The Maturation of mRNA: Will Moderna and BioNTech Ever Be More Than Viral Sensations?

Their vaccines helped beat back a global pandemic, shattering pharmaceutical sales records in the process. Now comes the hard part.

August 2022

Key Takeaways

- The US$38-40 billion in revenues that Moderna and BioNTech each expect to generate from the start of 2021 through 2022 likely represents their commercial high-water mark. It will also leave each with close to US$20 billion with which to develop new drugs.
- As COVID-19 becomes endemic, each company's ongoing COVID revenues could amount to roughly US$5 billion a year. Both will seek to shore up this base through new bivalent shots.
- At this point, Moderna and BioNTech face little competition in messenger RNA (mRNA), thanks to their co-exclusive license to a key aspect of the technology and their years of know-how in mastering mRNA's many idiosyncrasies.
- While there is obvious overlap between their markets, Moderna and BioNTech are charting very different paths going forward.
- In BioNTech's main area of focus—cancer—rewards are high, odds of success low, and the company's early results only so-so. Still, the adaptability of its technology offers a high degree of promise.

What Moderna and BioNTech have accomplished since the outbreak of COVID-19 in late 2019 is astounding. In less than a year, the two fledgling biotech firms harnessed an unproven, oft-dismissed technology to create a safe and highly effective vaccine. Since then, about 5 billion doses have been produced, preventing tens of millions of deaths and allowing people and businesses worldwide to return to a semblance of normalcy. As the capstone to decades of research in genetics, immunology, nanotechnology, and artificial intelligence, their mRNA-based COVID vaccines are perhaps the singular biomedical achievement of our time, as well as record-shattering commercial successes. Yet, their success begets the question: once you have produced the highest-selling drug in history, how do you top it?

The short answer is you probably cannot. "There is a good chance these companies never end up generating US$19 to US$20 billion dollars a year in revenue ever again,"[1] says David Glickman, a Health Care analyst at Harding Loevner. The companies' combined market cap, which crested at more than US$300 billion in November 2021, has since fallen by almost two-thirds. "I think a lot of investors who don't ordinally invest in biopharma assumed the companies would keep selling billions of boosters forever and translate their technology to other areas like HIV and cancer just as fast, notwithstanding the unprecedented measures undertaken by governments to fast-track approvals and production to battle a global pandemic," says Glickman. "Neither assumption, it turns out, was very realistic."

> "Setting aside for a moment the impossible bar they set for themselves," says David Glickman, a Health Care analyst at Harding Loevner, "any other biotech company would like to be in their spot."

There are two ways of looking at the position Moderna and BioNTech find themselves in. On one hand, their best years are probably already behind them; on another, they are still relatively early-stage firms with proven advantages in a powerful new biomedical modality and close to US$20 billion each with which to develop promising drug candidates.

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Shoring up the Base

So, what does the growth opportunity for Moderna and BioNTech look like even if they never outgrow their 2021-22 COVID-19 profits? The answer depends in part on how fast and how far their COVID vaccine businesses decline as the disease becomes endemic. "I have to remind people that 'endemic' doesn't mean 'disappear,'" says Glickman. Although COVID has defied prior predictions, scientists see parallels between how it is behaving and the paths followed by the strain of influenza behind the 1918 Spanish Flu, whose descendants even today account for almost all cases of influenza A.[2] There are of course many other factors beyond the virus's evolutionary success that make forecasting the companies' COVID-related revenues challenging, such as how fast the virus's mutations occur, whether transmissibility continues to rise, whether average symptoms moderate more or restrengthen, the rate of hospitalization and death among the unvaccinated, and how all those unknowns interact with antivaxxer sentiment and pandemic fatigue.

Reflecting the uncertainty around such forecasting, Glickman has modeled several scenarios. In the one he regards as most likely, he assumes a modest, but still-sizable, portion of the developed world's population, including most of the elderly and most people with underlying conditions, get yearly boosters well past the middle of this decade. By his estimate, that results in revenues of about US$5.5 billion each for Moderna and BioNTech from 2025 through 2031. He has also created a "bull" scenario for the vaccines (which can be thought of as a bearish scenario for humanity) by raising forecast revenues by a few billion and a "bear" (for the vaccines) scenario lowering them by a similar amount. "The point is, at a minimum you're still looking at revenues of over a billion dollars a year, and more likely four or five times that, which even at the companies' current healthy rate of investment would more than cover total operating expenses including R&D," says Glickman.

The companies are taking steps to inject some more predictability into their COVID-19 franchises. One is keeping COVID vaccine efficacy rates high. Both are testing bivalent vaccines that specifically target the Omicron variant while also providing an enhanced antibody response to the ancestral strain. Another effort is developing a pan-COVID vaccine offering an enhanced T-cell response to a broader spectrum of mutations. In what may turn out to be the first approved application of mRNA technology beyond COVID, they are also working on mRNA vaccines against the flu, which have the potential to be combined with COVID protection in an mRNA seasonal "two-fer," providing a level of convenience for patients and cost savings for insurers that could improve the take-up rates for their COVID shots.

Moderna has been especially aggressive in its pursuit of a combined COVID-flu shot. A limitation on the effectiveness of traditional flu vaccines is that current methods require manufacturers to start production in the spring based on the strains in circulation on the opposite side of the globe. Leveraging the flexibility and speed of mRNA production technology, Moderna says it would be able to wait until closer to the start of flu season to design its formulation and could potentially even tweak its flu and COVID-19 shots intra-season. Moderna envisions countries contracting for the shots on a flat-fee yearly subscription basis, protecting its revenues in years when COVID infections and uptake are low while ensuring supply during higher-infection years.

A problem is the preliminary results for Moderna's flu shot were not spectacular. In phase 1 trials, the vaccine produced levels of flu titers, a marker of immunity, that were about the same as for Sanofi's Fluzone, the high-dose vaccine that is the most effective flu product on the market. The side effects for Moderna's shot, however, were slightly worse—more akin to the aches, chills, and low-grade fever that often accompany Moderna's COVID-19 vaccine than the sore arm typically caused by a flu shot.

> Moderna's thinking on its potential seasonal mRNA two-fer seems to be that if the effectiveness is at least as good as the best currently available flu shot and the side effects are no worse than for the COVID-19 vaccine alone, it might still have a winner.

The company is trying different formulations to reduce the side effects and has begun clinical testing of a combined flu and COVID-19 vaccine. Its thinking seems to be that if the effectiveness is at least as good as the best currently available flu product and the side effects are no worse than for the COVID vaccine alone, it might still have a winner.

"While I think Moderna needs to get the side effects under control, I can't really argue with the strategy," says Glickman. But he also finds it interesting that the side effects have been so difficult to bring under control. The antigens in the mRNA shot that cause the body's immune system to ready its defenses against the flu are essentially the same as the antigens in the traditional flu vaccine, so why would the side effects be more severe? Glickman speculates it may be due to just how differently mRNA vaccines work from a traditional vaccine. In standard vaccine production, genetic material from the targeted pathogen is combined in the factory with a stable cell culture such as bacteria or hamster cells to churn out specific virus proteins, which are then injected to stimulate an immune response in the recipient. In an mRNA vaccine, the production of those proteins occurs inside the patient's body. Perhaps recruiting the recipient's own cells to produce these proteins will always result in more of a wallop in terms of side effects.

Genesis of Edge

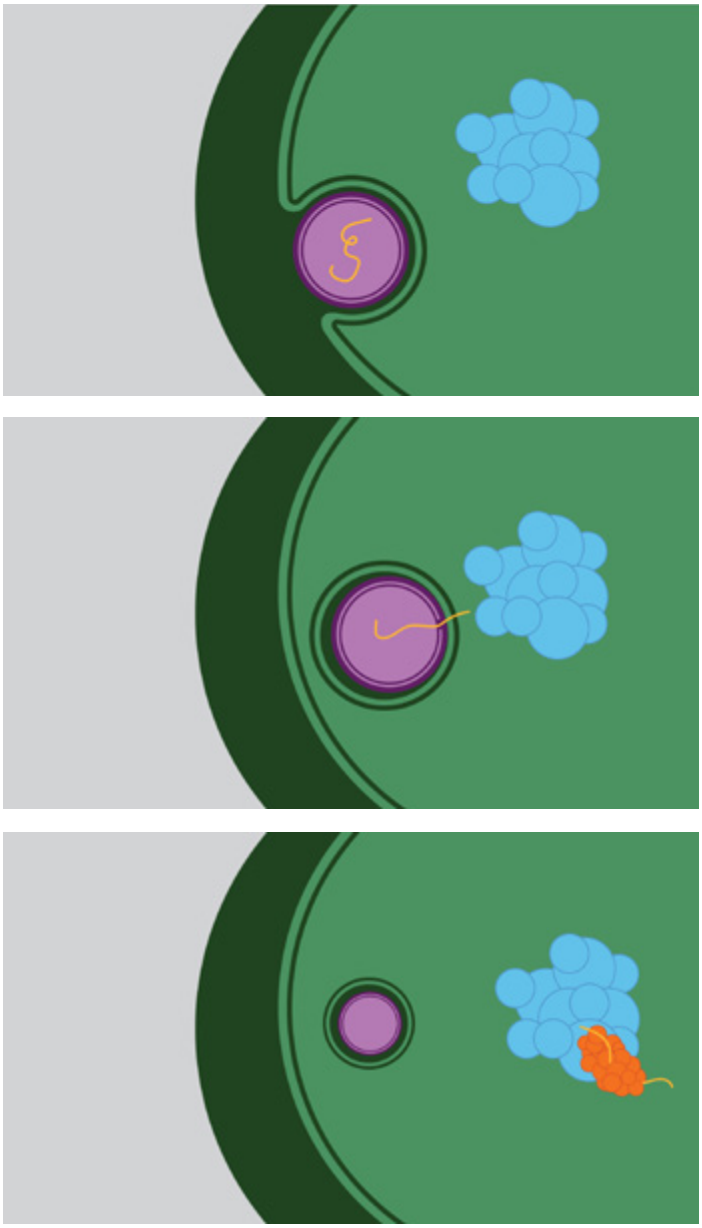
There is one factor working strongly in favor of Moderna and BioNTech's future revenue trajectory. "It's hard to overemphasize just how radically different and powerful the mRNA technology is," Glickman says, "And at this point, they largely have the field to themselves." To understand how that came about, you must appreciate how challenging it has been to master the power of mRNA to harness the body's own disease-fighting machinery. What makes mRNA such an attractive technology also makes it difficult to work with. Unlike gene therapy techniques used to manipulate DNA, which operate on a cell's nucleus and imprint changes in the body forever, mRNA operates in the cell's watery outer layer, or cytoplasm. Once a strand of mRNA—be it a strand naturally formed in the nucleus and traversing the short distance to the cytoplasm, or a synthetic strand designed to enter the cell from the outside—delivers its genetic code, the strand breaks apart and dissolves harmlessly. But its impermanence means mRNA is incredibly fragile. For years, researchers struggled to keep synthetic mRNA intact long enough to enter the cell, eventually hitting on a method of encapsulating their strands in tiny blobs of fat called "lipid nanoparticles." Even then, the immunogenic response *within* each cell had a vexing habit of destroying the mRNA before it could transmit its instructions to the cell's protein-making apparatus.

A big breakthrough came in 2005, when a pair of scientists at the University of Pennsylvania realized that naturally occurring mRNA avoids being degraded too fast by disguising itself, swapping one of its nucleotides (its basic structural units) with a different one. When the researchers applied the same disguise to their synthetic strands, the results were dramatic: the synthetic mRNA was allowed to convey its instructions fully, where they needed to go.

> When other firms say that they are using "modified mRNA," they may have figured out another way to extend the half-life of their drug candidates, says Glickman, but "it's not the same technique licensed by Moderna and BioNTech that could one day earn its discoverers the Nobel Prize."

Today, Moderna and BioNTech are the co-exclusive licensors of the UPenn technology, for which each paid a total of about US$75 million in licensing fees between 2017 and 2019.[3] They will each shell out about another US$660 million in royalties across 2021 and 2022. When other firms say that they are using "modified mRNA," they may have figured out another way to extend the half-life of their drug candidates, says Glickman, but "it's not the same technique that could one day end up earning its discoverers the Nobel Prize."

Moderna and BioNTech's advantages don't end with the UPenn technology. Once a drug compound is discovered and delivery vehicle settled upon, the formulation of that package is not usually a differentiator. But in the case of ever-voluble mRNA, *how* the mRNA and its packaging are prepared is also a key determinant of success. The structure of the lipid, the ratio of mRNA to lipid, and the temperature and speed at which they're mixed together in the formulation are all pivotal in determining whether each parcel is the exact right size with the precise electrical charge that will allow it to secure admission without spilling its cargo outside the cell.



mRNA in Action: Synthetic mRNA (yellow strand) shown entering the cytoplasm encased in its lipid nanoparticle and having its genetic code translated by the cell's ribosomes (blue structures), which then use those instructions to produce the desired proteins (depicted in orange).

Moderna and BioNTech's intellectual property (IP) advantages—both their exclusive access to UPenn's patented technology and the know-how they have amassed over a decade of cooking up mRNA-carrying fat balls—shape the competitive landscape. The other companies pursuing mRNA COVID-19 vaccines have struggled: Sanofi abandoned its effort last fall; a handful of Chinese firms are still in phase 1 or 2 trials; and a third reported preliminary phase 3 results that indicate more antibody protection than a traditional virus vaccine but with significantly less effectiveness than Moderna and BioNTech's shots.

An August 2022 lawsuit by Moderna against BioNTech alleging infringement over certain aspects of its IP, meanwhile, suggests the period of relative peace between the two might be coming to an end as the technology moves into its next phase.

Pipelines in the Sand

Given their shared history of successfully developing COVID-19 vaccines, Moderna and BioNTech will forever be linked, but in terms of strategy moving forward, they are charting very different paths.

At its core, Moderna is an mRNA platform company that is agnostic about which diseases it takes on. Among the drugs it has in clinical trials are vaccines for HIV, Zika, Epstein-Barr, RSV (a source of severe illness in children and seniors), and CMV, a pathogen that is a leading cause of birth defects. In November, the company published positive phase 2 trial data on a therapy for heart failure that uses mRNA to stimulate the regeneration of heart tissue. Future treatments include stimulating cartilage growth to ease arthritis and collagen production to smooth out wrinkles.

BioNTech, in contrast, is primarily an oncology company; it utilizes mRNA as its main, but not exclusive, platform for cancer drugs. While the company is flexible about using the technology outside oncology (including a promising multiple sclerosis treatment), 14 of its 21 mRNA trials are focused on common and deadly cancers.

An audacious possibility being pursued by both BioNTech and Moderna is a personalized mRNA cancer vaccine. Scientists have long known the immune system can destroy cancer cells under certain circumstances. Cancer cells, however, have an ability to elude detection because sometimes their antigens are difficult for an individual's immune system to recognize naturally. Researchers have found ways to stimulate the immune system to better target cancer cells more generally; BioNTech aims to improve the effectiveness of those therapies by priming the immune system to target and eliminate cancer cells expressing the antigens specific to each patient's cancer.

This degree of customization is only made possible by the adaptability of mRNA technology and the speed with which it allows therapies to be created. As BioNTech and Moderna showed in the early stages of the race for the COVID-19 vaccine, once you know what protein you're targeting it takes almost no time to design a new mRNA drug. Forty-eight hours after the genetic sequence of the coronavirus was published online, Moderna had assembled the mRNA that would become the core of its vaccine. BioNTech's turnaround was even faster: just 24 hours to produce eight different prototypes. Six weeks later, both companies had vaccine formulations ready to move into clinical trials.

BioNTech has set itself a similar schedule for cancer patients. The company has said it will biopsy a tumor, sequence the genetic mutations behind it, develop the corresponding mRNA therapy, and have a drug ready for injection within about six weeks.

> In pursuit of its personalized mRNA cancer immunotherapy treatment, BioNTech will effectively seek to match its unprecedented turnaround time in the race for a COVID-19 vaccine and duplicate that for *every individual cancer patient*.

The quest, in other words, is to produce a bespoke vaccine for *every individual cancer patient*. Will it succeed? In June 2020, the company reported data from a phase 1 trial conducted in conjunction with Roche on patients who had failed previous therapies. The data were disappointing in terms of the drug's ability to shrink the patients' tumors. However, the immune response as measured by T-cell levels was high enough that the company has since moved on to phase 2 on two patient groups: one previously untreated, and one in which tumors have been surgically removed but cancer cells are still circulating in the bloodstream. A small separate phase 1 trial specifically on pancreatic cancer in which the mRNA treatment was administered in combination with conventional drug therapies showed a noticeable immune response and longer recurrence-free survival in half the treated patients.

Modeling the growth prospects of any early- to mid-stage biopharma company, even one whose most-successful established market isn't subject to as many variables and unknowns as COVID-19, is a little like constructing a house on shifting sand, the forecasts rising and falling with each encouraging or disappointing round of clinical trial results. That is why Glickman generally refrains from trying to assess every variable that might affect future revenues and profits and focuses instead on the key elements of Harding Loevner's process for identifying high-quality, growing businesses. "We always come back to four factors," he says. "Does the company have skilled management making smart capital allocation decisions in areas where they have a demonstrated edge? Is the business profitable and its balance sheet strong? Does it have a sustainable competitive advantage? And can it achieve growth?"

Glickman says he is confident Moderna and BioNTech pass the first three of those tests. As he has drilled down on BioNTech, he is especially encouraged by its potential to allocate capital to improve the usual long odds any new cancer drug faces in winning approval. "Some of the phase 1 results on the individualized cancer vaccines weren't earth-shattering," he says. "But if the problem was that another, or more focused, set of proteins is a better target, you can swap out the mRNA to make the antigen for it fairly easily. That's different than something like a small molecule drug, where you're much more locked in. Either it works or it doesn't. Plus, the more data BioNTech gathers, the more the artificial intelligence the company uses to determine which types of proteins to target should get smarter. That should help it to keep tweaking its drugs over time. So, as the company moves onto later trials, or even after a product is potentially approved, the results should keep getting better."

As for revenue growth, Glickman says it will be many years, if ever, before BioNTech and Moderna regain their high-water marks of 2021–22 but, as their new treatments start contributing, he does expect their sales to increase toward the end of this decade. In the case of BioNTech, he has taken the several billion in recurring annual revenue he expects from COVID-19 and penciled in another 5% to 40% each year from cancer treatments depending on how many of its initiatives eventually find success. Even at the high end the resulting revenues are still a far cry from the US$17 billion that the company is expected to receive in 2022, but it's also a level that most biotech companies its age "would be perfectly happy with," says Glickman.

And those high-end estimates, he says, are still conservative, tempered by the large number of unknowns at this juncture; a few clinical trials that demonstrate mRNA's efficacy against different cancers could lift his forecasts considerably. That's the thing about biomedical research. While the sands keep shifting, some foundations do stick. There's no guarantee that BioNTech and Moderna will find more breakout successes in their areas of exploration but, Glickman suggests, they both have a shot.

Contributors

Analyst David Glickman, CFA contributed research and viewpoints to this piece. Research Associate Lydia Yuan also contributed research.

Endnotes

1 The US$38 billion in revenues BioNTech will earn across 2021 and 2022 represents its half of the US$76 billion in total revenues earned by the company and Pfizer, its manufacturing and distribution partner for its COVID-19 vaccine. Moderna, which has shipped roughly half the number of vaccines as Pfizer-BioNTech, will earn revenues of about US$40 billion over the same period.

2 "The Coronavirus Is Here to Stay—Here's What that Means," *Nature* (February 16, 2021).

3 Technically, the mRNA modification technique developed by UPenn's Katalin Karikó (who left the university in 2013 to work for BioNTech) and Drew Weissman, was sub-licensed by Cellscript, a small Wisconsin-based RNA research firm that had previously licensed the technology from UPenn to make research kits. Neither Cellscript nor UPenn has ever disclosed the terms of their split of the licensing fees and royalties from BioNTech and Moderna. Whatever it is, the combined US$1.3 billion or so in royalties they are receiving in 2021–22 doesn't include Pfizer's share—that pushes the figure to about US$2.0 billion.

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