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Supplementary information

Trends in gene therapy delivery technologies

In the format provided by the authors and unedited

Data and analysis

Core source. We conducted an outside–in analysis of the global pipeline for gene therapies (including both DNA and RNA therapeutics) utilizing data from Evaluate Pharma (accessed February 2025), PharmaProjects and public information, including news releases on program status and pipelines on company websites. In several cases, we supplemented data available on Evaluate Pharma with new pipeline information available via press releases or in literature, and in others we excluded Evaluate Pharma asset-level data where it was dated (for example, a program was discontinued). We additionally validated our data by cross-referencing assets against active clinical trials (ClinicalTrials.gov) to see whether assets were in at least one trial. We only analyzed clinical and commercial-stage assets (for example, phase I/II/III, filed, approved and on-market), and excluded preclinical research programs.

To create Figure 1 (Gene therapy pipeline by modality and delivery system) and Figure 2 (Gene therapy pipeline by therapeutic area and delivery system), we had to map assets to a specific modality/delivery system/therapeutic area/stage of development. Details on mapping are below.

Stage of development. Late-stage assets were defined as those in phase III (or beyond), filed, or approved; early-stage assets were defined as phase I/II. As in gene therapy and rare disease more broadly, some assets can achieve regulatory approval with fewer than three phases; where the phase of an asset was unclear (for example, on Evaluate Pharma/company website as phase II/III) the later phase was always used. Phase I/II assets were classified as phase II, and phase II/III as phase III. Where programs had different phases in different (known) geographies, the later phase was used. The table below shows several examples of gene therapies in each phase (note that this is not an exhaustive list).

Product	**Company**	**Worldwide Phase**
Hemgenix	CSL	Approved
Zolgensma	Novartis	Approved
Roctavian	BioMarin Pharmaceutical	Approved
Leqvio	Novartis	Approved
Wainua	Ionis Pharmaceuticals	Approved
Tegsedi	Swedish Orphan Biovitrum	Approved
RGX-121	REGENXBIO	Filed
Kresladi	Rocket Pharmaceuticals	Filed
UX111	Ultragenyx	Filed
NTLA-2001	Intellia Therapeutics	Phase III
SRP-9003	Sarepta Therapeutics	Phase III
Giroctocogene fitelparvovec	Sangamo Therapeutics	Phase III
GTX-102	Ultragenyx	Phase III
Bepirovirsen	GSK	Phase III

Modality. Note that ‘gene therapies’ in this analysis refer to *in vivo* approaches such as clinical-stage *in vivo* gene editing therapies (for example, Intellia’s NTLA-2002 for hereditary angioedema, CRISPR’s CTX310 for cardiovascular disease) and exclude *ex vivo* cell therapies such as ex vivo gene-modified CAR-Ts or haematopoetic stem cells. Modality was classified by data available in Evaluate Pharma and validated by company website research. Many companies engineer modalities (for example, self-amplifying RNA) that then need to be combined into a “modality category”. All

modalities are combined to one of the following: DNA vector (AAV, other viral vectors, DNA plasmid), gene editing (including CRISPR, base, and prime editing), RNAi (siRNA), antisense oligonucleotides (ASOs), and other gene therapy (for example, saRNA, dsRNA, RNA editors, ncRNA).

Delivery system. Delivery systems were largely validated via literature and/or research on public sources (for example, company websites) as clinical-stage biopharma companies are often involved in substantial engineering of delivery vehicles (for example, Avidity Bioscience's novel antibody–oligonucleotide conjugate platform). Delivery systems were combined in one of a few groups: AAV and other viral vectors (AAVs, lentiviruses, retroviruses, herpes-simplex virus), lipid nanoparticles (LNPs) and other particles (LNPs, PNPs, VLPs, endosomal escape vehicles), conjugates (including chemical/protein-based conjugates). In some cases, particularly for the ASO modality and/or sensory organ assets, they may be delivered without a vehicle; in this case, they are assigned as being "naked". In some cases, assets can be said as having more than one delivery vehicle (for example, targeted LNPs often have antibody fragment "conjugates" on their surface, so could be classified as either a conjugate or LNP). In such cases, assets were categorized as one or the other depending on the exact nature of the platform.

Therapeutic area. Assets were mapped to one therapeutic area using Evaluate Pharma (and validated). As assets can be in development for multiple indications (although this is rarer for gene therapy), we chose the therapeutic area assigned to the asset's most advanced indication. The therapeutic area relevant to symptom/disease manifestation was chosen, and not the organ system where the gene is most richly expressed (for example, VERVE-102 for heterozygous familial hypercholesterolaemia is tagged as cardiovascular even though the gene target (PCSK9) is expressed in the liver). Therapeutic indications were combined into the following categories: anti-infective, blood, central nervous system, cardiovascular, gastrointestinal, musculoskeletal, oncology, respiratory, sensory, and various.