **integrity** of research, the health professions, and the pharmaceutical industry.

Reimbursement and Access (1)

FDA-approved gene therapy products (non-oncological) (as of Jan 26, 2024)		
Casgevy	Sickle cell disease, ß-thalassemia	Hematology
Elevidys	Duchenne muscular dystrophy	Neurology
Hemgenix	Hemophilia B	Hematology
Luxturna	RPE65 mutation-associated retinal dystrophy	Ophthalmology
Lyfgenia	Sickle cell disease	Hematology
Roctavian	Hemophilia A	Hematology
Skysona	Cerebral adrenoleukodystrophy (CALD)	Neurology
Vyjuvek	Epidermolysis bullosa	Dermatology
Zynteglo	ß-thalassemia	Hematology
Zolgensma	Spinal muscular atrophy (SMA)	Neurology

Reimbursement and Access (2)

List prices at launch (US) of gene therapy products (non-oncological) approved by the FDA in 2023		
Casgevy	Hematology	USD 2.2 million
Elevidys	Neurology	USD 3.2 million
Lyfgenia	Hematology	USD 3.1 million
Roctavian	Hematology	USD 2.9 million
Vyjuvek	Dermatology	estimated treatment cost per year: USD 630,500

Reimbursement and Access (3)


Public Health Ethics:
Mapping the Terrain

James F. Childress, Ruth R. Faden,
Ruth D. Gaare, Lawrence O. Gostin,
Jeffrey Kahn, Richard J. Bonnie,
Nancy E. Kass, Anna C. Mastroianni,
Jonathan D. Moreno, and Phillip Nieburg

Journal of Law, Medicine & Ethics, 30 (2002): 170–178.
© 2002 by the American Society of Law, Medicine & Ethics.

General moral consideration in public health ethics (Childress et al., 2002):

- Producing benefits;
- Avoiding, preventing, and removing harms;
- Producing the maximal balance of benefits over harms and other costs (often called utility);
- Distributing benefits and burdens fairly (distributive justice) and **ensuring public participation**, including the participation of affected parties (procedural justice);
- **Respecting autonomous choices and actions**, including liberty of action;
- Protecting privacy and confidentiality;
- Keeping promises and commitments;
- Disclosing information as well as speaking honestly and truthfully (often grouped under **transparency**);
- Building and maintaining **trust**.

Reimbursement and Access (4)

Under which conditions should medicinal products be reimbursed by health insurance?

- Efficacy/effectiveness vs. efficiency as basis for reimbursement decisions;
- Reimbursement of off-label use/non-approved medicinal products;
- Procedure for reimbursement decisions.

Which prices should be reimbursed by health insurance?

- Health outcomes-based pricing (P4P);
- Procedure for determining reimbursement prices.

Reimbursement and Access (5)

Direct Medical Costs

Examples

- Inpatient or outpatient care
- Physician visits
- Rx medications and their administration
- Durable medical equipment

Private and public insurance programs typically pay providers directly, and patients are responsible for co-pays

Indirect Costs: Productivity Loss

Examples

- Forced retirement
- Absenteeism
- Presenteeism (when employees cannot fully function in the workplace)
- Reduction in community participation and volunteer service

Reduces income for patients and caregivers, while reducing productivity for employers, communities, society

Non-medical & Uncovered Healthcare Costs

Examples

- Necessary home or auto modifications
- Transportation and education costs
- Paid daily care
- Healthcare services not covered by insurance: experimental treatments, medical foods, and more

Out-of-pocket costs absorbed directly by families living with RD

https://everylifefoundation.org/burden-landing/

Reimbursement and Access (6)

The Pharmaceutical Industry in Figures

Key Data ✱ 2022

EMPLOYMENT IN THE PHARMACEUTICAL INDUSTRY

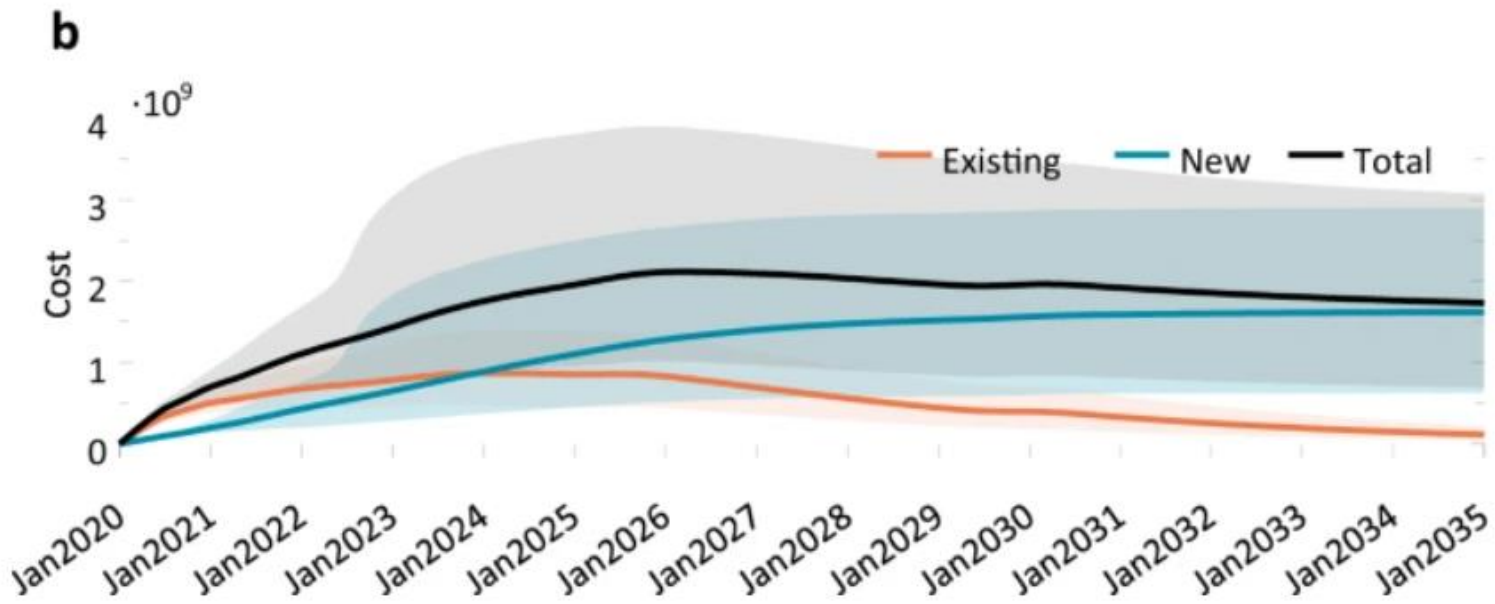
EFPIA 2020	Units		Units
Austria	16,335	Latvia	2,232
Belgium	40,464	Lithuania	1,220
Bulgaria	15,500	Malta	1,033
Croatia	5,987	Netherlands	20,000
Cyprus	1,755	Norway	4,500
Czech Rep.	18,000	Poland	16,121
Denmark	25,686	Portugal	9,100
Estonia	380	Romania	35,000
Finland	6,178	Russia	n.a
France	99,310	Slovakia	2,287
Germany	115,519	Slovenia	11,969
Greece	26,500	Spain	48,867
Hungary	28,300	Sweden	13,156
Iceland	500	Switzerland	47,000
Ireland	42,000	Turkey	42,291
Italy	66,400	U.K.	72,000
TOTAL			835,590

Reimbursement and Access (7)

European companies with FDA- or EC-approved gene therapy products in their product portfolio (as of Jan 26, 2024)			
Adstiladrin	Oncology	Ferring Pharmaceuticals	
Casgevy	Hematology	CRISPR Therapeutics	Partnership with Vertex Pharmaceuticals
Elevidys	Neurology	Roche Holding AG	License from Sarepta Therapeutics
Kymriah	Oncology	Novartis AG	
Libmeldy (EC)	Neurology	Orchard Therapeutics	
Luxturna	Ophthalmology	Roche Holding AG	Developed by Spark Therapeutics
Strimvelis (EC)	Immunology	Orchard Therapeutics	Acquisition from GSK
Zolgensma	Neurology	Novartis AG	Developed by AveXis

Reimbursement and Access (8)

Fig. 5: Simulated monthly spending on patients treated with gene therapy.



Wong, C.H., et al. The estimated annual financial impact of gene therapy in the United States. *Gene Ther* **30**, 761–773 (2023). https://www.nature.com/articles/s41434-023-00419-9.

= ca. 72.5 USD/capita and year
= ca. 0.5 % of total US healthcare spending

Reimbursement and Access (9)

Policy Recommendations	
Incentivize R&D and marketing of new gene therapy products;	Beneficience, Utility
Adopt pricing policies to incentivize marketing and avoid market withdrawals on economic grounds (➔ EU: Zynteglo, Skysona);	Beneficience, Justice, Respect for Persons, Solidarity
Ensure a transparent decision-making process on reimbursement of off-label use and non-approved gene therapy products;	Justice
Integrate patients' (and their families') perspectives in HTA processes;	Respect for Persons
Incentivize R&D of gene therapies for rare diseases.	Justice, Solidarity

Research Ethics (1)

Ethical Challenges of Gene Therapy Clinical Trials

- **Risk-benefit ratio;**
- **Fair participant selection;**
- **Vulnerability and informed consent.**

Research Ethics (2)

Risk-Benefit Ratio

– **Potentially life-long biological activity and potential carcinogenicity and unpredictable SAEs** of gene therapies;

➔ **Need for a careful risk-benefit analysis**, particularly in the case of gene therapies for **children and non-life threatening diseases**.

➔ FDA (2020): „When there is limited previous human experience with a specific GT product, administration to several subjects concurrently may expose those subjects to unacceptable risk. Most first-in-human trials of GT products should stagger administration to consecutively enrolled subjects, for at least an initial group of subjects, followed by staggering between dose cohorts. This approach **limits the number of subjects who might be exposed to an unanticipated safety risk**."

Research Ethics (3)

Fair Participant Selection

- Tension between principles of equity (= equal access to clinical studies) and non-maleficence (= duty to protect potential research participants from harm);
- **Tension between imperative to include different groups of patients** (e.g., children, patients with different courses of disease) **and the duty to protect research participants**;
- Respect for children's (future) autonomy.

Research Ethics (4)

Gene therapy and editing

Gene therapy and editing represents a combination of techniques used to manipulate disease related genes. The use of these techniques should adhere to the following guidelines:

- The use of gene therapy and somatic genome editing should conform to standards of medical ethics and professional responsibility.
- Patient autonomy should be respected, and informed consent should always be obtained. This informed consent process should include disclosure of the risks of gene therapy and editing, including the fact that the patient may have to undergo multiple rounds of gene therapy, the risk of an immune response, the potential problems arising from the use of viral vectors and off-target genome effects.
- Gene therapy and editing should only be undertaken after a careful analysis of the risks and benefits involved and an evaluation of the perceived effectiveness of the therapy, as compared to the risks, side effects, availability and effectiveness of other treatments.
- Gene editing of germline cells has scientifically unresolved risks and should not be clinically applied. This does not preclude testing gene editing or other similar research.

WMA DECLARATION OF REYKJAVIK – ETHICAL CONSIDERATIONS REGARDING THE USE OF GENETICS IN HEALTH CARE

Adopted by the 56th WMA General Assembly, Santiago, Chile, October 2005,
revised by the 60th WMA General Assembly, New Delhi, India, October 2009
and by the 70th WMA General Assembly, Tbilisi, Georgia, October 2019

Research Ethics (5)

Vulnerability and Informed Consent

- Particular **safeguards in case of research with children** (➔ CIOMS guidelines);
- False hopes and expectations of many patients ➔ “miracle cure”;
- Situations of extreme distress, choc or despair (e.g., post-ACS) ➔ high levels of vulnerability, irrationality and non-comprehension.

Early Access Programs

- Ethical **conditions for setting up an EAP** for gene therapies;
- **Selection of participants**;
- **Reimbursement** by health insurance;
- Global Access Programs: **Fair allocation** of free-of-charge treatments.

Thanks for your attention!

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