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Supplementary information

The landscape for lipid-nanoparticle-based genomic medicines

In the format provided by the authors

Dataset and analysis

Database assembly

We assembled 538 *in vivo* genomic medicine assets from 273 companies, representing all publicly available clinical products that we could source by the end of December 2021, primarily by using EvaluatePharma's database and their two-tiered classification based on the technology employed by the product:

1) Technology category (Conventional or Biotechnology)
2) Technology (for example, small molecule chemistry, monoclonal antibody)

The technology category used was "Biotechnology". Within that, we pulled all products with the following search criteria (technologies):

1. DNA and RNA therapeutics
2. Gene therapy
3. Genome editing
4. Vaccines (specifically DNA and mRNA vaccines in the subtype)

Within each of these categories, we down-selected products that are in clinical phases (I–III), marketed, and filed.

Each asset was a unique product, which could target multiple indications. We gathered the following information for each asset: company, drug name, pharmacological class, formulation (lipid nanoparticle (LNP) or not), stage of development (clinical phase I–III, filed, approved, filed, discontinued, marketed) from official company websites, company financial documents, clinical trial registries, news releases, scientific publications. Other databases such as PharmCube were used for cross-checking. Assets noted on company websites but not publicly disclosed were excluded from the analysis owing to insufficient information being available.

Pipeline analysis

Having identified *in vivo* genomic medicine assets that are marketed or in clinical development, we categorized each product into four major segments based on the cargo type and underlying mechanisms of action. These segments were defined as follows:

- ***Gene addition/replacement***: enablement of a cell to express a new gene and/or replace a defective/missing gene; transduction is *in vivo*
- ***Gene expression control***: change in the gene expression by targeting product of transcription or translation (for example, siRNA or antisense oligonucleotide)
- ***Gene editing*****:** change of cellular DNA using site-specific, targeted nucleases (for example, CRISPR, zinc fingers, TALENs)
- ***DNA/RNA vaccines***: injection of genetically engineered DNA/RNA to produce an immunological response

The total number of *in vivo* genomic medicine assets in each segment is shown in Table S1. Example companies and products are shown in Table S2.

Table S1 | **Number of unique *in vivo* genomic medicine assets included in the analysis**

***In vivo* genomic medicine segment**	**Total**	**Marketed/filed**	**Phase III**	**Phase II**	**Phase I**
Total	**538**	**27**	**59**	**277**	**175**
Gene addition and replacement	223	8	23	137	55
Gene expression control	183	12	26	84	61
Gene editing	7	0	0	4	3
DNA and RNA vaccines	125	7	10	52	56

Table S2 | ***In vivo* genomic medicine segments with example companies and marketed products**

Asset segment	**Description**	**Example companies**	**Example products**
Gene addition and replacement	Enablement of a cell to express a new gene and/or replace a defective/missing gene; transduction is *in vivo*	Biomarin, Bluebird, Spark	Luxturna (2017), Zolgensma (2019)
Gene expression control	Change in the gene expression by targeting product of transcription or translation (e.g. siRNA, ASO)	Alnylam, Ionis	Spinraza (2016), Onpattro* (2018)
Gene editing	Change of cellular DNA using site-specific targeted nucleases (e.g. CRISPR, ZFNs, TALENs)	CRISPR Therapeutics, Editas, Intellia	No approved products to date
DNA and RNA vaccines	Injection of genetically engineered DNA/RNA to produce an immunological response	BioNTech, Moderna	Comirnaty* (2020), Spikevax* (2020)

*Delivered using lipid nanoparticle technology; source and composition of the LNPs shown in Table S6. ASO, antisense oligonucleotides; siRNA, small interfering RNA; TALENs, transcription activator-like effector nucleases; ZFNs, zinc finger nucleases;

LNP penetration

Having identified *in vivo* genomic medicine products, we next calculated LNP penetration, defined as the percentage of LNP-formulated assets in the overall *in vivo* genomic medicine pool, by assessing the formulation of each asset. LNP-formulated *in vivo* genomic medicine assets and overall LNP penetration in each segment are shown in Table S3. Table S4 lists unique LNP-formulated products by *in vivo* genomic medicine segment and stage of development.

Table S3 | **Number of unique LNP-formulated *in vivo* genomic medicine assets included in analysis**

Asset segment	Total	Marketed/filed	Phase III	Phase II	Phase I
Total	**40 (7%)**	**3**	**4**	**11**	**22**
Gene addition and replacement	8 (4%)	0	0	4	4
Gene expression control	5 (3%)	1	0	1	3
Gene editing	2 (29%)	0	0	1	1
DNA and RNA vaccines	25 (20%)	2	4	5	14

Table S4 | **List of LNP-formulated *in vivo* genomic medicine assets**

Asset segment	Marketed/ filed	Phase III	Phase II	Phase I
Gene addition and replacement	0	0	Reqorsa mRNA-4157 mRNA-3927 mRNA-3705	mRNA-2752 MRT5005 mRNA-6231 MEDI1191
Gene expression control	Onpattro	0	ND-L02-s0201	ALN-VSP NBF-006 INT-1B3
Gene editing	0	0	NTLA-2002	NTLA-2001
DNA and RNA vaccines	Comirnaty SpikeVax	ARCT-154 ARCoV CVnCoV mRNA-1647	ARCT-021 Covigenix VAX-001 DS-5670 PTX-COVID19-B mRNA-1893	BNT161 CV7202 ChulaCov19 mRNA Vaccine CoV2 SAM vaccine mRNA MRK-1172 mRNA MRK-1777 mRNA-1010 mRNA-1283 mRNA-1345 mRNA-1388 mRNA-1443 mRNA-1653 mRNA-1851 mRNA-5671

Market sizing (top-down forecast)
We estimated the overall market of each genomic medicine segment based on projected sales of drugs (sourced from EvaluatePharma, BCG analysis, and guidance from company earnings updates where relevant).

For 2021, the market for all LNP-enabled *in vivo* genomic medicines was worth $51.2 billion, based on sales of Onpattro, Comirnaty and Spikevax (Figure S1). Onpattro, an siRNA therapeutic designed to silence expression of *TTR*, is in the "Gene expression control" segment, while the COVID-19 mRNA vaccines, Comirnaty and SpikeVax, are in the "DNA and RNA vaccines" segment and were responsible for nearly all of the sales.

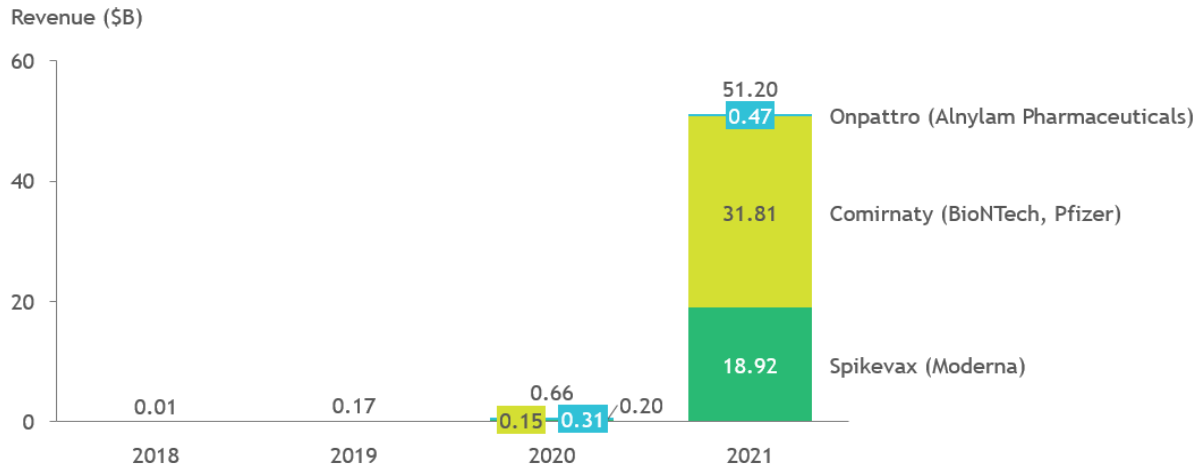

Figure S1 | **Market for LNP-enabled *in vivo* genomic medicines**.

For each segment, we applied a growth rate based on expected changes in addressable populations (that increase in incident rate) and BCG insights into market dynamics and LNP penetration over time. Estimations of the total market across the four genetic medicine segments are shown in Figure S2, and assumptions of LNP penetration from 2026–2036 are displayed in Table S5.

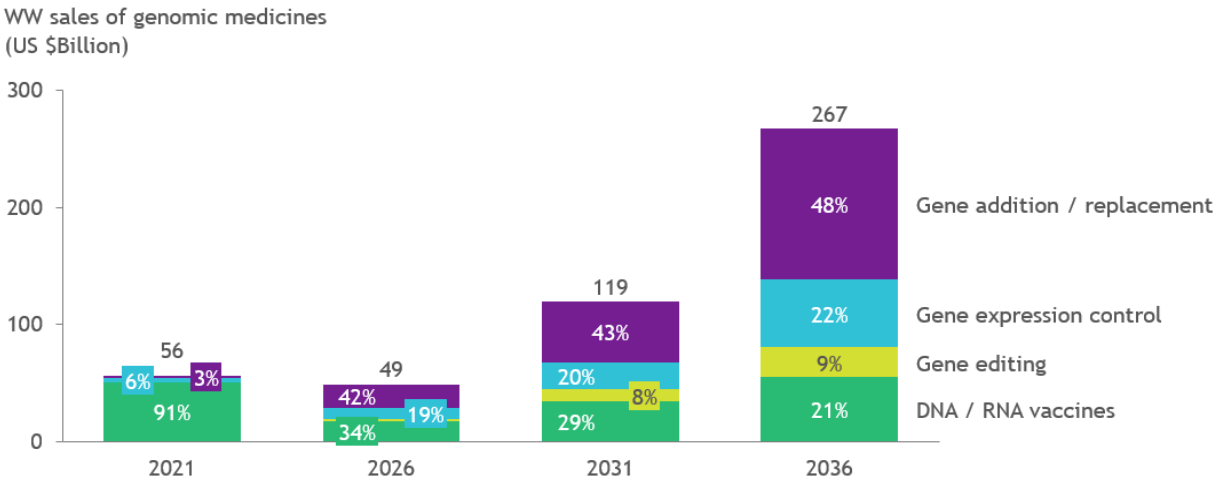

Figure S2 | **Forecasted market for *in vivo* genomic medicines overall (including LNP-enabled medicines).**

Table S5 | Estimates of LNP penetration across *in vivo* genomic medicine segments

Genomic medicine segment	**2026**	**2031**	**2036**
Gene addition and replacement	4%	7%	10%
Gene expression control	3%	5%	7%
Gene editing	29%	33%	37%
DNA and RNA vaccines	100%	40%	40%

Table S6 | **Source and composition of LNPs for marketed/filed assets**

Marketed/filed asset	**Company**	**LNP source**	**LNP composition**
Onpattro	Alnylam Pharmaceuticals	Licensed from Arbutus Biopharma	13.0 mg (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA), 3.3 mg 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1.6 mg α-(3'-{[1,2-di(myristyloxy)propanoxy] carbonylamino}propyl)-ω-methoxy, polyoxyethylene (PEG2000-C-DMG) 6.2 mg cholesterol USP
Comirnaty	BioNTech and Pfizer	Licensed from Acuitas Therapeutics	0.43 mg ALC-0315 = (4-hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate) 0.05 mg ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N ditetradecylacetamide 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 0.2 mg Cholesterol
Spikevax	Moderna	In-house	1.93 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC])