Pricing strategy and social benefits of gene therapies. Towards a revised value-based framework for HTA

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Executive Summary

Gene therapies are emerging in the recent years as an innovative class of medicinal products allowing the treatment of very severe conditions and bringing an enormous advancement to the standard of care thanks to their single administration mode and ability to specifically alter the disrupted protein-coding sequences. However, the high listing prices (on average $1.2 mio per dose) coupled with an increasing pressure over payers' budgets are raising concerns over their affordability. Furthermore, the difficulty to assess their real economic value and to achieve satisfactory cost-effective thresholds is further complicated by the lack of unambiguous clinical endpoints in clinical trials and few long-term safety evidences. In such a context, this research investigates the price determinants of gene therapies in order to understand the motives for the enormous listing prices and subsequently proposes an advancement to the traditional health technology assessment model used to evaluate the cost-effectiveness of these products by analyzing the relevance of the indirect effects. This study builds its arguments on an emerging body of literature demanding economic evaluations to account for wealth effects and to move towards a societal perspective in order to acknowledge the real value of gene therapies (Angelis et al., 2020; Coyle et al., 2020; Garau et al., 2015; ICER, 2019).

The methodology based on literature review is supplemented by insights gathered from 15 semi-structures interviews conducted with various healthcare practitioners and professionals active in the pharmaceutical industry. Additionally, in order to minimize any possible correlation with patients' socio-economic status that would have biased the cost estimation, the sample of diseases used for the analysis was reduced to conditions displaying only significantly high relative contribution of de novo mutations. A further restriction to pediatric neuromuscular and neurodevelopment diseases was necessary in order to assure consistency across symptoms and illness' management.

From the price determinants analysis, which investigate the manufacturer's motives and logics for their price setting decisions, it can be concluded that the large stakeholders' perceived value for gene therapies is the leading aspect driving the high price mark-up. Furthermore, the need for specialized infrastructure investments, coupled

with strict handling and storage requirements and difficulties to achieve economies of scale due to small bath production also foster higher research and development costs compared to more traditional medicinal products. When moving to the estimation of the economic burden of the disease, the total average lifetime costs for the defined average disease amount to $3'434'928. Of these, 58% ($1'997'473) is represented by the indirect component, composed by patient productivity loss and caregivers' lifetime income loss, while direct (medical and non-medical) costs represent the remaining 42% ($1'437'454). The indirect costs are likely to represent a lower bound as the phycological burden for caregivers was not taken into consideration but represents a further weight for the entire healthcare system. These results are calling for an update of HTA models towards the inclusion of wealth effects as traditional frameworks to evaluate gene therapies' cost-effectiveness might miss out on important elements of value and thus underestimate their real economic benefits for the whole society. It is believed that the active inclusion of indirect effects permits to overcome the increasing payer's scrutiny by lowering ICER valuations. This approach, together with the use of a QALY-based capping model and the adoption of a higher QALY cost-effectiveness threshold, are identified as the most promising way forward in order to assure a sustainable future for gene therapies and to guarantee patient access to them.

Due to the aforementioned welfare effects, it is a very rational question to ask whether public interventions should be directed towards financing gene therapies' development. Since European legislation already provides important indirect incentives for the commercialization of orphan drugs in the form of tax credits, market exclusivity and user fee waivers, it is believed that a more profound approach represents the adequate solution to solve affordability challenges, to change private developers' incentives for price setting and to strengthen non-financial public incentives for drug development. The embracement of an open innovation model to run R&D processes allowing to strengthen the cooperation with public organizations, permits to accelerate the drug development and facilitate the access to those resources that represent critical costs for gene therapies manufacturing. The benefits arising from the establishment of a share-information culture between private and public entities need however to be balanced against the ability to stay competitive on the market and to maintain profit margins. A further tool identified to achieve a long-term sustainable commercialization of gene therapies and to

facilitate reimbursement decisions is the use of managed entry agreements. These innovative pricing agreements between payers and manufacturers permit to link the reimbursement of the drug to its performance. While, shifting part of the financial and outcome risk towards pharmaceuticals, they allow payers to avoid repayments of those products not providing measurable improvements in the patient health status (performance-based linked reimbursement schemes) or not achieving enough solid post-marketing evidences (coverage with evidence development schemes). Patients can also profit from a faster market access, aspect very important in the case where the disease is characterized by an unmet medical need. In such a scenario, the availability of patient registry data becomes an essential prerequisite for a successful use of managed entry agreements. Again, cooperation between private developers and governments become essential to facilitate the access to patients' medical data and to promote the use of collection programs.