Strategies to Better Align Investments in Innovation for Therapeutic Development with Disease Burden and Unmet Needs

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Yale SCHOOL OF MEDICINE

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Disclosures

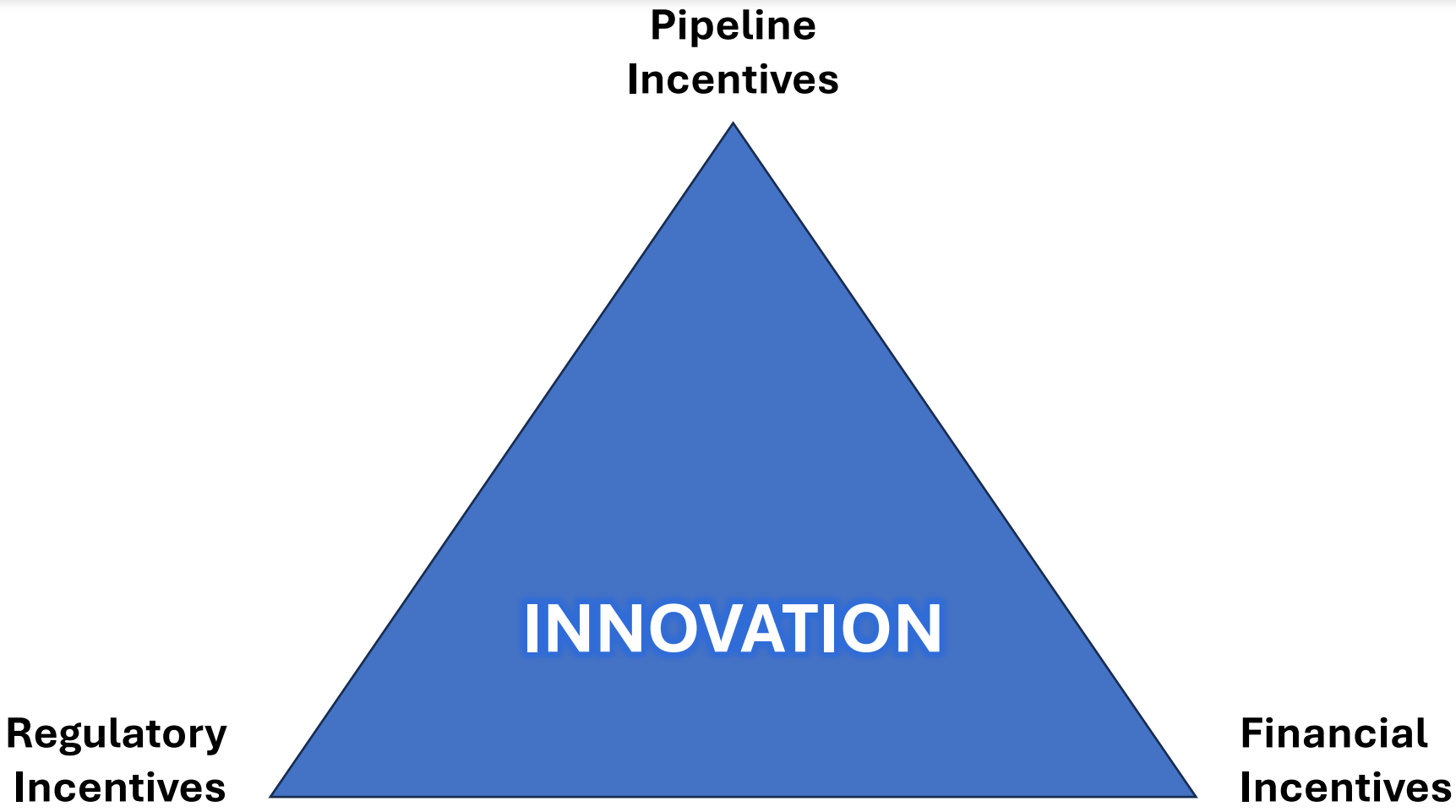
I have no relevant financial relationships with commercial entities that produce health-care related products or services relevant to the content of this presentation.

I receive research funding from Arnold Ventures for the Yale Collaboration for Regulatory Rigor, Integrity, and Transparency (CRRIT), the Stavros Niarchos Foundation for research related to new R&D and manufacturing models, and the U.S. Food and Drug Administration for a study focused on representation in oncology trials.

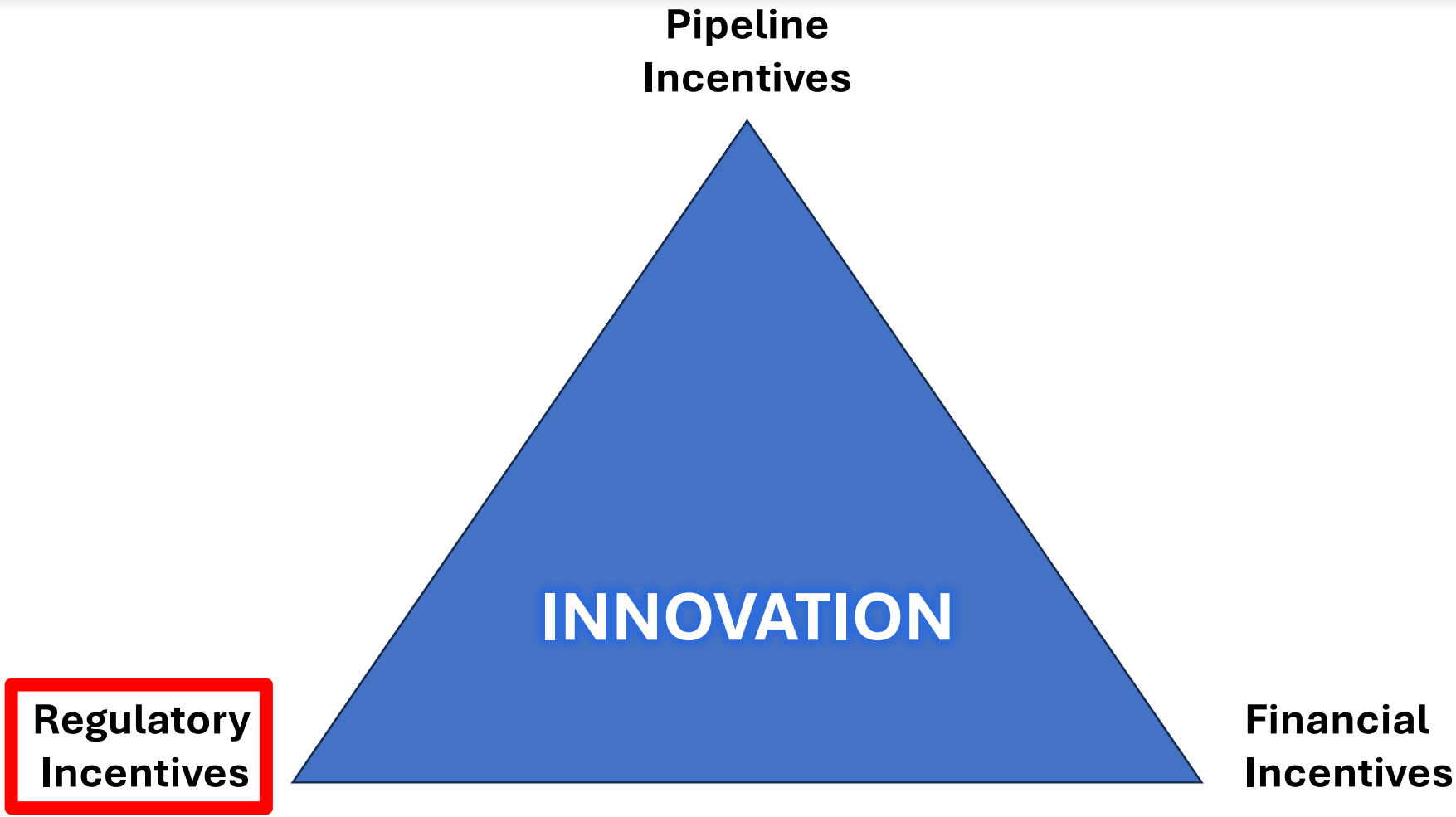
I chair the Doctors for America FDA Task Force whose work is funded by Arnold Ventures. I also sit on the board of Universities Allied for Essential Medicines North America. These are both unpaid volunteer positions.

I am currently a fellow with The Roosevelt Society Reimaging America Fellowship for which I receive an honorarium.

Focus to date has been on downstream incentives for innovation



Use of regulatory incentives to shape standards for market authorization



Overview of FDA expedited development and review pathways for drugs and biologics

Pathway	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Qualifying Criteria	Intended to treat a **serious condition** AND nonclinical or clinical data demonstrate the **potential to address unmet medical need**	Intended to treat a **serious condition** AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	Treats a **serious condition AND fill an unmet need** based on a demonstrated effect on a surrogate endpoint or intermediate clinical endpoint	Treats a **serious condition** AND, if approved, would provide a significant improvement in safety or effectiveness
Incentives	Increased interaction with FDA Rolling review	Increase interaction with senior FDA leadership Rolling review	Approval based on unvalidated surrogate endpoint or intermediate clinical endpoint	Decrease in review time (10 months to 6 months)

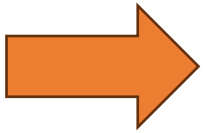
Expedited regulatory programs effective at shortening development and review times

- Shorter clinical development times (1-2 years)
  - accelerated approval
  - breakthrough therapy designation
- Shorter combined clinical development and review times (1-2 years)

With faster market access has come shifts in evidence considered by FDA

How it started

- 2 or more adequate and well-controlled investigations
- Placebo-controlled or active comparators
- Clinical endpoints
- Traditional approval pathways and regulatory designations



Zhang et al. *JAMA Network Open*. 2020;3(4):e203284.

With faster market access has come shifts in evidence considered by FDA

How it started	How it's going
• 2 or more adequate and well-controlled investigations	• 1 adequate and well-controlled investigation + confirmatory evidence
• Placebo-controlled or active comparators	• Single-arm trials
• Clinical endpoints	• Surrogate markers
• Traditional approval pathways and regulatory designations	• Special regulatory programs and expedited review pathways

Zhang et al. *JAMA Network Open*. 2020;3(4):e203284.

Unanswered questions at the time of FDA approval

Clinical effectiveness	Including among “real-world” populations
Long-term safety	Including among “real-world” populations
Comparative effectiveness	
Association of surrogate endpoints with clinical outcomes	

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Recommendation: Interagency approach to tackling unanswered public health questions

- Answering key regulatory and scientific questions sponsors may not been incentivized to
- Pooling together resources and expertise across the research enterprise
- Shifting the burden away from individual clinicians and patients in making treatment decisions when absent adequate evidence

JAMA | Special Communication | INTEGRATING CLINICAL TRIALS AND PRACTICE

Why Evidence Generation Should Matter to Payers and How They Can Help

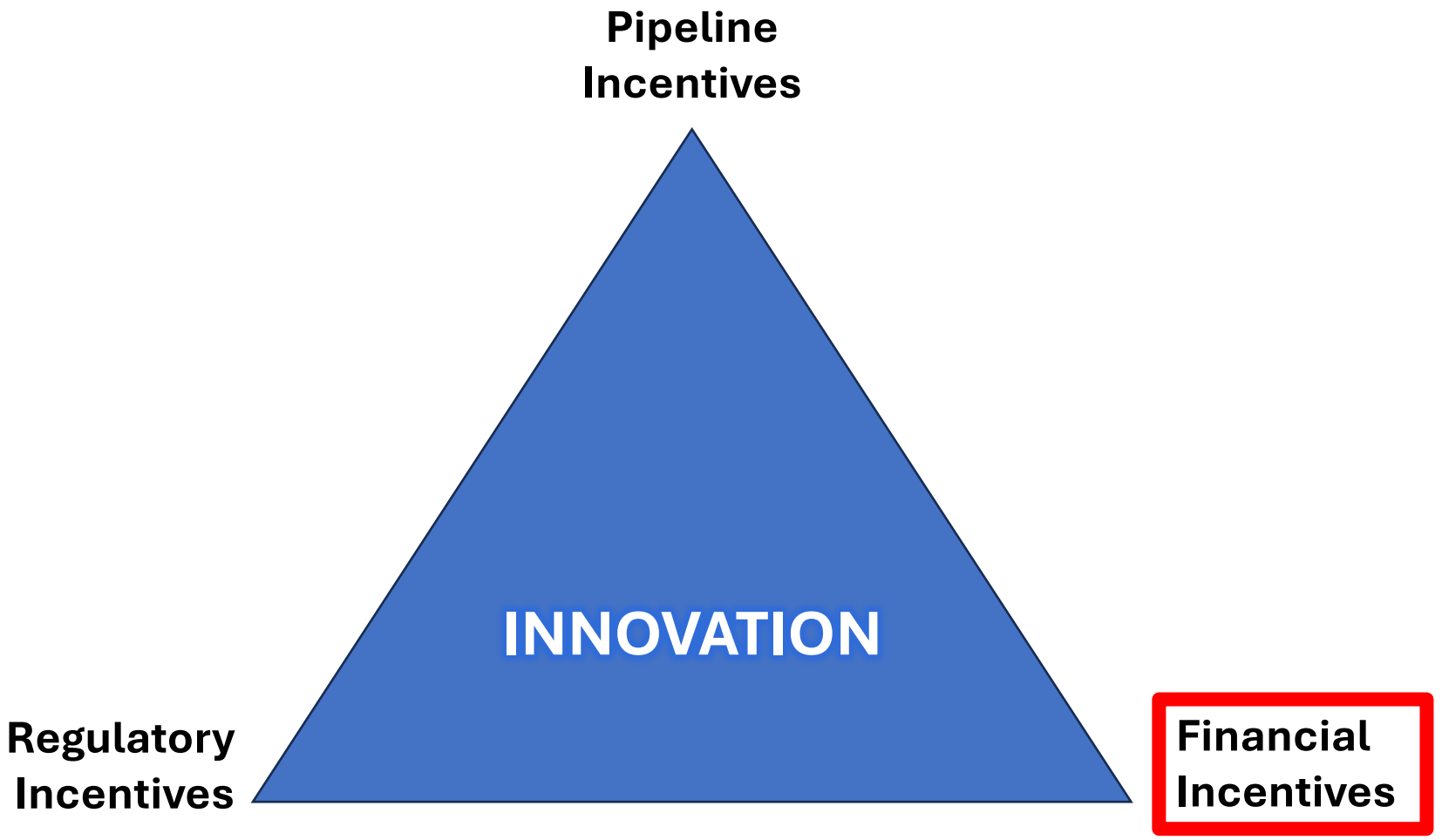
Ali B. Abbasi, MD; Lesley H. Curtis, PhD; Lee A. Fleisher, MD; Robert M. Califf, MD

Medicare's National Coverage Determination for Aducanumab — A One-Off or a Pragmatic Path Forward?

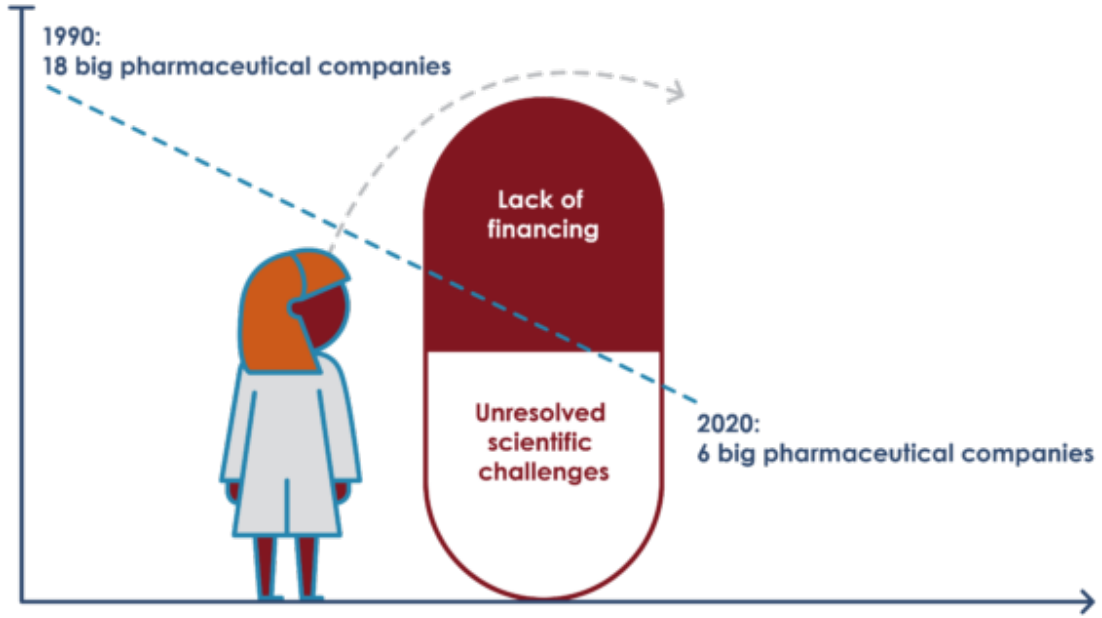
Sanket S. Dhruva, M.D., M.H.S., Reshma Ramachandran, M.D., M.P.P., M.H.S., and Joseph S. Ross, M.D., M.H.S.

In April 2022, the Centers for Medicare and Medicaid Ser- decline. Since the pivotal studies supporting FDA approval of adu- as coverage with evidence development (CED). The agency is stat-

Coupling regulatory and financial incentives to address “market failures”



Case study: innovation of novel antimicrobials



Increased Consolidation and Decreased Antimicrobial R&D in Pharmaceutical Industry
(Image Credit: *ReAct-Action on Antibiotic Resistance)*

- **Various regulatory and financial incentives have been attempted**
  - Qualified Infectious Disease Product (QIDP) designation [FDA]
  - 5 years of additional regulatory exclusivity [FDA]
  - Limited Population Pathway for Antibacterial/Antifungal Drugs [FDA]
  - New Technology Add-On Payment [CMS]
    - Removal of “substantial clinical improvement” requirement in 2019

Current focus on downstream, financial incentives for antimicrobial innovation

- Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act
- Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act

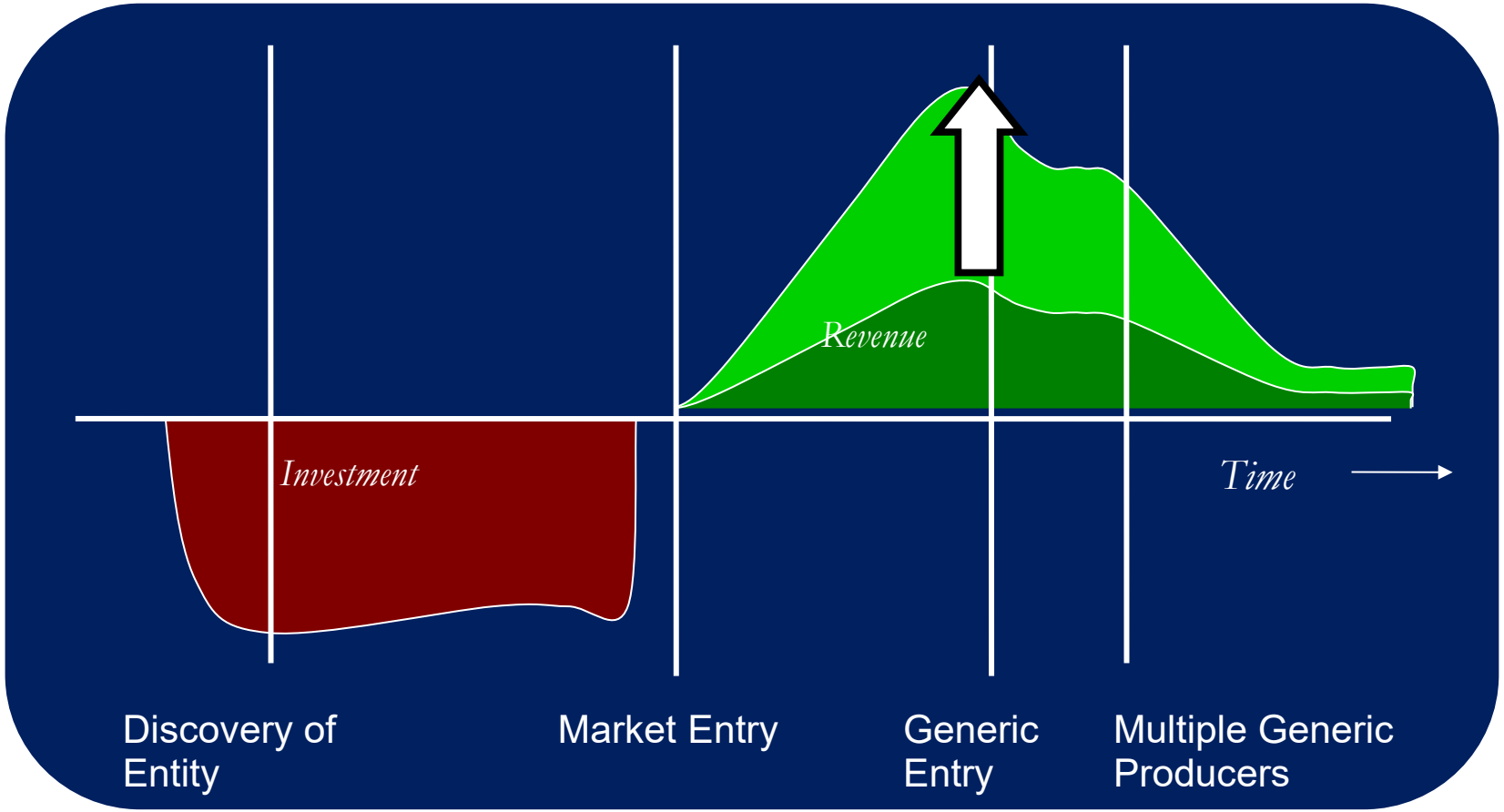
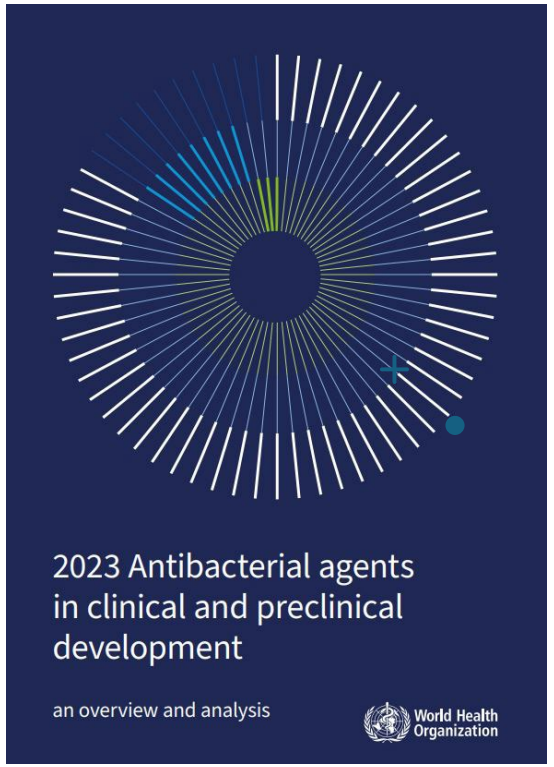


Figure courtesy of AD So & the JHSPH IDEA Initiative

Continued dearth of innovative antimicrobials

- WHO's conclusion: *Overall, antibacterial agents in the clinical pipeline combined with those approved in the last six years* ***are still insufficient*** *to tackle the ever-growing threat of the emergence and spread of drug-resistant infections.*



OPEN ACCESS ORIGINAL RESEARCH

bmjmedicine

Check for updates

Evidence at time of regulatory approval and cost of new antibiotics in 2016-19: cohort study of FDA approved drugs

Mayookha Mitra-Majumdar [1], John H Powers III,[2] Beatrice L Brown,[1] Aaron S Kesselheim [1]

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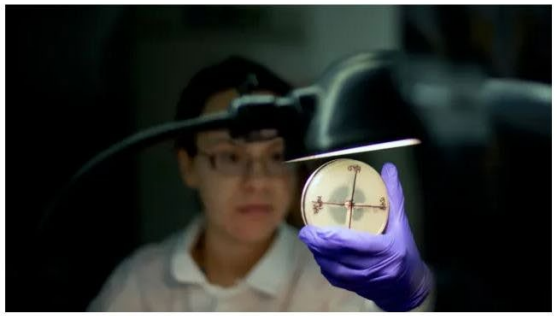
Why the PASTEUR Act is no cure for antimicrobial resistance

BY RESHMA RAMACHANDRAN AND JOHN H. POWERS, OPINION CONTRIBUTORS - 12/13/22 1:30 PM ET



(AP Photo/David Goldman)

Recommendation: Learning from public R&D experience

- Major public R&D advances made at the following facilities:
  - U.S. Army Medical Research Institute of Infectious Diseases
  - Salk Institute
  - Walter Reed Army Institute of Research*
- Opportunity to shift from COCO to GOGO/GOCO models

Institute of Medicine. 2002. *Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military.* Washington, DC: The National Academies Press.

TABLE 3-4 Vaccines Available to U.S. Military Personnel as IND Products

Product	Manufacturer
Botulinum toxoid vaccine, pentavalent	BioPort Corporation
Tick-borne encephalitis vaccine, inactivated	Baxter-Immuno Vertriebs GmbH*

* Although the DoD did administer the tick-borne encephalitis vaccine, inactivated, as an IND product (AFEB, 1993), it does not now have an active IND application for the vaccine and cannot administer it to U.S. military personnel. The vaccine is available in Europe; DoD and the manufacturer are having ongoing discussions about pursuing U.S. licensure for the vaccine (Personal communication, R. Tucker, October 25, 2001; USAMMDA, 2001a).

SOURCES: Adapted from FDA (2001b, 2002a) and USAMRMC (1999).

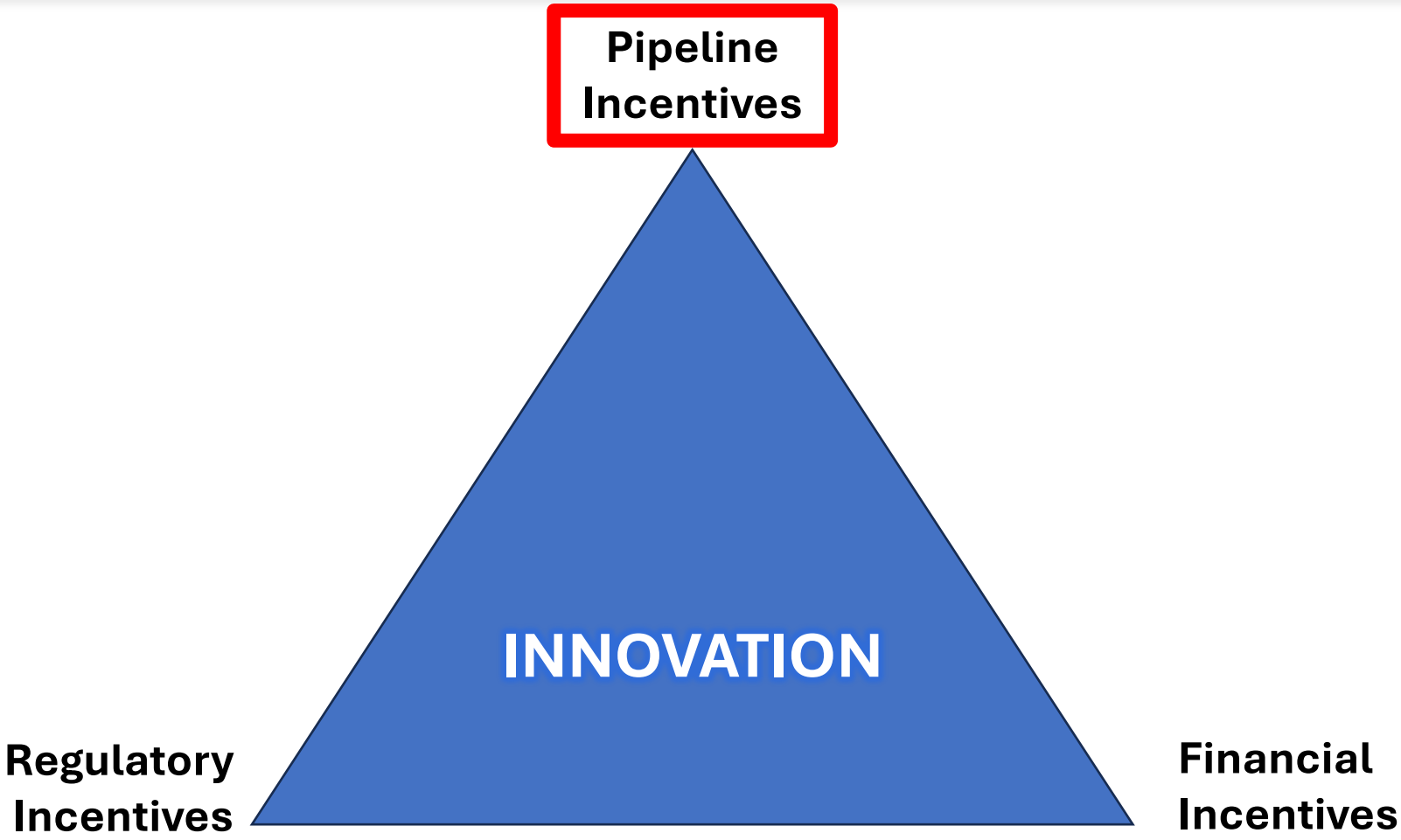
TABLE 3-5 Vaccines Administered as INDs That Are No Longer Being Produced and That Are of Limited Availability

Product	Manufacturer
Argentine hemorrhagic fever (Junin virus) vaccine, live, attenuated	The Salk Institute
Chikungunya virus vaccine, live, attenuated	The Salk Institute
Eastern equine encephalitis vaccine, inactivated	The Salk Institute
Q fever vaccine, inactivated	The Salk Institute
Rift Valley fever vaccine, inactivated and live, attenuated	The Salk Institute
Tularemia vaccine, live, attenuated	The Salk Institute
Venezuelan equine encephalitis vaccine, live, attenuated and inactivated	The Salk Institute
Western equine encephalitis vaccine, inactivated	The Salk Institute

NOTE: All the vaccines listed in this table were initially developed in U.S. Army laboratories. The vaccines underwent further development and scale-up production (at pilot level for investigational use) at the Swiftwater, Pennsylvania, plant of the Government Services Division of the Salk Institute (French and Plotkin, 1999). The plant is now owned and run by Aventis Pasteur, Inc., and does not include a government services division.

SOURCE: Pittman (2000).

Strategic use of government funds and resources to move across pipeline



Promising health technologies languishing in the “Valley of Death”

Promising gene therapies, shelved for financial reasons

Disease	Sponsor
Has data in humans	
ADA-SCID	Orchard
Chronic Granulomatous Disease	Orchard
Wiskott-Aldrich Syndrome	Orchard
X-Linked SCID	Academic
CLN7	Taysha
Fabry Disease	Amicus/Freeline
Phenylketonuria	Homology
No data in humans	
CDKL5 Deficiency	Amicus
Angelman Syndrome	Amicus/Taysha
SLC6A1 Epilepsy	Taysha
Fragile X Syndrome	Taysha
Prader-Willi Syndrome	Taysha
KCNQ2 epilepsy	Taysha
FoxG1 Syndrome	Taysha

Table: J. Emory Parker/STAT

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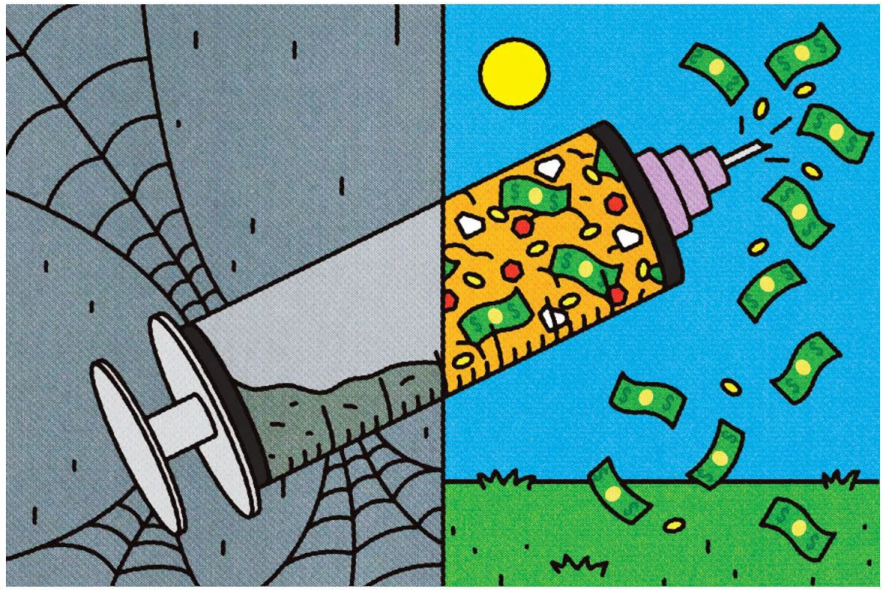


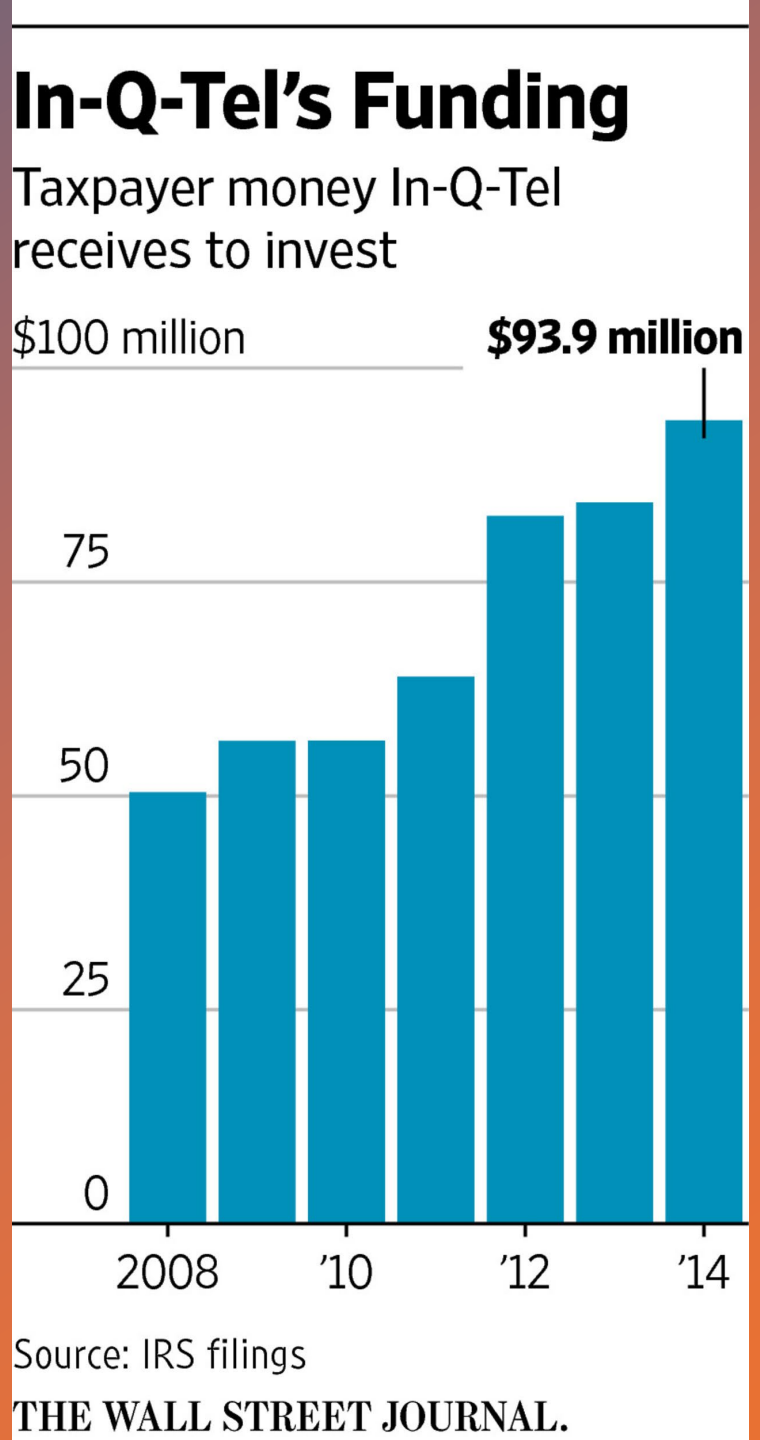
How a Big Pharma Company Stalled a Potentially Lifesaving Vaccine in Pursuit of Bigger Profits

by Anna Maria Barry-Jester

Oct. 4, 2023, 5 a.m. EDT

Recommendation: The public as a venture capital firm

- In-Q-Tel (IQT) – a non-profit venture capital firm funded by the CIA
- Independent, but all investment decisions cleared by CIA
- Limited transparency of investments
- Attracts parallel outside investment to small businesses



Recommendation: The public as an end-to-end drug developer

- Operation Warp Speed demonstrated capability of federal government in channeling and coordinating funding and resources
- Shifting once-shelved therapeutics toward market authorization and access
- Could this be built off of existing entities (e.g. ARPA-H, NCATS) or should a new entity be established?

ARPA-H

Who We Are

ARPA-H advances high-potential, high-impact biomedical and health research that cannot be readily accomplished through traditional research or commercial activity. ARPA-H awardees are developing entirely new ways to tackle the hardest challenges in health.

NIH National Center for Advancing Translational Sciences

Goal 1: Advance Development of and Access to More Treatments, Particularly for Diseases With Unmet Needs

Goal 3: Accelerate Translational Science by Breaking Barriers and Boosting Efficiency

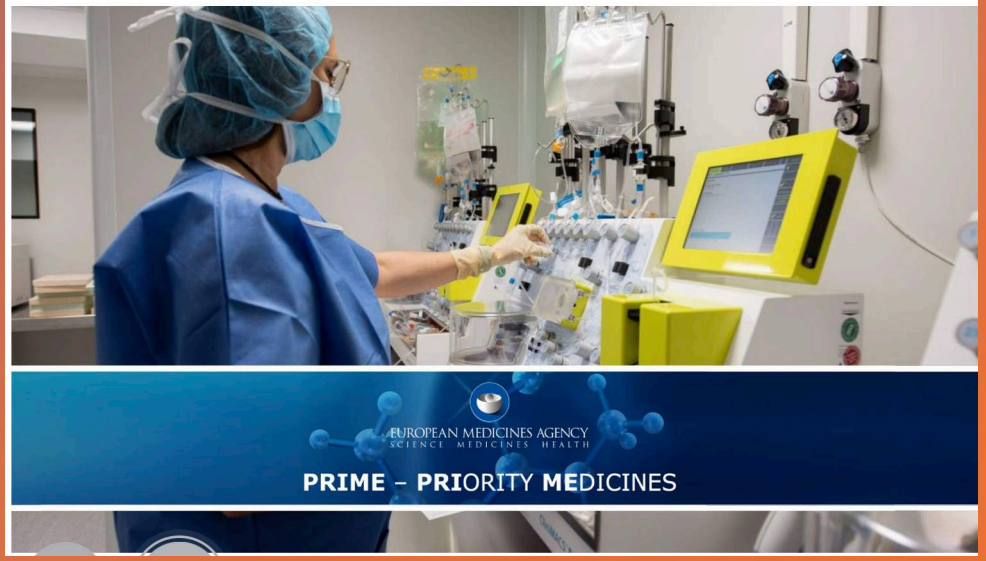
Recommendation: The present (and future?) of public R&D

- CAR-T treatment developed by public hospital in Spain
  - *Varnimcabtagene autoleucel* for acute lymphoblastic leukemia (ALL).
- **Health system considerations:** CAR-T is a personalized treatment – a decentralized, public model is more scalable than relying on a single manufacturer to process blood
- **Cost savings:** cost to health system is 89,270 EUR (1/3 the cost of commercial CAR-T in Spain, 1/10 the cost of CAR-T in the US)

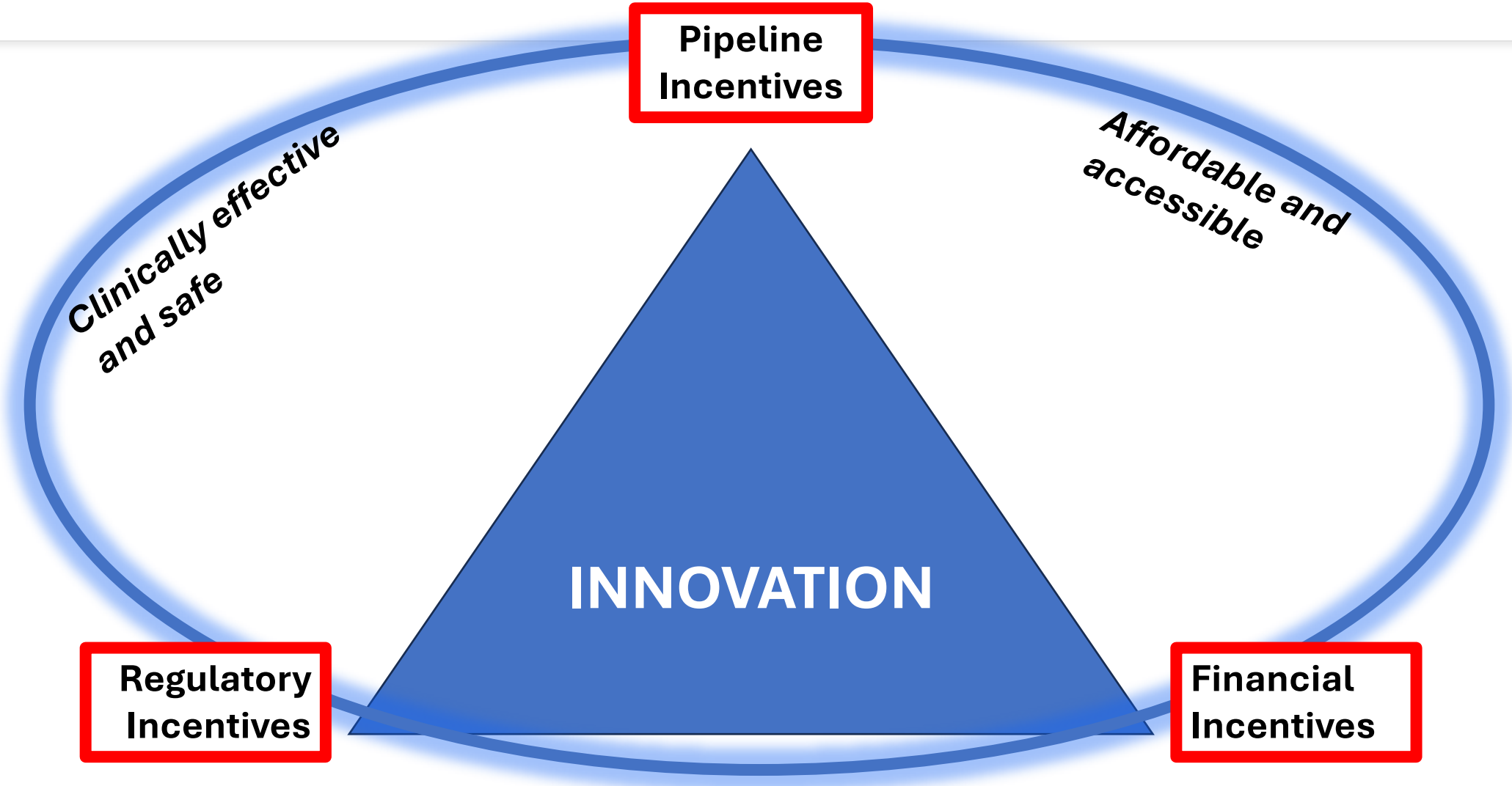
CMMI Proposed Cell and Gene Therapy Affordability and Access Model Pilot (2023)

Model	Test Question	Design
Cell & Gene Therapy Access	Does a CMS-led approach to administering outcomes-based agreements for certain cell and gene therapies improve beneficiary access and equity and reduce health care costs?	State Medicaid agencies would assign CMS to coordinate and administer multi-state outcomes-based agreements with manufacturers for certain cell and gene therapies.

The CAR-T ARI-0001 developed by the Hospital Clínic obtains the PRIME designation from the European Medicines Agency



How do we align incentives that enables affordable access to true innovation?



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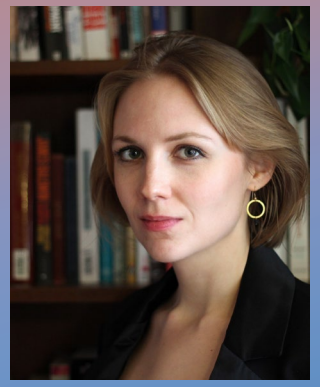

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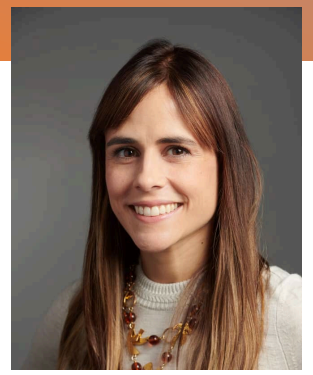

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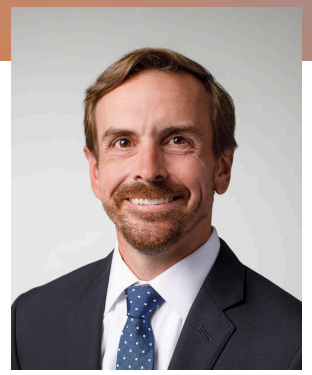

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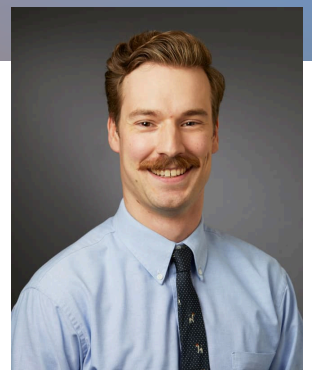

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Thank You!

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