Misalignment of Academia and Industry Impedes Clinical Gene Therapy for Rare Diseases

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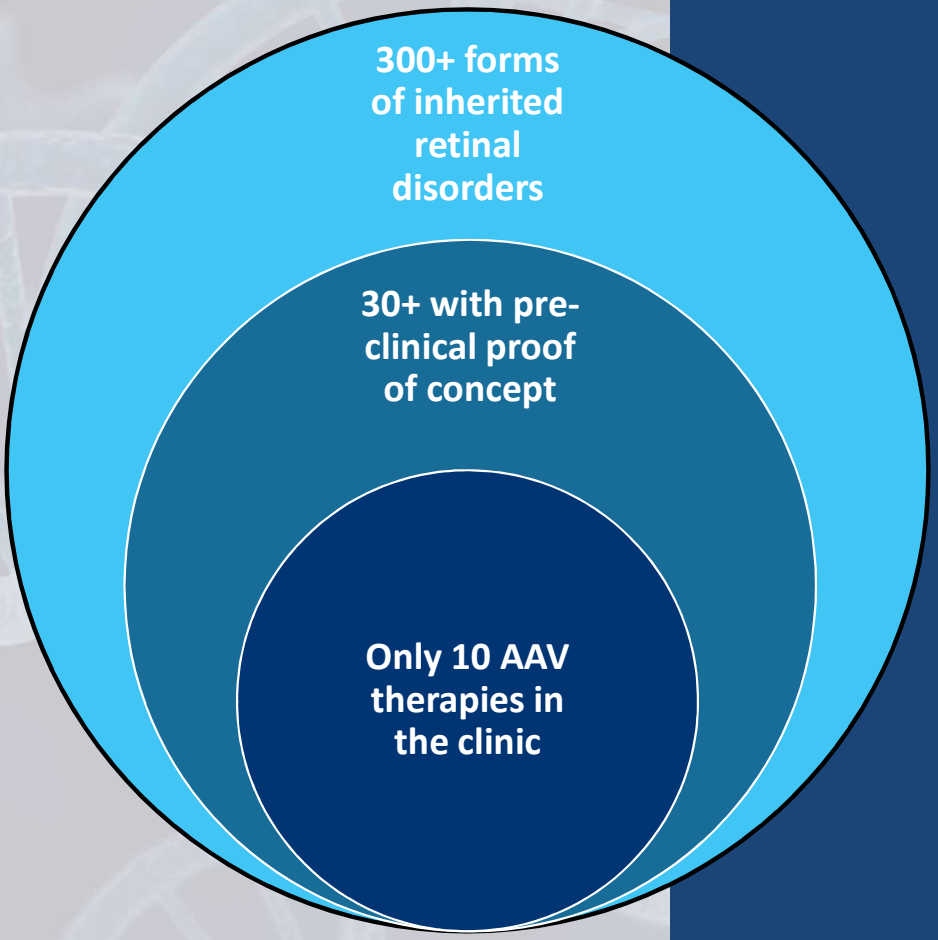
About Odylia

We are a non-profit organization working with members to bring therapies for rare diseases from the lab into clinical trials

Odylia's Challenge

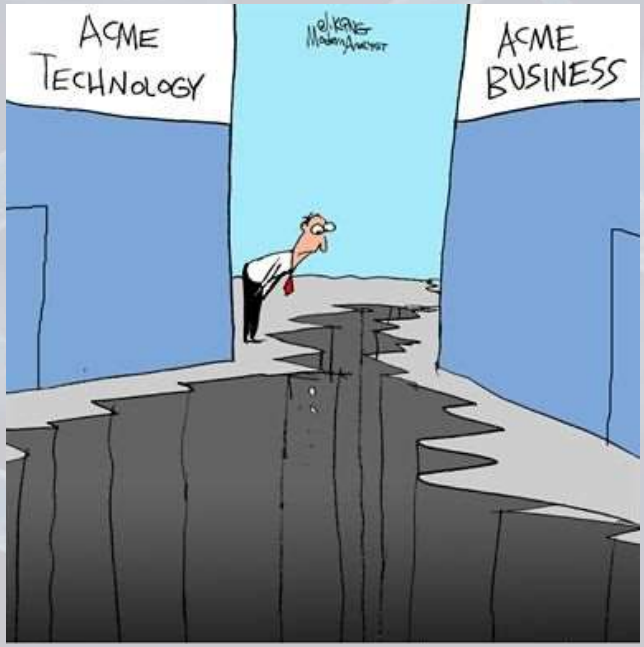
- Initial Focus: Inherited Retinal Diseases (IRD) leading to blindness
- 300+ Forms of Inherited Retinal Disease
- Majority are ultra-rare (affects less than 1 : 1,000,000 people)
- Pre-Clinical Proof of Concept for ~ 30 genes
- Limited commercial model for clinical trials due to low prevalence
- Exactly one FDA AAV approved to date (Luxturna™)



Need: A large number of rare genetic disorders each impact a small number of individuals

Solution: Rapid and economically viable development of gene augmentation therapies

Gap: Status quo does not efficiently move proof-of-concept to clinical products



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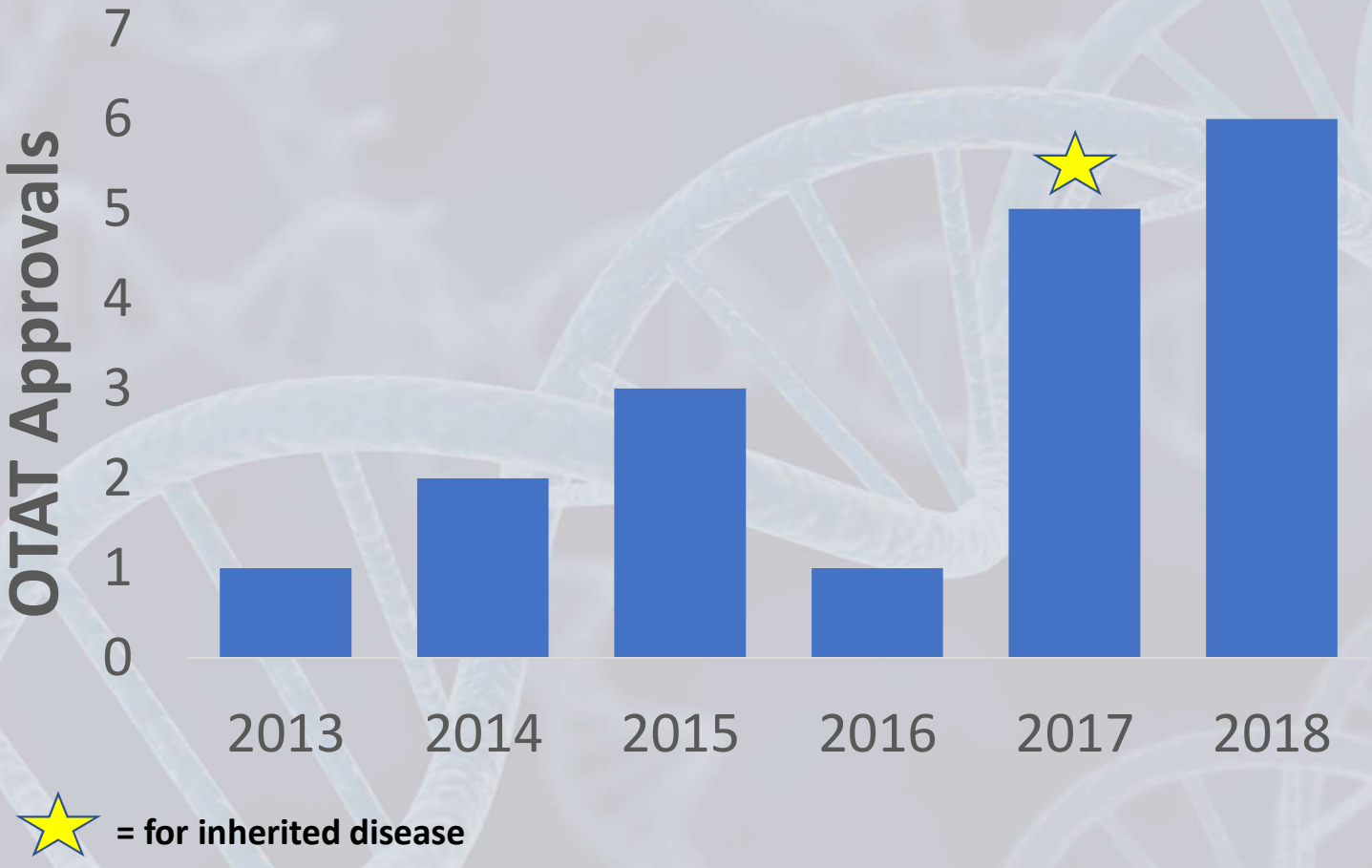
Gene therapy has begun to walk
Will it ever run?



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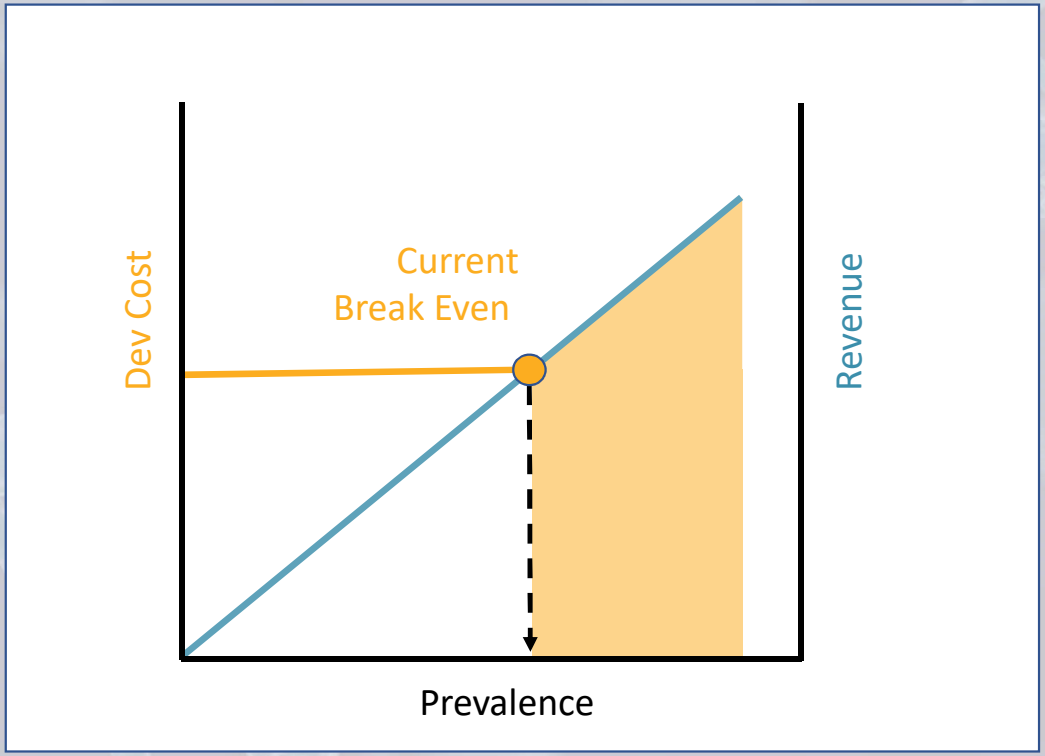
Therapies are being left behind in the lab

- High attrition rate between targetable diseases and what reaches BLA
- Successful clinical proof-of-concept generally finds commercial support
- Commercial models for rare diseases may not support IND-enabling investment
- Drop off is between bench and clinic

Example

- RPGRIP1: Inherited retinal disorder leading to blindness in early adolescence
  - 2010: Transgene efficacy demonstrated
  - 2017: Acquired by Odylia
  - 2018: Commercial sponsor engaged

Prevalence vs cost drives commercial feasibility



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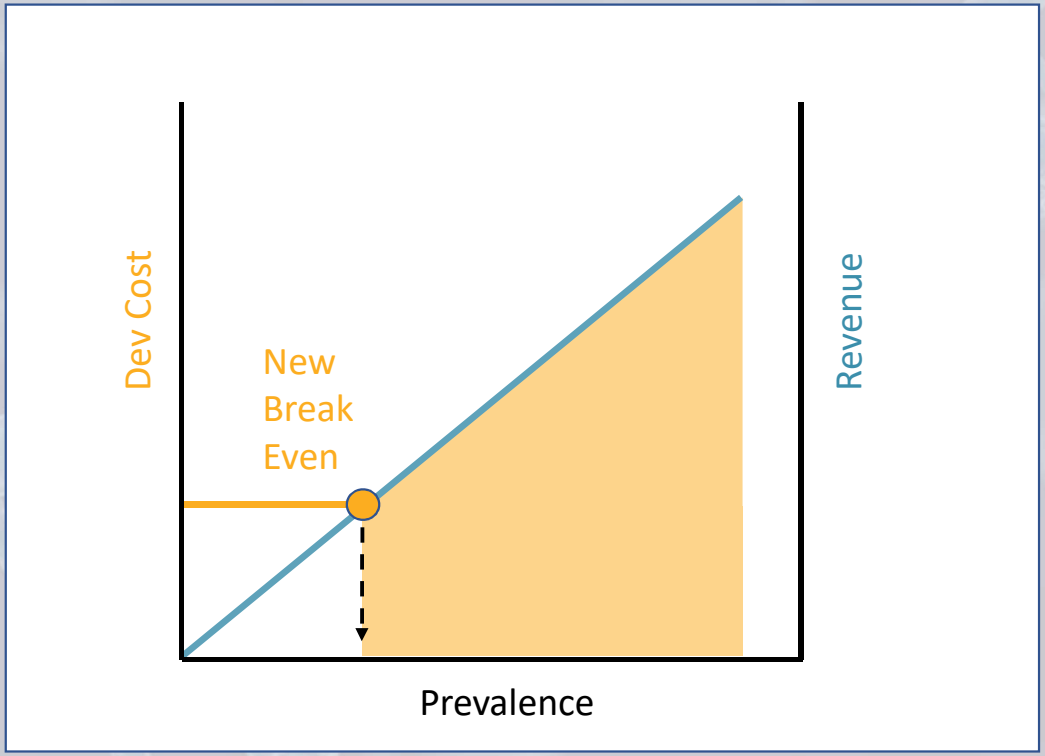
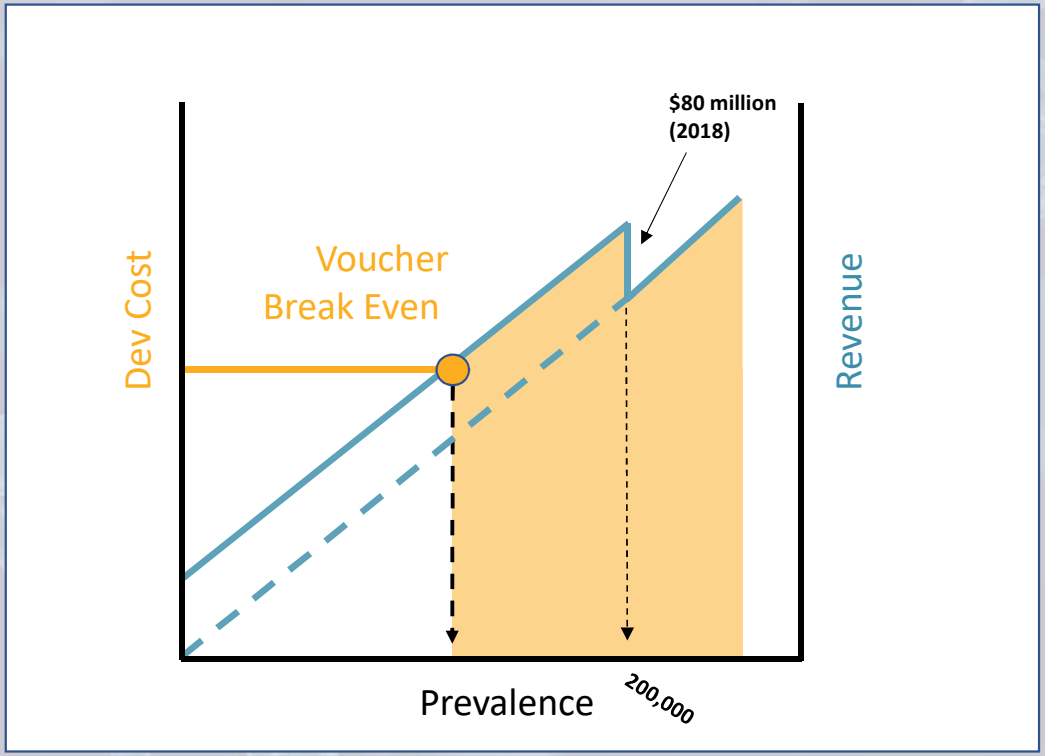


Priority review vouchers create opportunity



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Priority review vouchers create opportunity

Disease	Drug	Company	Voucher Price (millions)
Duchene Muscular Dystrophy	eteplirsen	Sarepta	$125
Batten Disease	Cerliponase alfa	BioMarin	$125
Leber Congenital Amaurosis 2	voretigene neparvovec-rzyl	Spark	$110
X-linked hypophosphatemia	burosumab-twza	Ultragenyx	$80

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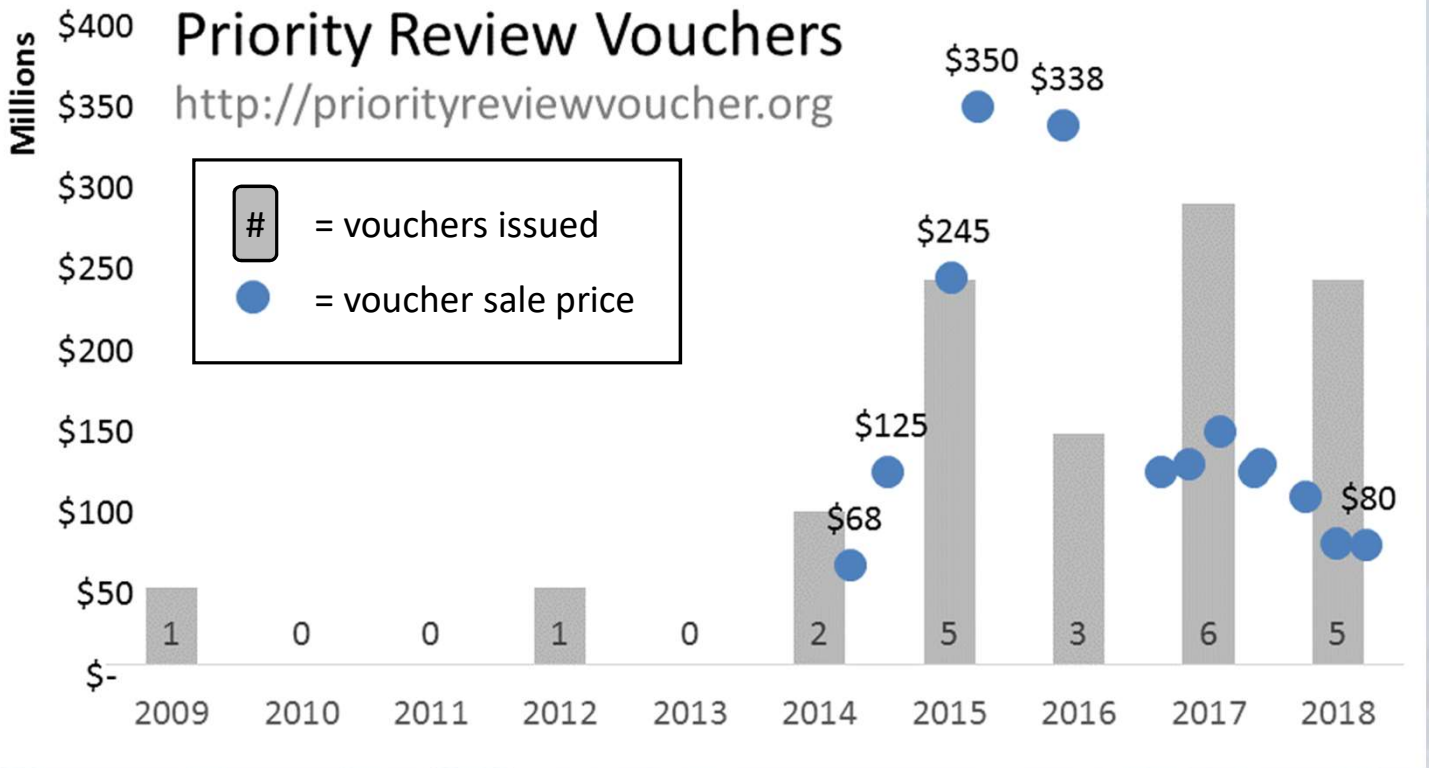
Can it continue?



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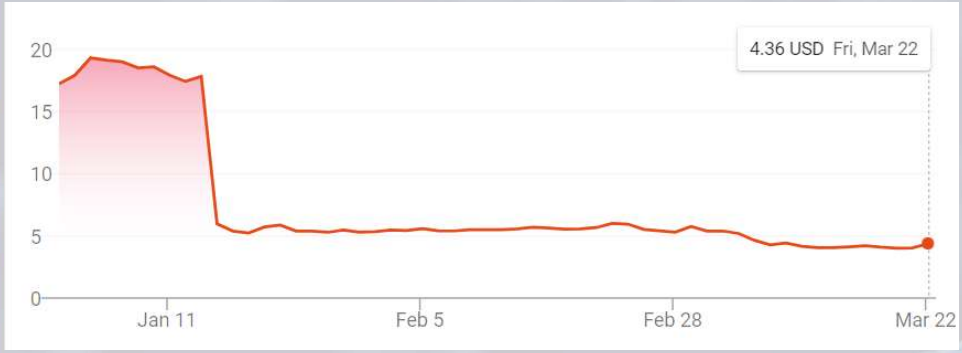
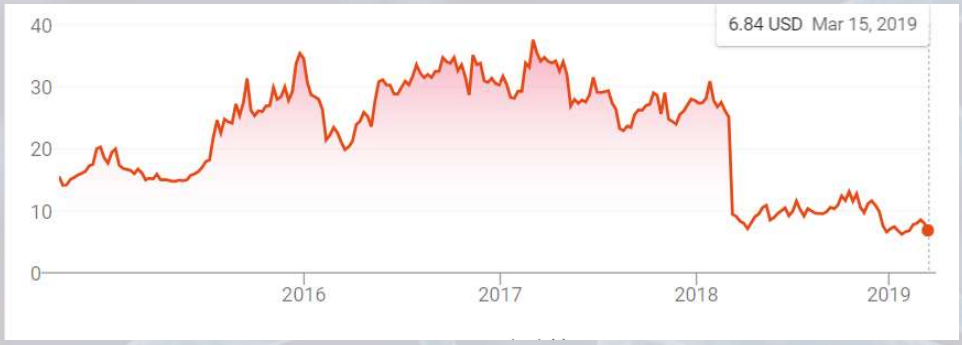
The Root Causes of Slow Progress

- Anticipated but unproven durability of therapies complicates reimbursement models
- Complex manufacturing with small but growing precedent for acceptable quality standards
- Commercial programs set the standard for the field
- Competition over limited pools of patients reduces cooperativity and increases duplication of effort between developers
- Single opportunity for treatment raises expectation for first in human trials

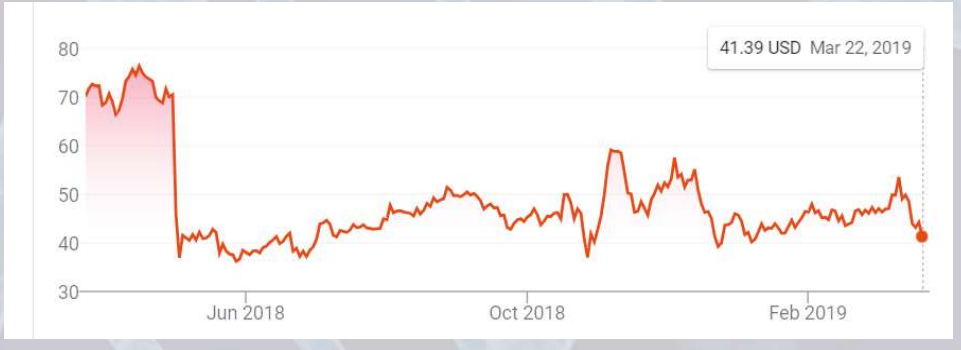
<u>These are multiplied for ultra-rare indications</u>



- Failed Phase II diabetic nerve pain
  - -$451 million



- Failed Phase II acne
  - **-$895 million**



- Phase III Safety Concerns hypercholesterolemia
  - **-$892 million**

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The bar is set (very) high

- A failed trial can cost 10x more than the total cost of development
  - Failed clinical trials average a $800 million to $1.2 billion reduction in valuation [1]
  - Reduction in value is real and justified
  - HIGHLY risk averse environment

- Risk aversion necessitates de-risking
  - Multiple animal models, large numbers of animals
  - Iterative vector optimization
  - Commercial grade materials for first dosing

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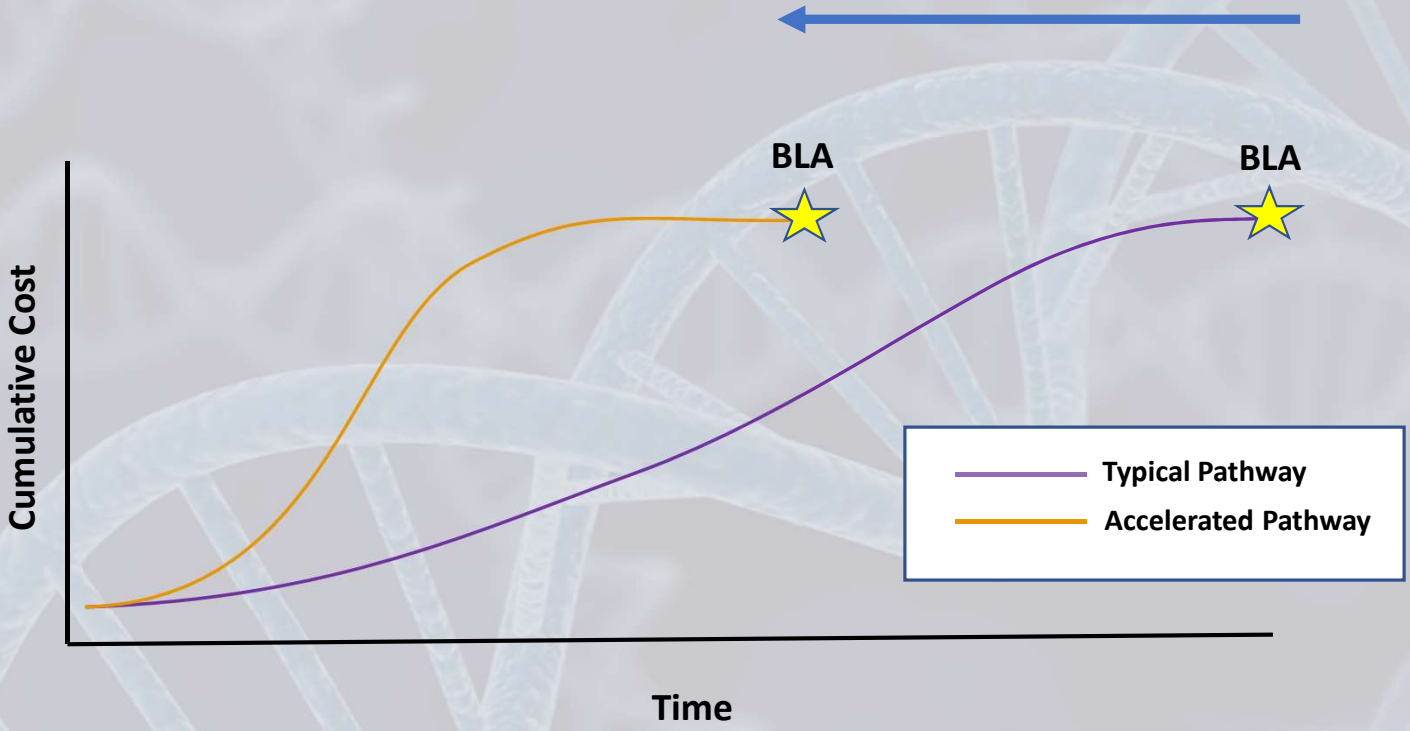
1.Huss, Ralph. October, 2016. The High Price Of Failed Clinical Trials: Time To Rethink The Model Retrieved from: https://www.clinicalleader.com/doc/the-high-price-of-failed-clinical-trials-time-to-rethink-the-model-0001

Gene therapy is has extremely high expectations

- Precedent is important, but not binding
  - Well funded programs have paved the way
  - “Economically challenged” programs must justify changes to status quo
  - Those challenges must be backed by supporting data
- There is a economic and moral obligation to have reasonable expectation of efficacy in the first patient
- Single opportunity to treat necessitates confidence in dose from the very first patient
  - No healthy controls

Costs are shifting to early development phases



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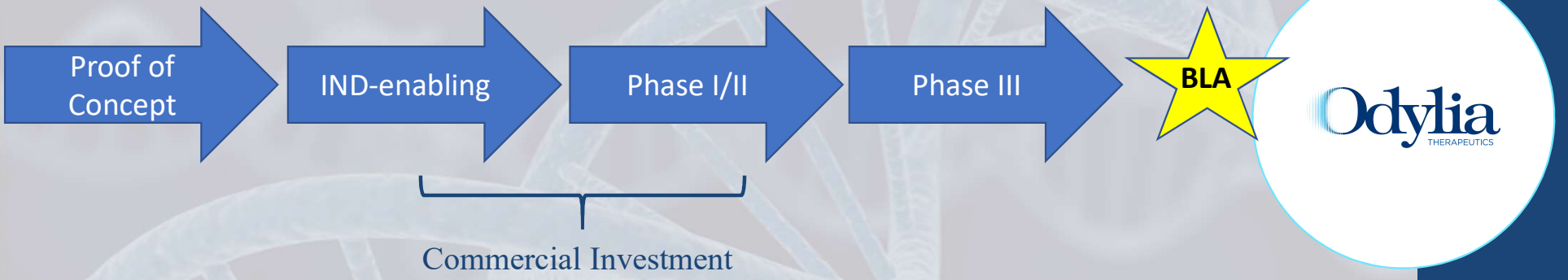
Front loading costs is incompatible with iterative design



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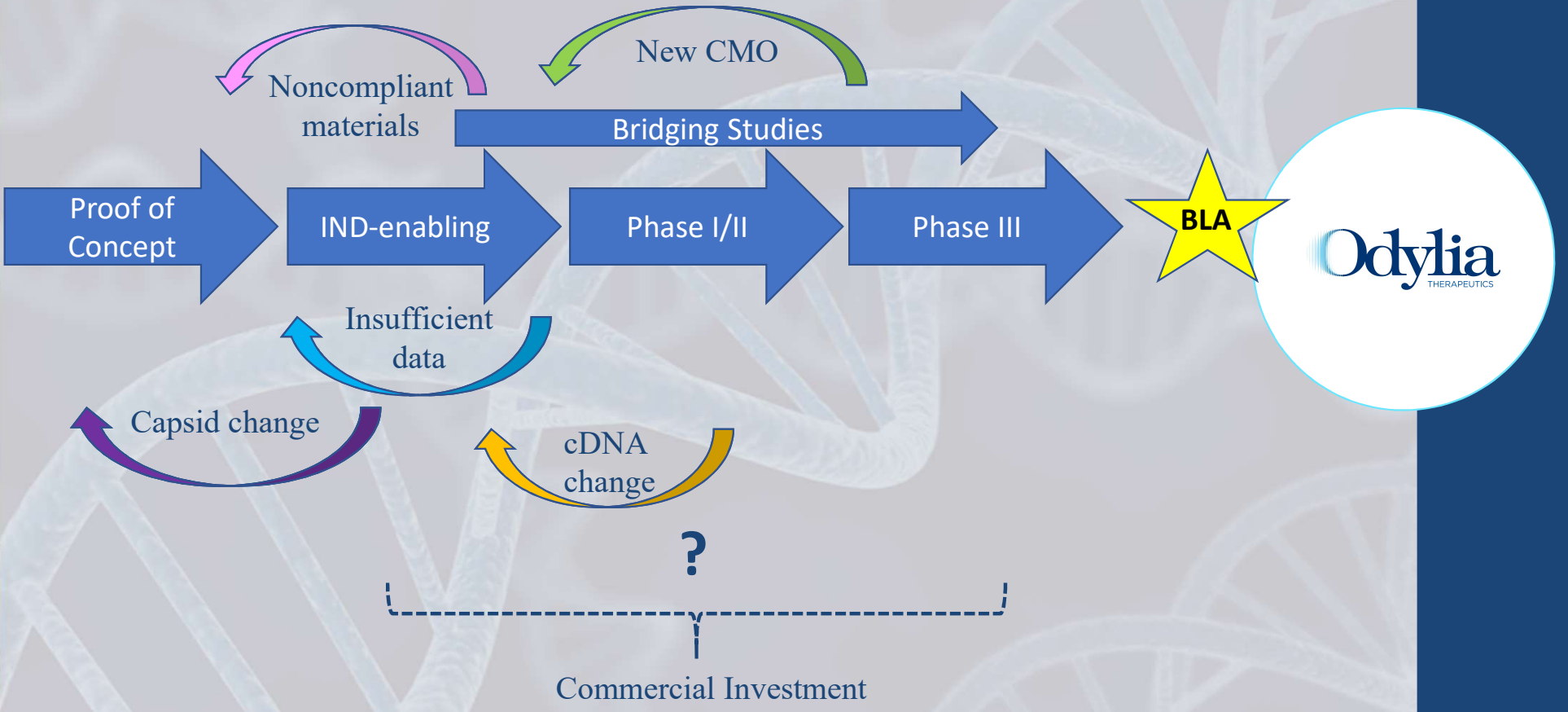
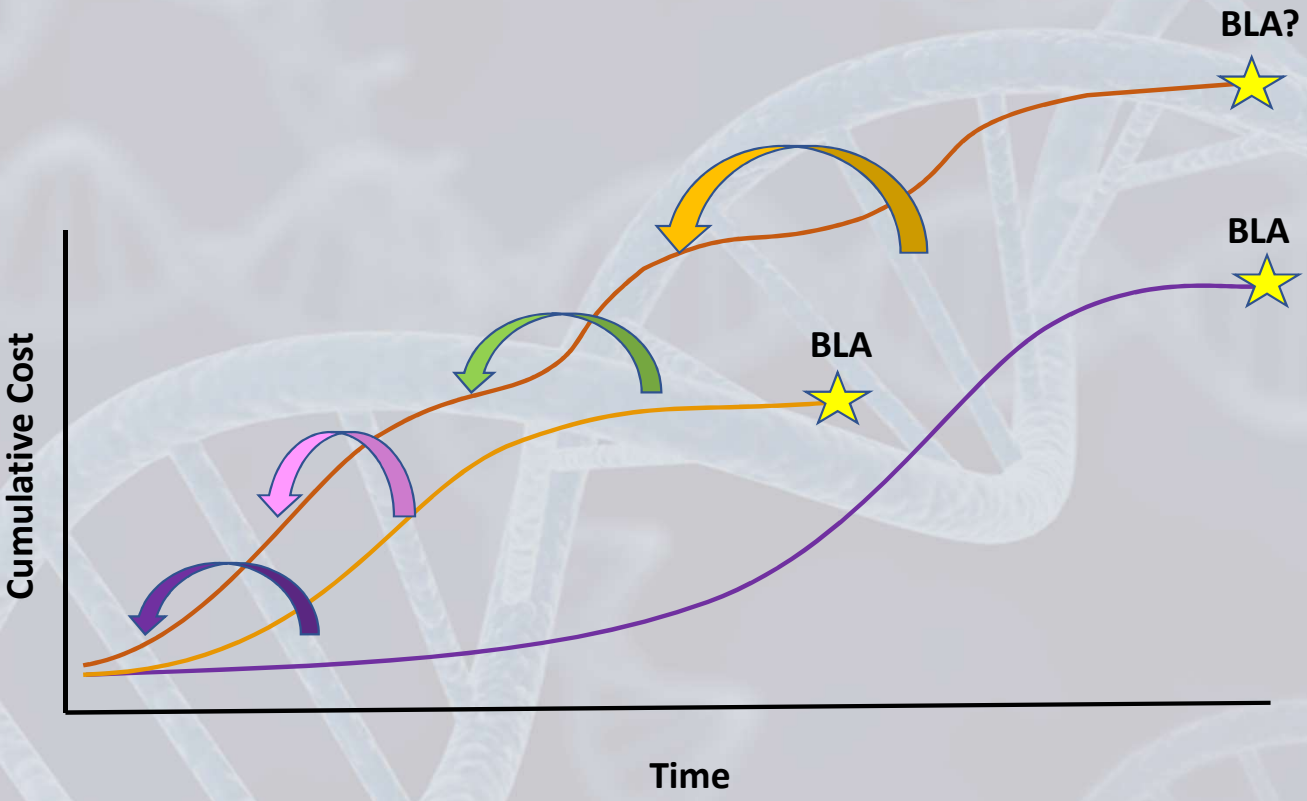


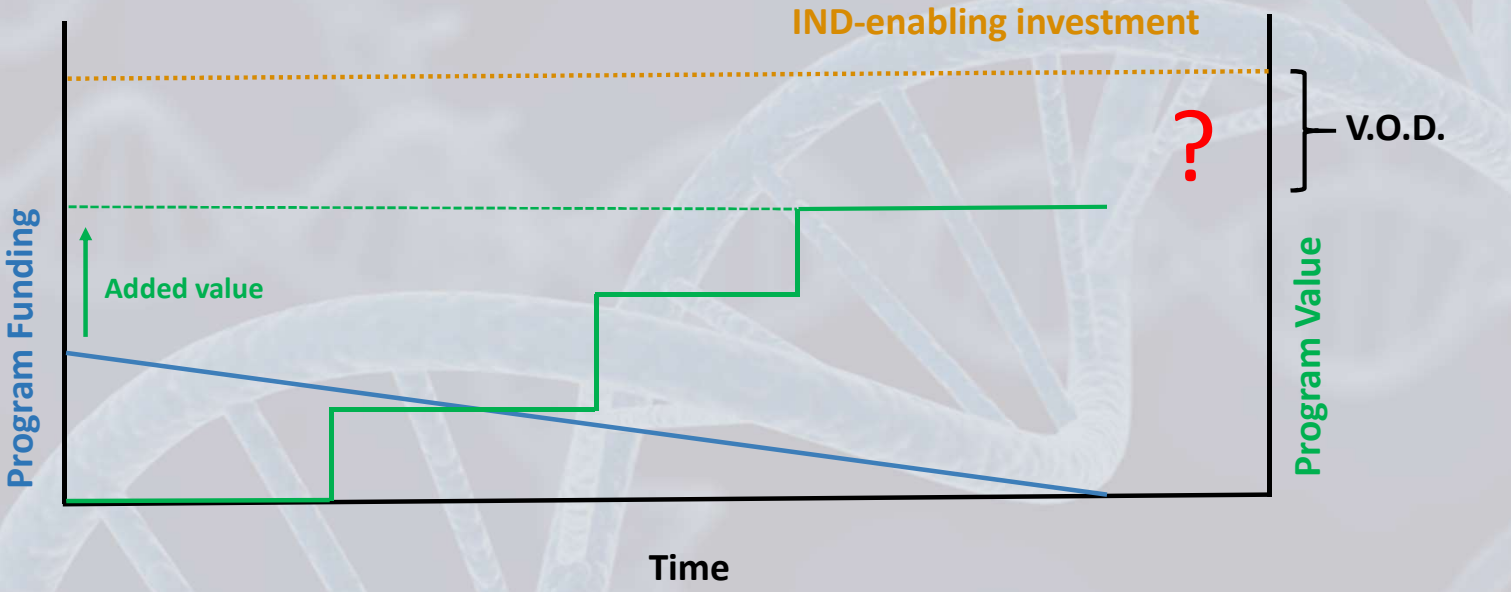
Late stage iteration impedes progress



Where are we stalling?

- Academic programs are generally not sufficiently de-risked to be attractive for commercial investment
- There is a gap between the research strategy of academia and the expectations of data packages from industry
- The high standards set by industry are unobtainable by academic researchers
- Commercial developers do not want to invest in programs lacking rigorous data
- There is just enough of a incentive to tie up tech transfer, yet very few viable paths forward

Front loaded costs expand the “valley of death”



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Increase Funding

Lower Cost of Commercialization

Increase Value

Translationally focused proof-of-concept studies can build value earlier

- Academic research becomes translationally focused too late in the development process
- Lack of a commercial image of the vector leads to study designs that do not move toward the clinic
- Forward-looking study designs ensure data will support commercial and regulatory expectations

There is no centralized resource of best practices

A best practices “Playbook” could give early-stage guidance

- Step-by-step guide on how to how to design a research strategy that gives IND-enabling data from the beginning
- Guidance outcome measures, timepoints, dose escalation, data/appendixes, etc
- Would prevent later repetition of studies at CROs to fit the needs of the IND
- Adherence to these practices throughout development would made programs more attractive for investment or grant funding opportunities

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Playbook resources

- Empirically gathered collection of best practices for clinical AAV development
- Boilerplate legal templates
- Network of process enabling for-profit and non-profit service providers
- Template SOPs and DMFs built on established platforms

Standardization of processes across multiple indications and multiple service providers will greatly streamline vector development

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Open source DMFs can provide a living guide to best practices

- Work with developers and manufacturers to create a publicly accessible DMF for a real-world program
- Use of a platform vector technology would allow partially reusability for future programs
- Standardization would allow efficient modification for future vectors
- Grow a database of open-source DMFs for a body of platform vectors and platform production processes

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Data regarding rare disease patients and therapies are used inefficiently

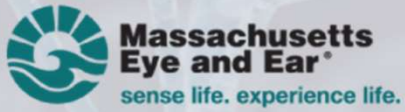
- Natural history studies are highly informative for gene therapies
  - Lack of placebo control arm necessitates understanding of disease progression
- In competitive environments, multiple developers may compete for natural history study participants
- Developers sit on relevant but unused data to maintain competitive advantage

A professionally managed, central repository of data would reduce duplication of effort

Summary

- High cost of failed trials leads to a highly risk averse development environment
- Expectations for early pivotal data in trials front-loads development costs
- Upfront costs are a prohibitive barrier for commercialization of many academic programs
- Centralization of data, best practices, platform vectors, and platform manufacturing can guide efficient development and de-risk programs

Thank You



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