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IS THE GENE THERAPY REVOLUTION SUSTAINABLE AND AFFORDABLE?

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BACKGROUND

- More than 200 phase 2 and 3 gene therapy trials are currently underway, which may translate into 40 new products being approved for clinical use in the next decade (1)
- This development boom will profoundly change the treatment landscape of many rare genetic conditions through the potential of curative treatments for patients
- Despite the scientific advancements and potential benefits to patients, there is significant global variability in uptake of gene therapies currently on the market
- Questions arise on whether the adoption of gene therapies into clinical care threatens the financial sustainability of health systems particularly with concerns regarding their higher upfront prices, uncertainty in long-term clinical benefit and potential safety aspects (2)
- For gene therapy development to be sustainable, gene therapies have to provide sufficient returns (risk adjusted) to developers whilst concomitantly being affordable for payers
- Sustainability is therefore a function of value delivered by the gene therapy (and corresponding price achieved), total affordability to the health system, the cost and risks of development and treatment, and patients treated
- The question of what constitutes gene therapy sustainability to developers and healthcare systems has never been more critical

OBJECTIVES

- To conduct an analysis into factors affecting the sustainability of gene therapy development within the key target disease areas
- To develop a framework for considering viability and sustainability, when targeting disease areas at the start of development

METHODS

- Desk research was conducted to consider gene therapy sustainability from the following perspectives
  - Healthcare systems: review of trends associated with drug and healthcare spending
  - Industry/developers: a search on ClincalTrials.gov was performed to identify ten key disease areas for gene therapy targeting in Phase I-III trials which provide a spread of different challenges faced by payers and developers

Commercial attractiveness matrix

- Cogentia 'commercial attractiveness matrix' was developed (through an internal workshop) to rank and consider the development, commercial and access challenges for the 10 disease areas, comprising the following parameters:
  - Disease prevalence
  - Patient age in clinical trials (years)
  - Disease burden
  - Direct treatment costs
  - Current treatment options available
  - Annual cost of comparator
  - High price precedent (Y/N)
- Desk research was performed to obtain information to populate the matrix (based on a review of published literature sources)
- Once populated, each matrix parameter was scored using a scale of commercial attractiveness *
  - Scores were evaluated & aggregated to highlight some potential challenges around gene therapy economic viability/sustainability within that therapy disease area. Each factor was not weighted, as without a model framework or further preference based research or Delphi exercise, there was no way of effectively establishing weightings

* Scores are assigned to each disease area using colour coding with dark green (commercially favourable) worth 4 points, mid-green worth 3 points, light green 2 points, yellow 1 point and orange (commercially unfavourable) 0 points

RESULTS

- Across the 10 disease areas in gene therapy development there were differences in parameter rating indicating variability in challenges to commercial sustainability (**Table 1**)
  - DMD and SMA type I were the most highly rated for commercial attractiveness with overall average score of 3.4 (across the 7 parameters)
  - Parkinson's disease and Wet AMD were scored the least commercially attractive with overall average scores across the 7 parameters of 1.0 and 0.3, respectively
- High overall scores for DMD and SMA type I were as a result of:
  - High disease burden: maximum scores of 4 for DMD and SMA
  - High cost of comparators on the market: maximum scores of 4 for DMD and SMA
  - Relatively common rare disease: 'prevalence' scores of 3 and 4, respectively
  - Dosing early in life: 'age in clinical trial' scores of 3 and 4, respectively
  - High resource use: 'direct treatment cost' scores of 2 and 3, respectively

Table 1 Ranking of commercial attractiveness of gene therapy targeted disease areas using Cogentia matrix

DISEASE AREA	PREVALENCE	AGE IN CLINICAL TRIALS (YEARS)	HIGH DISEASE BURDEN	DIRECT TREATMENT COSTS	CURRENT TREATMENT OPTIONS	HIGH COST OF COMPARATOR/ YEAR	HIGH PRICE PRECENDENT Y/N	OVERALL AVERAGE
DMD	3	3	4	2	4	4	4	3.4
SMA type I	4	4	4	3	1	4	4	3.4
MPS Type I	1	4	4	3	2	3	4	3.0
Haemophilia A	3	1	1	4	1	4	4	2.6
Fabry Disease	4	1	2	2	1	3	4	2.4
Sickle cell disease	3	2	3	2	2	2	1	2.1
GM1 Gangliosidosis	0	3	4	3	4	0	0	2.0
Cerebral ALD	1	3	4	3	3	0	0	2.0
Parkinson's Disease	0	0	3	2	2	0	0	1.0
Wet AMD	0	0	2	0	0	0	0	0.3
Average	1.9	2.1	3.1	2.4	2.0	2.0	2.1	

All comparisons are relative and based on subjective assessment. Other reviewers may come to different conclusions. Scores assigned to each disease area using the colour coding dark green worth 4 points, mid-green worth 3 points, light green 2 points, yellow 1 point and orange 0 points.

- In comparison, wet AMD scored considerably lower, primarily due to its low prevalence (score 0/4), relatively cheap alternatives available on the market (direct treatment costs score: 0/4), and late age of disease onset (age in clinical trials score: 0/4)
- 'Prevalence' was most impactful with lowest average across all the parameters, whilst scoring highly for DMD and SMA type I

Sustainability – Healthcare systems (**Supplement**)

- Healthcare spending as a proportion of GDP has been increasing over the last two decades (3)
- Countries' drug spending share of healthcare is around 15% (ranging from 9–20% in 2018) (4)
- The OECD project that forecast healthcare spending to rise +2% over GDP growth through to 2030 (5) This was before the Covid-19 pandemic, and it is likely that growth will therefore be higher (with both potential higher absolute spend and lower growth)

Sustainability – Industry and developers (**Supplement**)

- As with any drug development there needs to be sufficient incentive and returns for developers to invest in R&D
- For sustainability, the hypothesis is that cumulative net profits need to outweigh risk-adjusted, capitalised development costs
- A proxy for the sustainability of gene therapy development is to consider cumulative revenues, which are a combination of price, market share, and target population
- There are some case studies where the return on investment could have been negative (e.g. Glybera and Strimvellis due to the ultra-rare ADA-SCID indication). However these are contrasted with a range of treatments that have delivered a very significant return on investment (e.g. Zolgensma, Kymriah, Yescarta)

Supplement available on request by emailing: enquiries@cogentia.co.uk

DISCUSSION

- This analyses highlights the breadth of economic factors that can contribute towards the commercial attractiveness of target disease areas within the gene therapy pipeline
  - There is no one size fits all with different developers are addressing different challenges, with a range of unique approaches
- With "one and done" or curative treatments, picking the optimal target indication is important for long-term success and sustainability
- DMD, SMA, MPS, Fabry and haemophilia do all present disease areas that are commercially suited for gene therapy
  - At the heart of the challenge is disease prevalence which proves impactful since at the extreme low end it is 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, treatment use earlier in life, and existing high resource use costs
  - DMD and SMA rate highly attractively as a result of both 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 precedence
  - Disease areas such as wet AMD score less well, primarily due to high disease prevalence, relatively cheap alternatives, and higher age of onset
- 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 what is sustainable for the long term

CONCLUDING REMARKS

- Drug costs and spending has risen, and continues to rise as a % of GDP, however, there is no reason to consider that the emergence of gene therapies is not sustainable from a payer perspective, as long as price reflects value delivered with enough patients to gain sufficient return
- Having a simple framework to aid disease area targeting, and target product profile refinement, at the preclinical stage should promote the long-term sustainability of gene therapy
- This framework aims to promote a structured discussion of the likely challenges associated with a particular disease area or indication, and thereby ensure that "if" the project is successful, there can be a reasonable confidence with commercial sustainability for the developer
- The range and scoring is relative and there is no reason why a product in a low scoring disease area (e.g. wet AMD) cannot be a commercial success if realistic consideration is applied towards potential achievable price, cost of treatment delivery and demonstration of long-term effects and safety

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