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FRAMEWORK FOR GENE THERAPY DISEASE AREA TARGETING

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INTRODUCTION

- The volume of gene therapies in development has risen sharply over the last decade with the FDA anticipating that 10-20 cell and gene therapies will be approved per year by 2025[1,2]
- There is significant investment in gene, cell and RNA companies, with series A financing Q1 to Q3 2021 totalling more than $2.8bn
- However there has to be a question mark over if every target will end up a "winner". Particularly in light of previous case studies (Glybera) and bluebird bio's withdraw from Europe
- When deciding on what to target with a gene therapy, or where to direct a particular platform it makes sense to have the "end in mind" to avoid a late stage disappointment

OBJECTIVE

- To devise a framework that will support early decision making around which disease area to target for a gene therapy. A framework that aligns both a payer and a manufacturer perspective, and supports investment and sustainability

METHODS

Case studies of currently approved gene therapies were reviewed (Development path, uptake, HTA, and commercial performance) → *Draft framework of factors that influence commercial performance* → *Pressure tested at an internal workshop, and external validation* → *Framework for evaluating potential market access and commercial issues in prioritising targets*

RESULTS

- Relevant case studies that were reviewed were Glybera, Zolgensma, Strimvelis, Luxturna and Zynteglo
- There are many factors that contribute to commercial success, and a return on investment, and ultimately many trade offs. But some of the key observations were that for a target disease to have maximum commercial should have the following characteristics:
  1. Be relatively prevalent in rare disease terms
  2. Administered as early in life as possible, with the potential for benefits to accrue over a full lifetime
  3. Disease burden should be high
  4. Healthcare resource use should be high, with significant cost-savings expected in those who receive a gene therapy
  5. Current treatment options should be limited and offer challenging benefit: risk profiles
  6. Treatments currently approved for the disease should be expensive, setting a precedent for high pricing and offering a simple like-for-like cost offset

RESULTS

- A framework with 7 elements was proposed, and then used to evaluate a range of current disease areas targeted by gene therapies

Figure 2 Proposed framework and scoring for 10 target disease areas

DISEASE AREA	PREVALENCE	AGE IN CLINICAL TRIALS (YEARS)	DISEASE BURDEN	DIRECT TREATMENT COSTS	CURRENT TREATMENT OPTIONS	COST OF COMPARATOR/ YEAR*	HIGH PRICE PRECEDENT Y/N
Parkinson's Disease	~10 million worldwide	30-75	Symptoms include uncontrollable tremors, bradykinesia, deteriorating cognitive function	$30-60k per year. Includes hospital inpatient + outpatient appts, non-acute institutional care	Carbidopa-levidopa, deep brain stimulation	$50-100k (one off)	N
Wet AMD	~3 million worldwide	50+	Most people move from diagnosis to legal blindness in 10 years without treatment	$10-20k per year, including diagnostic and assistance with daily activities	Lucentis, Eylea	$20-40k	N
Duchenne Muscular Dystrophy	5/100,000	4-7	Rapidly progressive, lethal neuromuscular disorder. Common to be wheelchair-bound by age 8-14. Life expectancy <30 years	Ranging from $10k-80k per year as disease progresses	Corticosteroids, Viltepso, Exondys 51, Vyondys 53	$300k-$1m	Y
Haemophilia A	5/100,000	18+	Life expectancy around normal with extensive treatments	BioMarin put the cost of lifetime treatment of haemophilia A at $25m	Factor VIII, Hemlibra	$400-$700k	Y
MPS Type I	1/100,000	4 months+	Significant developmental delay + cognitive decline. Life expectancy <10 years	Poorly documented, likely to be well over $100k per year in severe disease	Aldurazyme/HSCT	$200-500k	Y
Fabry Disease	10/100,000	16-50	Type 1 leads to excruciating pain in extremities, and progressive renal insufficiency. Life expectancy 58-75 years	~$60k per year, including hospital admissions, surgery, diagnostic imaging, ERT	Fabrazyme, Galafold	$200-400k	Y
Cerebral Adreno-leukodystrophy	2/100,000	>17 years	Progressive neurological symptoms with rapid loss of function. Life expectancy in childhood CALD 5-10 years post-diagnosis	Poorly documented. Estimated at >$100k/year driven by 24/7 care	HSCT	$150-200k (one off)	N
Sickle Cell Disease	30/100,000	12-35	Sickle cell crises, infections, anaemia with vaso-occlusive crises. Life expectancy 45-50 years	~$60k per year, higher depending on number of VOC	Adakveo, Oxbryta	$100-150k	Somewhat
SMA Type I	10/100,000	<6 months	Type 1 is typically fatal within 2 years, and involves a lack of developmental milestones	$100-200k per year, driven by hospital visits, rehabilitation and other costs	Spinraza, Evrysdi	$350-750k	Y
GM1 Gangliosidosis	0.5/100,000	0.5-12	Type 1 is the most severe, characterised by developmental regression. Life expectancy in type 1 is 2-3 years	Varies based on type. Type 1 has costs ~ $150-200k/year	No approved treatment	-	N

Assessment based on Cogentia review of published sources. Disease prevalence taken from Orphanet, with the exception of Parkinson's disease and wet AMD. Other costs and descriptive text based on analysis of public sources. Colour coding spans commercially favourable (deep green) to commercially unfavourable (orange). All comparisons are relative and based on subjective assessment. Other reviewers may come to different conclusions. Disease burden based on more severe forms of disease, where gene therapies would be used. Costs of comparators based on US prices. Scores are assigned to each disease area using colour coding with dark green worth 4 points, mid-green worth 3 points, light green 2 points, yellow 1 point and orange 0 points.

Figure 3 Disease area scoring within framework

DISEASE AREA	OVERALL AVERAGE
DMD	3.4
SMA type I	3.4
MPS Type I	3.0
Haemophilia A	2.6
Fabry Disease	2.4
Sickle cell disease	2.1
GM1 Gangliosidosis	2.0
Cerebral ALD	2.0
Parkinson's Disease	1.0
Wet AMD	0.3

DISCUSSION

- The value and return on a development project, will ultimately rest on the product profile and the value that it delivers. That value will be based on many factors, and the context, which at the point of starting a development programme are not known or uncertain. The matrix is therefore subjective and directional, and useful for relative ranking
- High scores for DMD, SMA type I, MPS I, Fabry and haemophilia are as a result of being relatively common rare diseases, with patients dosed early in life, a high disease burden, relatively high resource use, and expensive comparators already on the market that have set a price precedent
- Disease areas such as wet AMD scored considerably lower, primarily due to a high prevalence, relatively cheap alternatives, and age of onset
- There is no reason why a product in a low score disease area (such as Wet AMD) cannot be a commercial success. For this to be the case, there would just need to be a realistic consideration of potential price that could be achieved, costs of delivering the therapy, ability to recruit patients, and demonstration of long-term effects and safety
- The presence of a number of gene therapies in development across the whole range of selected disease areas, suggests that developers have considered the challenges, and are developing approaches to address them
- Using the matrix prospectively in the early preclinical decision around which indication, or patient population to target, provides direction and should facilitate careful consideration around sustainability for the long term

CONCLUSIONS

- There are no shortcuts to doing a detailed opportunity assessment when considering which disease, indication, or patient subpopulation to target for gene therapy development
- Having a simple framework to aid disease area targeting, and target product profile refinement, should promote the long-term sustainability through investing with realistic views on what value is possible
- This analysis highlights the breadth of economic factors that can contribute towards the commercial attractiveness of target disease areas
- There is no one size fits all – and different developers are addressing different challenges, with a range of unique approaches
- Disease prevalence is a challenge since at the extreme low end it's harder for manufacturers to gain sufficient returns, but at the high-end there are question marks over affordability for payers
- Other key factors include the existence and high cost of comparators, use earlier in life, and high resource use

REFERENCES

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