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Supplementary information

Evolution of the market for mRNA technology

In the format provided by the authors

Supplementary information | Details of the dataset and analysis approaches

Database assembly

We assembled a list of 180 pipeline assets from 31 companies (see table below), which represents all publicly available information we could gather by the end of July 2021 on commercially focused mRNA R&D activities. For each pipeline asset, we gathered the following information: company, drug name, stage of development (preclinical, clinical phase I, II, III, approved, discontinued), biological targets (mechanism of action), therapeutic area, detailed indications targeted, partnership. Each pipeline asset represents a unique product, which could target multiple indications. The list of pipelines and assets plus related information were sourced from the following places: 1. company official websites, and financial/earning updates; 2. Clinical trial registries: e.g., ClinicalTrials.gov, chictr.org.cn; 3. news releases, PubMed publications; 4. other databases used for cross-check purposes e.g., Evaluate Pharma. Only publicly disclosed mRNA pipeline assets that are actively in development were included in the analysis. Some companies may have more assets in development but these may not be publicly undisclosed, which we excluded from our analysis.

Number of pipeline assets included in analysis

Company	Total	Prophylactic vaccine	Therapeutic vaccine	Therapeutic
Moderna	**30**	15	2	13
BioNTech	**19**	5	7	7
Stemirna	**17**	5	9	3
CureVac	**12**	6	3	3
TranslateBio	**10**	4	0	6
Ziphius	**10**	10	0	0
Biorchestra	**9**	3	0	6
Arcturus	**9**	2	0	7
Lifanda Bio (Zhuhai)	**8**	3	1	4
BDGENE Therapeutics	**6**	1	1	4
RNAimmune	**5**	3	1	1
Ethris	**5**	3	0	2
RNACure	**5**	1	1	3
Longuide	**5**	4	1	0
eTheRNA	**4**	1	3	0
Rejuvenation Technologies	**4**	0	0	4
Versameb	**3**	0	0	3
Pantherna	**3**	0	0	3
pHion	**3**	0	3	0
Walvax / Abogen	**2**	2	0	0
ReCode Therapeutics	**2**	0	0	2
Globe Biotech	**1**	1	0	0
Biocad	**1**	1	0	0
CanSino	**1**	1	0	0
Daiichi	**1**	1	0	0
HelixNano	**1**	1	0	0
GlaxoSmithKline	**1**	1	0	0
GreenLight	**1**	1	0	0
20Med Therapeutics	**1**	0	0	1
HDT Bio	**1**	1	0	0
Total	**180**	**76**	**32**	**72**

Pipeline analysis

We categorized each product/pipeline candidate into prophylactic vaccine, therapeutic vaccine and therapeutics categories based on their underlying mechanisms of action. We further segmented them into subclasses:

- prophylactic vaccines were further segmented into COVID-19 and other infectious diseases
- therapeutic vaccines were further segmented either based on mechanism of action (single antigen e.g., KRAS, HPV E6/7 versus multiple antigens), or based on application: single cancer type focused versus multi-cancer type i.e. personalized cancer vaccine (PCV)
- therapeutics were further segmented based on the mechanism of action (antagonists, immune activators, protein replacement, gene editing machineries, other non-immune stimulators), or based on therapeutic area application (oncology, respiratory, rare genetic disorders, others)

Revenue forecasts

Representative pipeline selection. 15 major indications were selected for revenue forecasts across prophylactic vaccines, therapeutic vaccines and therapeutics. The 15 indications cover 75 pipeline assets (from preclinical to marketed), accounting for ~70% of total mRNA pipeline assets with clear disclosure of indications (Table S1). Then revenues of a single representative pipeline asset were assembled based on the forecasts for the indications it is targeting within these 15 indications. Revenues for the rest of pipeline assets (that were excluded from initial forecast) and additional pipeline assets expected to initiate in the next 15 years (beyond the current 180) were extrapolated based on the 15 indications and 75 pipeline assets estimated. Representative indications were selected in indications where we saw sufficient activity: 1) ≥2 clinical/commercial stage assets, or 2) 1 clinical/commercial asset but ≥1 preclinical stage assets; or 3) No clinical/commercial asset but >5 preclinical stage assets (e.g. influenza). A detailed list of selected representative pipelines and indications is provided in Table S1.

Table S1 | Representative indications forecasted in revenue model, and other major indications targeted

Disease-focused		**Clinical-stage assets**	**Preclinical assets**
Infectious disease prophylactic vaccine			
Forecasted	COVID-19	mRNA-1273, BNT162, Stemi-LNP, Abogen-Covid19, ARCT-021	17
	Influenza	No	12
	Rabies prophylaxis	CV-7202, GSK 3903133A	2
	Respiratory syncytial virus (RSV) infections	mRNA-1345, mRNA-1172	1
Others	Chikungunya virus	mRNA-1944	0
	Metapneumovirus infections; parainfluenza virus infections	mRNA-1653	0
	Cytomegalovirus infections	mRNA-1647	0
	Zika	mRNA-1893	0
	Epstein-Barr virus infections	No	1
	Hand-foot-mouth disease	No	1
	Herpes simplex viruses	No	2
	VZV	No	1
	HIV	No	3
	Tuberculosis	No	2
	Nipah	No	1
	Lassa, yellow fever	No	1
	Human papilloma virus	No	1

Therapeutic vaccine: indication-specific

Forecasted	KRAS-mutated cancers of the lung, colorectum and pancreas	mRNA-5671	2
	HPV OPSCC	BNT-113	3
	NSCLC	CV-9202	1
	metastatic castration-resistant prostate cancer (mCRPC)	BNT-112	1
Others	Ovarian	BNT-115	0
	TNBC	BNT-114	0
	Melanoma	BNT-111	0
	Acute myeloid leukaemia	No	1
	Kidney cancer	No	1

Therapeutic vaccine: basket

Forecasted	Solid tumours	mRNA-4157, BNT-122	3

Therapeutic

Forecasted: oncology	Melanoma	CV8102, BNT-131, MEDI 1191	1
	SCCHN	CV8102	1
	Lymphoma	mRNA-2752, mRNA-2416	1
Forecasted: rare	Ornithine transcarbamylase deficiency	LUNAR-OTC (ARCT-810)	1
Forecasted: respiratory	Cystic fibrosis	LUNAR-CF, MRT-5005	3
Forecasted: others	Myocardial ischaemia	AZD-8601	1
Others: rare	Methylmalonic acidaemia	No	1
	Phenylketonuria (PKU)	No	1
	Amyotrophic lateral sclerosis	No	2
	Autoimmune hepatitis	No	1
	Fabry disease	No	1
	Glycogen storage disease type I	No	1
	Glycogen storage disease type III	No	1
	Propionic acidemia	No	1
Others: respiratory	Idiopathic pulmonary fibrosis	No	2
	Primary ciliary dyskinesia	No	3
	Pulmonary alveolar proteinosis	No	1
	Pulmonary arterial hypertension	No	2

Launch timeline. We assigned an expected launch year for each pipeline based on its phase and industry average years to next stage as shown in Table S2. We also assigned a distribution of likelihood for early or late launches, based on Table S2.

Table S2 | Assumptions on launch year distribution corresponding to current stage of pipelines

Years to approval	Preclinical	Phase I	Phase II	Phase III	% of total
Accelerated	1	1	1	2	20%
Normal	2	2	2	2	60%
Delayed	3	2	2	3	20%

Expected launch year by current phase	Preclinical	Phase I	Phase II	Phase III
Accelerated	2026	2025	2024	2023
Normal	2029	2027	2025	2023
Delayed	2031	2028	2026	2024

Sales forecast for non-COVID-19 assets

We applied a top-down and a bottom-up approach as described below. Essentially, the top-down approach served as a check that we would not wildly overestimate the market by assuming too high probabilities of success and unrealistically high shares for mRNA assets amongst all available modalities for the various indications.

1. Bottom-up forecast

Representative pipeline unadjusted sales forecast. We based our forecasts on the US market first for the representative pipelines, where data is usually easiest to obtain. For each indication, we estimated peak sales based on the following dimensions for the US market, and then applied a ramp-up curve. The assumptions of the following dimensions are specific to each indication.

- Targeted population of the drug (addressable population)
- Penetration of treatment
- Share of mRNA among other modalities
- Pricing of mRNA therapies (we benchmarked existing innovative therapies)

We then extrapolated our forecasts from the US to worldwide sales using the following dimensions:

- Typical delay in launch time for ex-US markets (for example, lag time in Asian markets can range from none to several years)
- Price discount from US
- Penetration discount from US
- Population differences

Probability of success. We referenced baseline probabilities of success for different phases and indications based on prior publications (REF. 1, lead indication industry average 2000–2015 for clinical probabilities of success and REF. 2 for preclinical probabilities of success). We further adjusted the probability of success based on the current proof of technology, scientific mechanism of action and technical readiness to address challenges presented in the class (Table S3).

Table S3 | Probability of success assumptions[1,2]

		Preclinical	Phase I	Phase II	Phase III
Prophylactic vaccine	Infection	10%	32%	40%	85%
Therapeutic vaccine	Cancer: therapeutic vaccine	5%	8%	10%	40%
Therapeutics	Cancer treatment	5%	8%	10%	40%
	Genetic/rare disease	8%	22%	29%	70%
	Respiratory	5%	8%	10%	40%

1. Wong, C. H., Siah, K. W. & Lo, A. W. Estimation of clinical trial success rates and related parameters. *Biostatistics* **20**, 273–286 (2019).
2. Takebe, T., Imai, R. & Ono, S. The current status of drug discovery and development as originated in United States academia: the influence of industrial and academic collaboration on drug discovery and development. *Clin. Transl. Sci.* **11**, 597–606 (2018).

Risk adjustment for each asset revenue curve and assembly of the total forecast. We further adjusted the bottom-up sales curve for each asset according to their clinical development risks (Table S3). For example, a preclinical therapeutic cancer vaccine asset has a 5% probability of getting approved, and thus the expected revenue after launch year (Table S2) will be 5% of its unadjusted revenue. We then added up all assets in the same category (i.e., prophylactic vaccines, therapeutic vaccines and therapeutics) to get to the total risk-adjusted sales of each category through 2035. The bottom-up approach was cross checked further with top-down estimates.

2. Top-down forecast

We estimated the market of each representative indication based on the overall sales of drugs targeting the indication. The growth was estimated based on expected changes in addressable populations (i.e. increase in incidence rate) and BCG insights into the market dynamics. We estimated the share of mRNA assets amongst other modalities.

Sales forecast for COVID-19 vaccines

The market size for COVID-19 mRNA vaccines was estimated separately, also using a bottom-up approach and a top-down approach. However, given the highly dynamic nature of the market for COVID-19 vaccines, these estimates are even more challenging to make than market forecasts in other areas. Although it seems clear that COVID-19 vaccines will account for the majority of the sales for mRNA-based products in the next few years, the extent to which their sales persist is highly uncertain, and this is reflected in our focus on applications beyond COVID-19.

1. Bottom-up forecast

We estimated the number of people who will be newly vaccinated for COVID-19, and getting boosters from 2021 to 2035, for both developed countries and developing countries. We also assumed a price drop of ~25% after 2025. We also accounted for government purchases and donations to developing countries, and higher penetration of new/first time vaccinations in developing countries between 2022–2024. We accounted for the situation that due to the emerging variants, booster shots will likely have high penetration in the short term, while in the long term (after 2027), the market will shrink due to control of the COVID-19 situation and lowered price of shots (and possibly the introduction of a multi-variant vaccine, as seen with pneumococcal vaccines).

2. Top-down forecast

We referenced Moderna and BioNTech/Pfizer's 2021 Q2 earnings updates where they discussed their forecasted doses and COVID-19 vaccine revenue for 2021–2022. We also estimated the share of mRNA vaccine from 2021–2035 over other modalities based on progress on other modalities' historical sales, clinical profiles and development status.

Table S4 | Summary of opportunities and challenges of mRNA in three applications

	Prophylactic vaccine	Therapeutic vaccine	Therapeutics
	Cornerstone application and revenue source	*Promising niche space for mRNA*	*Opportunistic focus with potential in long-term*
mRNA mechanism of action	mRNA encodes antigen that simulates adaptive immune system against pathogens	mRNA encodes antigen of the abnormal cells (i.e. tumor cells) to stimulate immune system against abnormal cells	mRNA encodes missing/defective protein for therapeutic purpose, or immune cell engagement, or machineries to perform therapeutic functions
Therapeutic areas	Infectious disease	Oncology	Rare genetic disease, oncology, respiratory, others (immunology, cardiovascular)
Examples	○ COVID-19 ○ RSV, CMV, influenza, HPV, HMPV/PIV3	○ Personalized cancer vaccine (PCV) ○ KRAS-mutated lung/colorectal cancer	○ Cystic fibrosis ○ OX40L in ovarian cancer ○ Bispecific T-cell engager ○ CRISPR/Cas9 gene editing machineries
Supply of pipelines	○ 42% of all mRNA pipelines ○ Most mature with marketed products in COVID-19 and 12 clinical-stage assets	○ 18% of mRNA pipelines but likely to boost in multi-TAA TxV (e.g. PCV) upon clinical POC ○ 10 clinical-stage pipeline assets	○ 40% all mRNA pipelines, but scattered in multiple therapeutic areas ○ 9 clinical-stage assets across 5 major therapeutic areas
mRNA advantages over other modalities	○ Clear advantages in protection rate (i.e. COVID-19), speed of R&D ○ Faces challenges in safety, CMC, transportation and cost of manufacturing	○ Advantages in multi-TAA TxV, while faces competition from VLP/peptide for single antigen	Unclear advantages over other modalities: ○ Protein replacement: major competition from gene therapy, lag in phase and lack of sustainability; also faces competition from existing/traditional recombinant products ○ Immune stimulators/other stimulators: major competition from mAbs, mRNA can encode and express ligand more easily ○ Gene editing machineries: competition from gene therapy, likely advantage in safety, disadvantage in sustainability; both faces challenges in organ targeting, immunogenicity etc.
Commercial opportunities	○ Large targeted population but with severe competition from established products and other modalities; pricing pressure is high	○ Significant commercial opportunity if clinically successful: Large population as early line treatment, significant pricing power and low competition from other modalities; yet faces challenges for CMC and commercialization model for PCV	○ Scattered indications, each with smaller and more targeted population with significant pricing power if clinically superior; faces competition from other modalities e.g. gene therapy, mAbs, bispecific antibodies, recombinant products
Clinical risks	○ Clinical risks in demonstrating protection rate across multiple-variants, safety issues in large population, but overall lowest clinical risk amongst the 3 applications given proof in COVID-19	○ High, given likely clinical strategy for earlier line patients in combo use, which potentially needs long-follow up and head-to-head comparison to I/O in pivotal trials	○ High, lack of understanding and high failure rate in I/O stimulators, organ delivery issues for generic diseases, immunogenicity issues for high dose, immature technology of gene editing as in vivo therapeutics