VALUATION INSIGHT
Life Sciences

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Gene Therapy Programs: Unaddressed Risks

INSIGHT: Gene therapy program valuations do not properly account for the risks of lower-than-projected treatment prices or reimbursement rates. Ignoring these risks likely results in overvaluation.

The Resurgence of Gene Therapy

Gene therapy is an experimental technique that involves altering DNA to treat or prevent disease. This may include replacing a mutated gene with a healthy copy, suppressing the expression of a mutated gene, or introducing a new gene to the body.

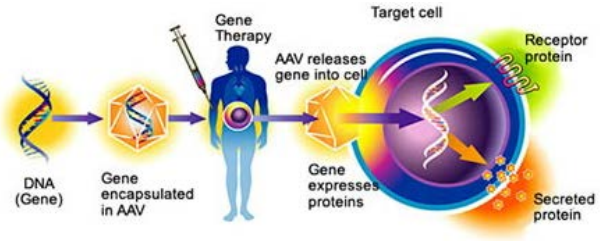
Gene therapy is potentially curative, but it remains risky. The field experienced a major setback in 1999 due to the death of a clinical trial participant, and safety concerns persist.

Nevertheless, gene therapy is experiencing a resurgence and has attracted investor attention. In 2015, public and private gene therapy companies raised $10 billion worldwide. Hundreds of therapies are in development and/or have clinical trials underway. However, no gene therapies have been approved by the FDA to date, and only two gene therapies have been approved in the EU.

Adeno-Associated Viral (AAV) Vectors

Viral vectors are a popular method of delivering therapeutic genes to target cells. Adeno-associated viral (AAV) vectors are small viruses with a genome of a single stranded DNA. They are non-integrating vectors (*i.e.*, do not become a part of the target cell's genome) and have been used in 40+ clinical programs. Their safety profile is promising. AAV vectors are non-pathogenic and are unlikely to cause an immune response that would destroy the virus and treated cells.

Dr. James Wilson of the University of Pennsylvania is considered the father of AAV gene therapy. Dr. Wilson's pioneering AAV work was exclusively licensed by REGENXBIO Inc. (RGNX). RGNX is developing a portfolio of AAV gene therapies and has sublicensed the AAV platform to several other companies.



Source: Lawrence Berkeley National Laboratory (www.lbl.gov)

Gene Therapy Valuations Are Highly Sensitive to Price & Reimbursement Assumptions

We analyzed programs arising from the RGNX AAV platform to examine the assumptions and methods prevalent in valuations of gene therapy treatments.

Despite sharing core technology, the early-stage gene therapy companies using RGNX's AAV platform have a wide range of market capitalizations and values attributable to their treatment programs. These market data are summarized below.

Implied Values of Gene Therapy Programs Using the RGNX AAV Platform

		RGNX Licensees *(See Note 1)*			
(In MM, excl. per share)	RGNX	AVXS	VYGR	DMTX	ADVM
IPO Year	2015	2016	2015	2015	2014
Share Price (7/26/16)	$7.90	$38.12	$14.49	$7.15	$3.21
Market Capitalization	205	879	369	178	88
Cash & Cash Equivalents	101	148	204	117	247
Interest-Bearing Debt	-	-	-	2	-
Value of Program(s)	$104	$731	$165	$63	($159)
% of Market Cap.	*51%*	*83%*	*45%*	*35%*	*(181%)*

The implied program values indicate the market's assessment of the likelihood and extent of treatment commercialization for each company. Based on our review, one of the primary factors driving these early-stage valuations is projected treatment price.

High Treatment Prices Pose a Risk

Analysts are forecasting high prices for gene therapies, with some costing as much as $700k to $1.3 million per treatment. This pricing is a result of limited patient populations, substantial R&D investments, and the value of forgone alternative treatments since many gene therapies are expected to be curative.

However, Glybera, the first gene therapy approved in the EU, effectively failed due to its record setting price of €1.2 million. This is more than three times higher than the next most expensive drug on the market, Soliris, which costs $400k per year. To date, only one patient has received the Glybera therapy. The prescribing physician had to personally call the CEO of the insurer to obtain coverage for the treatment.

With projected prices similar to Glybera, many gene therapies face the risk of limited insurance coverage and reimbursement. This is a critical consideration in valuing gene therapy programs. In addition, the treatments are for limited patient populations that,

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once treated, may be "cured." Thus, the patient population and any associated revenues will decline if the treatment succeeds.

Evaluating the Impact of Price & Reimbursement Risk

Early-stage therapies are often valued using the discounted cash flow (DCF) method. The inputs that drive the cash flow projections include:

- Patient population and penetration rate
- Treatment price
- Time to commercialization
- Upfront R&D investment

Appropriately accounting for risk in projected cash flows is a matter of judgment. The following inputs are commonly used by analysts of gene therapy companies to account for projection risk:

- Probability of clinical success (wide range)
- Discount rate (often 10% to 15%)

However, these variables do not account for key risks faced by gene therapy programs: (1) the treatment price will need to be lowered; (2) the treatment will not be reimbursed by payors; and (3) successful treatment will reduce the patient population.

Accounting for Price & Reimbursement Risk: One way to account for these risks is to apply probability adjustments to the projected revenue that reflect the likelihood of price acceptance and reimbursement. However, such adjustments are inherently subjective. An alternative approach is to test the effect of varying price and reimbursement rates on the valuation.

Representative DCF: Below is a representative DCF of a gene therapy for spinal muscular atrophy (SMA). *[Note: Two RGNX licensees, AveXis and Voyager, are developing SMA therapies.]*

This DCF includes forecasted patients based on the SMA population, and treatment prices and cash outlays that are consistent with other AAV gene therapies.

Assumptions for DCF Valuation: No Adjustment to Account for Price & Reimbursement Risk *-- Consistent with the Approach of Most Equity Analysts --*	
Patients Treated (2023-35)	9,400
Price per Treatment [k]	$1,000
Total Unadjusted Revenue (2023-35) [m]	$9,400
Probability of Clinical Success	20%
Total Risk-Adjusted Revenue (2023-35) [m]	$1,880
Upfront R&D and SG&A Costs (2016-2022) [m]	$345
Launch Year	2023
Discount Rate	10%
Net Present Value (@ 1/1/2016) [m]	$151
Internal Rate of Return	18%

This representative DCF, which excludes adjustments for price or reimbursement risk, results in an NPV of $151 million and an IRR of 18%. This effectively reflects a "best case" scenario.

Sensitivity Analysis: The analysis below shows the effect of changing price and reimbursement rate assumptions. The upper left is the "best case" scenario, reflecting full price acceptance and full reimbursement. The other outcomes show how reduced prices and/or reduced reimbursement affect value.

Sensitivity Analysis of DCF Valuation:
Applying Price & Reimbursement Risk Adjustments

(In Millions)	Probability of Reimbursement				
Price per Treatment	100%	90%	80%	70%	60%
$1.0 M	$151	$101	$49	($3)	($54)
$0.9 M	96	51	4	(42)	(88)
$0.8 M	40	0	(40)	(81)	(121)
$0.7 M	(15)	(50)	(85)	(120)	(155)
$0.6 M	(71)	(100)	(129)	(159)	(188)

Risks Not Accounted for in Most Valuations of Gene Therapy Companies

This analysis demonstrates that the valuation is highly sensitive to changes in price or reimbursement assumptions. For example, the program loses all value if the treatment price is $800k and the reimbursement rate is 90%. This low risk tolerance needs to be considered. Failure to do so results in systematic overvaluation.

Notes:
[1] REGENXBIO has licensed its AAV platform to four publicly traded firms: AveXis (AVXS); Voyager Therapeutics (VYGR); Dimension Therapeutics (DMTX); and Adverum Biotechnologies (ADVM).


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