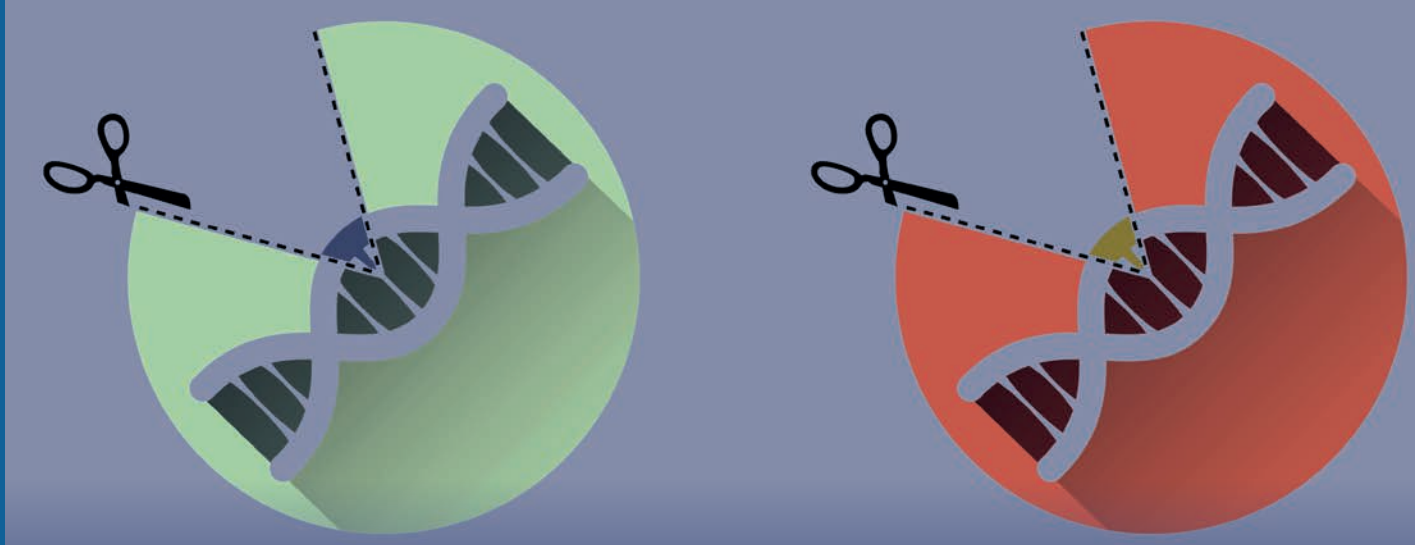

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Gene therapy ready to deliver

With a pioneering gene therapy now on the brink of approval, this feature highlights some of the key deals and news in the field in the past five years.

BioPharma Dealmakers

Since its inception, the field of gene therapy has encountered many hurdles—ranging from limited commercial interest for many years through to serious safety setbacks, challenges with effective gene delivery, and the establishment of regulatory pathways and commercialization strategies for a new therapeutic modality. Recent advances, however, have re-energized the field, and led to high-value deals (**Table 1**) and clinical successes (**Fig. 1**).

Many years of optimization of the main gene therapy platforms based on viral vectors such as adeno-associated viruses (AAVs) and lentiviruses are increasingly enabling effective delivery of therapeutic genes to particular tissues for many disorders. Among the leading candidates in the pipeline are those using AAV vectors for eye diseases, and one of these is poised to become the first gene therapy to gain approval in the United States. In mid-October, an advisory panel at the US Food and Drug Administration (FDA) voted in favour of the approval of Spark Therapeutics' AAV-based therapy voretigene neparvovec to treat an inherited form of blindness (**Fig. 1**). Spark Therapeutics is also developing a number of other gene therapy candidates, including SPK-9001 for hemophilia B, which is being developed with Pfizer through a deal signed in 2014 (**Table 1**).

Blood disorders such as hemophilia and β thalassemia are a prominent focus of several other companies in the field, including Sangamo Therapeutics, who signed a deal with Pfizer earlier this year to collaborate on their candidates for hemophilia A (**Table 1**). A leading company using lentiviral vectors, bluebird bio, has a candidate in phase 3 trials for β thalassemia.

Gene therapies for central nervous system disorders have also attracted substantial interest, including a headline ~$845 million deal in 2015 between Sanofi's Genzyme unit and Voyager Therapeutics, which is developing AAV-based gene therapies for disorders including Parkinson's disease (**Table 1**). AveXis, which is developing an AAV-based gene therapy (AVXS-101) for infants with spinal muscular atrophy, pulled in almost $270 million in an initial public offering last year.

Importantly, there are signs that some of the unique commercial and regulatory challenges in the field are beginning to be addressed, including the fundamental question of how to price a therapy that has the potential to be curative with a single dose. Disappointingly, the first two gene therapies to make it to the market in Europe—uniQure's Glybera, which was priced at $1 million per treatment before its market withdrawal and GlaxoSmithKline's Strimvelis, which is currently priced at €594,000 ($665,000) (**Fig. 1**)—have been a commercial flop. However, soon after the August 2017 approval of Novartis's genetically engineered CAR-T cell therapy Kymriah (tisagenlecleucel), which has a sticker price of $475,000, the company said that it has established an outcomes-based approach to reimbursement for Kymriah with the Centers for Medicare and Medicaid Services and that it was working to put this new pricing model in place with other stakeholders, providing encouragement that such approaches might be viable for gene therapies. Furthermore, earlier this year the FDA announced a Regenerative Medicine Advanced Therapy designation to accelerate the development of products such as gene therapies (**Fig. 1**), which could provide a further boost to the burgeoning pipeline, as well as to the regenerative medicine space more broadly.

Table 1: Selected high-value gene therapy deals

Date	Companies	Deal summary
June 2014	Dimension Therapeutics, Bayer	Bayer signed an agreement with Dimension Therapeutics for the development of a hemophilia A treatment. The deal involved $20 million upfront and up to $230 million in development and commercialization milestone payments.
December 2014	Spark Therapeutics, Pfizer	Deal signed to develop bio-engineered adeno-associated virus (AAV) vectors for the treatment of hemophilia B. Spark received an upfront payment of $20 million, with the potential to receive up to $260 million in milestone payments.
February 2015	Voyager Therapeutics, Genzyme	Potential $845 million ($100 million upfront and $745 in milestone payments) collaboration signed for the development of gene therapies for central nervous system disorders including Parkinson's disease.
April 2015	Bristol Myers Squibb (BMS), uniQure	BMS signed potential $2 billion deal to acquire gene therapy candidates from uniQure. The deal focused on the S100A1 program for congestive heart failure, which has a potential value of $254 million up to commercialization, and also includes nine other targets valued at up to $217 million each.
July 2015	Biogen, Applied Genetic Technologies	Biogen entered a collaboration with Applied Genetic Technologies Corporation to develop gene therapies for rare ophthalmic diseases. Biogen will pay an upfront fee of $124 million and milestone payments that could exceed $1 billion.
May 2016	Biogen, University of Pennsylvania	Biogen partnered with the University of Pennsylvania to develop gene therapies for eye, skeletal muscle and central nervous system disorders. The deal included $20 million upfront and $63 million in R&D, with up to $138 million in milestones for each of seven preclinical R&D programs.
May 2017	Sangamo Therapeutics, Pfizer	Sangamo signed a deal with Pfizer worth up to $545 million (with $70 million upfront) for the development and commercialization of gene therapy programs for hemophilia A, including SB-525, one of Sangamo's lead candidates.
October 2017	Ultragenyx, Dimension Therapeutics	Ultragenyx is set to acquire Dimension Therapeutics in a deal potentially worth $151 million.

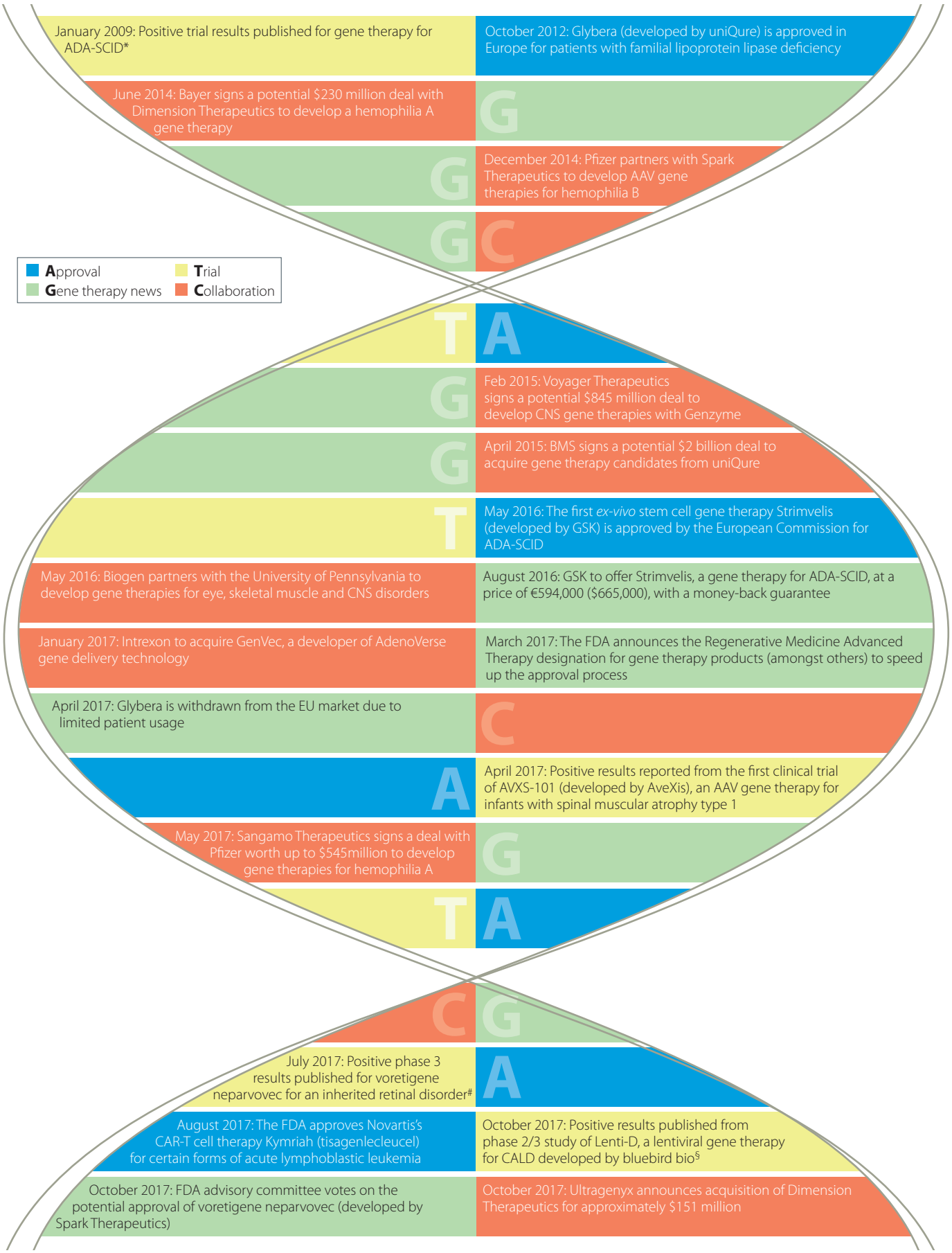

Figure 1: Gene therapy timeline. AAV, adeno-associated virus; ADA-SCID, severe combined immunodeficiency due to adenosine deaminase deficiency; BMS, Bristol-Myers Squibb; CALD, cerebral adrenoleukodystrophy; CAR, chimeric antigen receptor; CNS, central nervous system; FDA, Food and Drug Administration; GSK, GlaxoSmithKline. *N.Engl. J. Med.* **360**, 447–458; 2009. #*Lancet* **390**, 849–860; 2017. §*N.Engl. J. Med.* 4 Oct 2017; doi: 10.1056/NEJMoa1700554.