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The price of a human life

Gene therapy is already a reality for a small group of patients with rare diseases, but does it come at a cost?

The **Rett Syndrome Research Trust** announced in June that the biotech **AveXis**, will be developing the first human trial of a gene therapy for Rett syndrome. Amidst the excitement of a cure looming in the horizon many wonder about costs and timelines for the delivery of such treatment, if proven safe and efficacious. Rather than generating conjunctures, we could take look at the trajectory of some gene therapy drugs that are currently being marketed in Europe. Yes, they exist, and there is more than one!

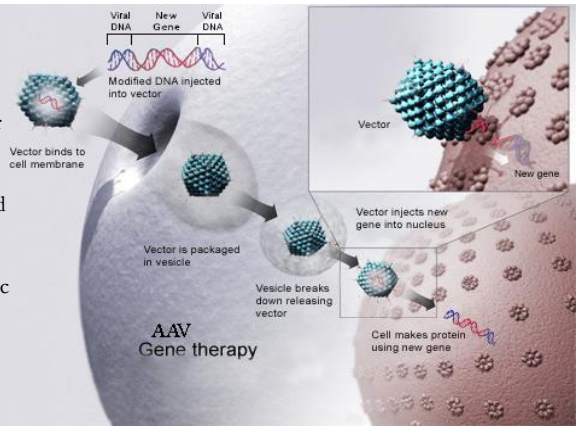
The first gene therapy treatment to ever be approved in the Western world goes by the commercial name of **Glybera®**, also known as alipogene tiparvovec. The European Commission granted the biotech uniQure with marketing authorization for Glybera® under exceptional circumstances in July 2012 [1] (*see below*). It is indicated to treat adults with lipoprotein lipase deficiency (LPLD), a rare genetic disease that results in multiple painful episodes of acute pancreatitis, and high risk of having heart attack or stroke. LPLD affects 1 out of 1 million people, and is extremely rare even compared to Rett syndrome, which affects about 1 in 12,000 individuals. Glybera® is made of a genetically engineered virus that carries a healthy copy of the gene that encodes the enzyme lipoprotein lipase, which is lacking in people with LPLD. The drug is given as a one-off treatment, which consists of multiple injections (up to 60) to the muscles of the upper and lower legs. Check the box above to see how it works.

That sounds amazing, but are there any catches? Yes many, but sciency stuff aside, the immediate drawback of Glybera® was its price tag, earning it the title of world's most expensive drug. Since the drug was released only one patient from Germany was commercially treated in September 2015 (over 3 years later) through a special agreement with DAK, a German health insurance provider, for the price of € 900,000. For the patient, it was all worthwhile, who is reported to be well and leading a symptom-free life. If you have been made to feel despondent by this price tag, be aware that Glybera® is an extreme example. There are only about 250 people with LPLD in all of Europe, and uniQure is thought to have spent over 100 million US dollars developing the drug. But health authorities, who have a limited pot of cash to share around, took a dim view of Glybera®'s clinical trial data. French and German regulators concluded that benefits from the treatment were insufficient to justify funding via national health insurance. Unable to recover their investment, in April 2017, uniQure announced that it will not renew Glybera®'s marketing authorization in Europe which expires this October.

Let us look at a more recent example. **Strimvelis®**, from GSK, is the first stem-cell-based gene therapy approved by the European Commission in May 2016 [1]. This treatment involves extracting the patietn's own stem cells (precursors to mature organ cells) and culturing them in a lab. Similarly, to the procedure illustrated above, a virus is used to deliver the healthy DNA package into the stem cells, but outside the patient's body. The 'fixed' stem cells are injected back into the patient where they multiply and replace the sick cells. It is a costly individualized treatment, and very few centres around the world are equipped to perform it. Strimvelis® is indicated for children with adenosine deaminase deficiency (ADA), a rare genetic disease that causes severe immune-deficiency, meaning these children's bodies are unable to fight of microbes. ADA affects about 1 in 100,000 people, thus the patient pool is larger than in LPLD. Despite requiring a more complex treatment procedure, Strimvelis® came with a lower price tag than Glybera®. So far, only the Italian medicines agency, has agreed to fund the treatment at € 594,000 per patient, which is less than the overall cost of the life-long enzyme replacement that children with ADA require. All the children treated in the clinical trial were still alive after the 7-year follow-up that led to market approval, and 75% could interrupt enzyme treatment [1]. Currently the only site licensed to administer the treatment is in Italy and patients from other countries will need to travel. With a larger patient pool than ADA, it is expected that gene therapy costs for Rett syndrome could be lower. It is noteworthy though that despite Strimvelis®'s trajectory being free of major setbacks, it took 1 year after marketing approval until the first patient was commercially treated (*see below*). As we turn our thoughts to recently diagnosed children with Rett syndrome, whose little bodies accumulate indelible marks left by the disease progression, one year of price negotiations after the cure is found seems too long a wait. While Rett syndrome charities have successfully funded research that may deliver a cure, as biotech companies pick up the venture of carrying a treatment through to approval, marketing, production, and public funding hurdles, it is never too early for patient advocacy groups to start asking some important questions: How long will price negotiations take? and Who is going to pick up the bill if local medicine agencies decide the treatment is not cost effective?

How *in vivo* gene therapy works

Once in contact with patient's cells, the virus known as AAV delivers its DNA package into the cell nucleus, the keeper of our genetic code, and helps these cells produce and sometimes release the 'healthy' protein. The virus is engineered so that it cannot make copies of itself, and hence cannot become infectious. It simply dies off after delivering its genetic payload, which is incorporated into the main genetic code of the treated cells and there should remain for the rest of that patient's life, at least in theory.



1 Touchot, N. & Flume, M. Early Insights from Commercialization of Gene Therapies in Europe. *Genes* **8**, doi:10.3390/genes8020078 (2017).

Timeline from start of the first safety and efficacy trials to the first commercially treated patients.