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Moderna (A)

We're a technology company that happens to do biology.

— Stéphane Bancel, CEO, Moderna

Noubar Afeyan, CEO of Flagship Pioneering (Flagship) and Moderna co-founder and chairman, and Moderna CEO Stéphane Bancel (MBA 2000), took a quick break between interviews with CNN and CNBC. It was late July 2020, and Moderna had just announced that their vaccine candidate for the novel coronavirus (COVID-19) had entered Phase 3 clinical trials in the U.S., signaling that the much-anticipated drug was only one step away from commercialization.[1]

Based in Cambridge, Massachusetts, Moderna was a biotechnology (biotech) company with an innovative platform approach to mRNA science. The last few months had seen an unprecedented acceleration of biological work around COVID-19 at Moderna. Bancel had read about the new infectious agent in early January that was causing a pneumonia like disease in early January, and emailed National Institute of Allergy and Infectious Diseases (NIAID) Director Dr. Anthony Fauci's team at the National Institutes of Health (NIH). Bancel said, "The day after, we learned it was not the flu, not bacteria. A day later, we learned it was a coronavirus, but not SARS or MERS."[a] Early in the second week of January, Chinese scientists in Wuhan announced they had isolated and fully sequenced the virus, setting off calls for full release of the details. On January 11, the gene sequencing data was posted on Virological.org.[b]

Two days later, January 13, using the genetic sequence posted online, the Moderna team finalized the design of a corona vaccine candidate against this new virus. By February 7, Moderna's engineers made a Phase 1 clinical study vaccine, and on February 24, after passing quality control testing, they shipped it to the NIH in preparation for preliminary tests (Phase 1 clinical study) in volunteers in

[a] SARS = Severe Acute Respiratory Syndrome; MERS = Middle East Respiratory Syndrome.

[b] Virological.org was a hub for prepublication data designed to assist with public health activities and research.

HBS Professors Marco Iansiti and Karim R. Lakhani, Post-Doctoral Fellow Hannah Mayer (University of St. Gallen), and Director Kerry Herman (Case Research & Writing Group) prepared this case. It was reviewed and approved before publication by a company designate. Funding for the development of this case was provided by Harvard Business School and not by the company. Professor Lakhani has been a paid key opinion leader for the company. HBS cases are developed solely as the basis for class discussion. Cases are not intended to serve as endorsements, sources of primary data, or illustrations of effective or ineffective management.

Seattle, Washington. Bancel said, "We did all this in two months. The fastest time anyone had done this before was 20 months, with SARS. It was a 90% reduction in time."

In some respects, Moderna's response to the crisis of the pandemic had been business as usual. After all, the company was organized to respond to health challenges like COVID-19. Founded in 2010 and designed from the ground up as a digital biotech company with a factory for in-house manufacturing capabilities, Moderna looked different from most biotechs. Yet despite $5.1 billion raised in funding, (of which $750 million came from several key strategic partners) and its innovative approach, Moderna had yet to bring a drug or vaccine to market.

In February, when the reality of the pandemic hit, Moderna pursued its COVID vaccine development within its existing organizational structure, and ran in parallel to its other drug development activities. All of its plans and investments over the past ten years—including a manufacturing facility opened in Norwood, Massachusetts, in July 2018—had situated the firm in a sweet spot to carry out rapid research, drug development, clinical trials and manufacturing.

Now, after a long day of virtual interviews with some of the nation's biggest news outlets, Afeyan and Bancel considered the next frontier for Moderna. As the vaccine headed into Phase 3 trials, and they looked to the reality of possibly distributing a vaccine to billions around the world, they considered the impact their efforts had on Moderna as an organization. Moderna's digital environment meant they continuously learned from every step on the production chain. But making enough vaccine for billions could transform the organization dramatically. The unprecedented scale of the challenge could swamp the organization and overshadow Moderna's other pipeline candidates. Further, was there risk in becoming branded a COVID company? Bancel noted, "We have seven vaccines in development, all of which could provide important medicines, as no vaccines exist against any of these viruses." He added, "How do we position ourselves outside of this? Should we do something orthogonal? What about our other vaccines?" Should Moderna set up a separate organization dedicated to COVID-19 vaccine development?

Traditional Vaccines and Drugs

Vaccines of all types aimed to expose the body to an antigen that might not cause the disease but could lead to an immune response to block or kill the virus once a person was infected. But the exact approaches to achieving this effect varied. Traditional pharmaceutical (pharma) companies typically worked on virus vaccines, injecting a weakened or inactivated form of the virus into the human body. Viruses typically caused diseases by reproducing thousands of times once in the human body. When weakened viruses were injected in the human body, they reproduced fewer than 20 times; because of their limited ability to reproduce, the disease did not break out, yet the low level of viral replication was enough to trigger the body to generate antibodies that would protect the vaccinated individual against that same strain of viral infection in the future. Vaccines for diseases such as chickenpox, measles, and polio all followed this approach. Proven to reduce disease, disability, death and inequity worldwide,[2] few medical interventions could compete with vaccines for their cumulative impact on public health and well-being of entire populations. Immunization efforts had eradicated smallpox globally, and eliminated measles, polio, and rubella from the Americas.[3]

An alternative to a weakened virus was to inject altogether inactivated viruses, which could not reproduce at all or cause the disease. Because the immune system still perceived that a virus had entered the body, it generated antibodies to protect against this interloper. While this type of vaccine typically required multiple doses to achieve immunity, its advantage lay in not subjecting the recipient

to even a mild form of the disease; it could thus be given to people with weakened immune systems. This approach had been used, among others, in Hepatitis A and rabies vaccines.[4]

Vaccine and Drug Development

Big pharma players, including industry leaders Johnson & Johnson, Merck, Pfizer and Roche, generally relied on traditional approaches to develop drugs, including vaccines. Traditional vaccine development typically began with research endeavors in university labs, medical science centers or smaller biotech firms, relied on years of research and were usually funded by government grants or private foundations.[5] This initial period of discovery was largely dedicated to isolating a pathogen and reducing its potency or inactivating it for use in a possible vaccine. These potential vaccines would eventually make it through the research phase, be tested on small animals, such as mice or rabbits, followed by larger animals like pigs or monkeys. Such preclinical testing helped to understand how the vaccine worked and how it might affect the human body.[6] (See **Exhibit 1**.)

During these periods of drug research with parallel pre-clinical (i.e., animal testing) efforts, multiple groups around the world could be working on similar ideas, including the development of vaccines against a virus or bacteria. Researchers conveyed progress through presentations at science conferences or peer-reviewed journal articles. Big pharma companies stayed close to such developments. Scientists working at pharma companies often came in only at this stage, attending such conferences and reading journal articles to get an overview of the most promising candidates. (See **Exhibit 2** for an overview of the top pharma companies.) When convinced of the idea's success and commercial viability, pharma representatives partnered with scientists to expand their research toward product development. This process could take up to 10 years, and many of ideas never moved past initial research.

Vaccine candidates that passed the research and pre-clinical testing stages moved into clinical trials, (i.e., tests in humans). This happened across three phases. In Phase 1, a small group of people volunteered to evaluate the safety, immune effect and tolerance across different drug dosages. In Phase 2, a larger group was used to confirm formulations and dosages. Phase 3 involved several thousand human volunteers to evaluate the protection provided by the vaccine. Such clinical trials often took multiple years, and could be conducted by third-party providers. Following successful completion of these trials, companies sought regulatory approval; in the U.S., at the national level from the Food and Drug Administration (FDA) and in the EU, at the international level. Regulators granted authorization for manufacturing new drugs or vaccines.

Once the regulators gave approval, manufacturing and shipping could commence. Many big pharma companies relied on third-party partners for these services, including licensing and contract manufacturers. They used elaborate demand-forecasting schemes to ensure that supply met demand; these often necessitated that pharma companies produce large quantities of a vaccine. This stage continued to see close cooperation between the pharma companies and regulators to ensure the accuracy of the demand forecasts. Upon introduction into the market, a new drug or vaccine continued to be monitored closely by the drug manufacturer and regulatory bodies.

Using mRNA as a Drug

Moderna's approach to developing vaccines (and drugs in general) was fundamentally different from that of big pharma. It relied on using messenger RNA (mRNA), a molecule that carried a genetic sequence, and lipid nano-particles (LNPs), a fat used to wrap up and protect the mRNA and deliver it into cells. The body's natural use of mRNA revolved around its role in providing the information needed to make corresponding proteins. The human body created hundreds of thousands of proteins—such as insulin or growth hormones—to function and survive.

To produce a protein, the body used the information contained in DNA (i.e., genes). Each cell contained only two copies of each DNA gene, but the body needs many more copies to make a protein. When a body needed to produce a particular protein, it made many copies of that protein's gene, in the form of RNA. These temporary RNA copies, called messenger RNAs, or mRNAs, move out of the cell's nucleus and into the cytoplasm, where they instruct the cell's ribosomes (the small particles that serve as protein factories) to produce the desired protein. Melissa Moore, chief scientific officer of platform research at Moderna said, "mRNA is basically a template that holds a code, or instructions, for a cell on how to manufacture proteins. It doesn't have anything to do with gene editing, because it doesn't function in the nucleus, so doesn't touch the DNA. But it does get the cell to behave in a certain way."

Moderna, and other companies that followed, took the use of mRNA to the next level by turning it into a drug. Following this logic, once an externally manufactured mRNA was injected into the body as a drug, the ribosomes in the cells read the injected mRNA like a code and made the protein the mRNA instructed them to make, thus leveraging the power of mRNA for the targeted production of proteins needed to fight diseases. mRNA functioned like a software instruction manual, instructing the body how to produce its own drugs.

LNPs were also important for the development of Moderna's drugs. LNPs served as the "delivery vehicles" for mRNA, clothing the mRNA in fats to ensure proper delivery into the human body. "mRNA is the software and LNPs are the hardware needed to make our therapeutics work," Moore said. "So we are not just an mRNA company; we are also a delivery company." If Moderna could prove that its approach worked in one single drug, it would work for all others as well. "mRNA is a platform like the iPhone," she added. "The individual drugs—preventative vaccines or therapeutic treatments—are like apps. If we get the platform to work, many, many apps can be developed on our platform."

Moderna's nature as a platform company meant that similar technologies could be used to develop multiple medicines in parallel, and learnings from one drug could spill over directly into others. This was in contrast to typical biopharma[c] companies that administered their research and development efforts and clinical trials in sequence, and the learning across drug candidates was minimal at best.

Moderna's Conception

Flagship Pioneering

Moderna started out as project LS18 in 2010 at Cambridge-based Flagship, at the time called Flagship Ventures. Though based on venture capital-type investment pools, Flagship was more than simply an early-stage investor providing money to promising business ventures. "We operate as an institutional innovation enterprise," said Afeyan. Trained as a bioengineer with a PhD from the Massachusetts Institute of Technology (MIT), Afeyan had founded Flagship in 2000 after serving as the founder and CEO of PerSeptive Biosystems, a leader in bio-instrumentation, and as senior vice president and chief business officer Applera, which acquired PerSeptive in 1998. Committed to spearheading radical innovations in medicines, Flagship followed a strict methodology for creating ideas through scientific innovation and entrepreneurship in revolutionary, untapped spaces. They were the founders, funders and owners of their portfolio companies, taking the leading role in the conception and growth of these firms, which initially start out as projects. "To understand the genesis of Moderna, one must understand Flagship," Afeyan explained.

[c] Biopharmaceutical companies manufactured their drugs by biological methods (i.e., in living organisms such as yeast, bacteria or mammalian cells).

Flagship followed a structured four-stage process for pioneering innovations through scientific discovery. First, they generated hypotheses believed to yield break-through innovations, asking the question "What if?" (e.g., "What if mRNA could be a drug?"). They called these "explorations." Second, if these explorations proved promising, they became prototype companies (ProtoCos). Flagship formed to test the feasibility of the concept. Third, if the explorations validated the science underlying the venture, ProtoCos turned into new companies (NewCos) and Flagship committed significant capital. At this point, while still an internal venture, Flagship and the venture team would recruit a broader team to develop the business further. Fourth, the NewCo was spun out to become a growth company (GrowthCo). At this stage, the company began forging investor relationships and outside partnerships. (See **Exhibit 3** for Flagship's process for pioneering.) Eventually, some of these GrowthCos ended up operating as public companies. Between 2013 and 2020, 20 Flagship GrowthCos completed IPOs,[7] including Moderna in December 2018, at a valuation of $7.5 billion.[8]

"This is not your typical unmet-need/breakthrough-solution approach to coming up with a business," Afeyan explained. "We subscribe to a Darwinian process, covering creation, iteration and selection of groundbreaking innovations for which no precedent exists. Asking 'What if?' questions propels you far into the future. It may be unrealistic or overly optimistic, but that's how radical innovation happens." Afeyan also believed that science in business was uniquely positioned to ask these questions and pursue such an approach. "Academic science searches for knowledge; science done in business searches for solutions. It goes where value is believed to exist imminently," he said, adding, "Our approach of thinking about the future state first and then developing solutions backwards is not necessarily a better way of doing science than the incremental innovations academia strives for—it's just different." Though there was no expressed need for mRNA as a therapeutic at the start, Afeyan believed in its potential, noting, "We deliberately looked into mRNA as a novel medicinal modality."

In 2010, Robert Langer, David H. Koch Institute Professor at MIT, an accomplished and decorated researcher and a key scientific advisor to Afeyan, directed Afeyan's attention to Dr. Derrick Rossi's recent research. At the time, Rossi was an investigator at Boston Children's Hospital and an Assistant Professor in the Stem Cell and Regenerative Biology Department at Harvard Medical School. His research on using mRNA to reprogram cells[9] led Afeyan to wonder: might it be possible not just to reprogram cells but to get patients to produce their own biological drug through the use of mRNA? Could Rossi's research insights provide a basis for developing a biotherapeutic drug rather than laboratory stem cells? Afeyan wanted to get these questions answered through more research and experimentation, so he set up a team to explore whether mRNA could be turned into a therapeutic. Langer and Rossi provided Moderna with key scientific direction early on, making them academic co-founders. In 2020, Langer continued to serve on Moderna's board.

"We had long had a vision of creating new types of medicines for humans," Afeyan said. "Plus, we had an interest in creating platform companies." mRNA fit all the bills: it was an unproven medicinal modality that could serve as a multi-product platform. "Developing drugs is the most rewarding thing to do in the pharma industry. But at this point, big pharma only pursues incremental innovations, which leaves the riskier, less proven approaches unexploited," Afeyan noted. Given the time and costs, pharma companies often focused on one product, committing enormous resources to them. Following Flagship's logic of a platform meant that if one drug worked under the given conditions, then many would work, allowing much faster time-to-market of new drugs once a proven method was in place.

Moderna's set-up as a multi-product platform company meant developing a different narrative for investors as well. "Our story to investors was different than what they knew from incumbent pharma companies. And so we also happened to attract different kinds of investors than you might see in big pharma," said Lavina Talukdar, head of Investor Relations. Moderna's platform nature was more

attractive to generalist investors accustomed to investing in pre-revenue, pre-earnings ventures, where the use of price-per-earnings ratios to value an investment—a standard indicator for big pharma companies—was less relevant. "These types of investors understand the value of digital platforms and learning effects, from having seen such effects in tech companies," Talukdar added. Traditional pharma investors required more information on the unique dynamics of Moderna's business model. "We also talk to investors focused on developmental stage biotech companies, who are interested in probability of success and time-to-market. This is a very different conversation than those we have with a tech or finance investor, who has experience with platform companies like ours," Talukdar concluded.

Deciding to Go Digital

As Moderna came together as a venture, Afeyan reached out to Stéphane Bancel, then-CEO at French diagnostics company bioMérieux, whom he had known for several years. Afeyan had been trying to recruit Bancel into Flagship as a senior partner for some time. He recalled, "Early on I saw he was a special person. I noticed how creative and impassioned he was, which was counterintuitive, given he was the CEO of a large public company." With Moderna taking shape, Afeyan called Bancel, saying, "I've got the thing you should work on. If you're not taking this, and it succeeds in a big way as I expect it will, then someday you're going to regret it." He managed to persuade Bancel to come onboard at Flagship and join Moderna as a board member; soon after, he became the company's CEO. Afeyan recalled, "He's resourceful, impatient and wants to achieve impact fast."

A native of France and an engineer by training with hands-on coding experience, Bancel had spent his entire professional career in the life sciences field. Having served in sales and manufacturing roles at Eli Lilly before joining bioMérieux as CEO in 2006, Bancel understood the power of digitization in the pharma field. "I have seen the disaster unintegrated data and systems can cause," he said. "I've been in places where I knew more about computers than the IT guys. I wanted Moderna to be a digital company from day one. For that to happen, we needed the IT to be built right, even if it meant considerable investments at a time when we didn't have revenue streams. Digitizing right from the get-go is much easier than doing this *ex post* on a legacy system."

By 2012, Moderna had a staff of about 20 people. Bancel quickly recognized the need to digitize when he walked into the office of one the small start-up's few scientists. The scientist had been working on an Excel spreadsheet, spread across two large screens, manually inputting a nucleotide sequence. He was proud of his progress but Bancel was horrified: "If any of the Excel cells had been wrong, the entire design of the drug would have been useless." To do away with the manual process, Bancel had a drug design studio set up, where drugs could be crafted easily and reliably on the computer rather than through manual work.[d]

To enable full digitization to further accelerate research and results, Bancel realized he needed a formal chief digital officer (CDO) to drive this. In 2015, he brought former colleague and ex-CIO at bioMérieux Marcello Damiani onboard. Fluent in digital technology and pharma, Damiani believed that business process engineering was the key to digitizing a firm and needed to come first before digitizing, and Bancel agreed. "Enabling Marcello to design the processes was key. Digitization only makes sense once the processes are done. If you have crappy analog processes, you'll get crappy digital processes." Damiani added "You cannot blindly translate manual processes into digital processes. The processes, once set, have to be redesigned to fit in a digital environment. It is important to do this exercise holistically rather than in silos, or else optimization will only happen in individual pieces."

[d] See https://vimeo.com/151182986 for more information on Moderna's drug design studio.

Damiani's dual title as Moderna's chief digital and operational excellence officer gave him a mandate for process engineering across Moderna's departments.

By 2016, Moderna had made quick progress towards becoming a fully digital biotech company. The digitization of processes was the first step in Bancel's vision for Moderna, followed by automating as many processes as possible. "We are at the beginning of a new S-curve.[e] How quickly we learn is the most important indicator for us. We have to keep learning really fast. That's what motivates me to push for automating as much as we can," Bancel explained. Going digital, however, was only the first step towards Bancel's vision of utilizing artificial intelligence (AI) in Moderna's processes. Becoming an AI-driven company required more than simply digitizing operations and promoting a digital cultural as part of Moderna's DNA. A layered, multi-step logic was key to becoming an AI factory, and doing it right from the outset would take time and resources.

Building the AI Factory

Damiani knew there were several principles that mattered in an AI-driven company. First: the cloud. "Operating in the cloud rather than building our own infrastructure was foundational to everything else we did. It was the first decision we made," Damiani said. (See **Exhibit 4** for Moderna's digitization building blocks.) He believed that storing data in the cloud was more secure than hosting it locally; cheaper than maintaining the infrastructure in-house; and more agile and resilient, with better disaster recovery solutions and less downtime. Moderna started using Amazon Web Services (AWS) in 2013, and deepened the relationship over time.

The second principle was integration. Both Damiani and Bancel had seen what siloed data could do to efficiency and productivity, so having data harmonized across systems, entered once and with the ability to flow freely to whichever team needed the data, was crucial. "At bioMérieux, before we undertook an IT transformation, just getting the current headcount was a feat," Damiani explained, adding, "The systems didn't work well together. Lots of data was just stored locally in Excel spreadsheets. At Moderna, we wanted business processes and data to be integrated. Having our lab instruments connected to each other through the Internet of Things also enabled data integration."

Automation and robotics were the next steps, although Damiani was cautious of automating and robotizing too early. "We needed to have maturity in our processes first. Removing error-prone manual activities was the initial step," Damiani noted. His team spearheaded "islands of automation," connecting them into a larger automated whole once each island was stable. The team operated the systems as manual-automated hybrids until they achieved automation across the board. Dave Johnson, head of Informatics, Data Science and AI, said, "Automating too much and too early is dangerous too."

As the whole system became connected, analytics and AI came into play. "AI is really the holy grail," Damiani said, adding, "We relied on digitization early on, not for the sake of digitization but for generating data. Today, we have a lot of structured data, for instance in research and pre-clinical production. When we run experiments, we collect even more data. This allows us to build better algorithms, which helps build the next generation of medication. It's a virtuous cycle." (See **Exhibit 5** for digital integration at Moderna.)

Moderna employed a mixed approach to sourcing digital solutions. They bought most of their systems to support undifferentiated processes, such as finance and human resources (HR) tools off-the-shelf. Damiani estimated that 85% of these kinds of tools were existing Software as a Service (SaaS)

[e] An S-curve in innovation management refers to the start of a new technological era in which performance increases rapidly.

solutions, such as Workday which Moderna used in HR. He estimated that around the same share of tools to support their company-specific processes and innovation, such as in research or technical development, were custom built.

Functions across Moderna adopted digital and AI at different rates, with pre-clinical leading the way, yet Damiani felt the organization was on pace. "We are at maybe 60% or 70% of my vision," he said. "Granted, recently established areas, such as clinical and commercial, lag behind, but overall we are in a great position." By early 2020, preclinical production had largely been automated and more automation, especially for clinical and research activities, was underway. This significantly reduced cycle times, allowing Moderna to move at a faster pace than pharma or even other biotech companies.

Johnson believed the use of AI gave Moderna a competitive advantage. "We use algorithms to support our decision making in different areas. For instance, in the clinical trial space, they give us predictions that humans wouldn't be able to make in a reasonable time frame," he said. "This allows us to scale with speed."

Johnson saw the road to developing an algorithm, from concept to deployment, as winding, rather than linear, and strongly dependent on the particular circumstances. "Data is always the most important element of any AI project. Luckily, we are in a position where our systems are integrated and we have large amounts of structured data we can use to build models," he explained. Any model started with an idea, sparked for instance when the business side faced a certain problem. First, Johnson's team undertook exploratory analyses to determine whether the problem could be tackled, and they then collected data and built a simple first model. Getting to a minimal viable product (MVP) model, with acceptable accuracy, took on average six months, though some models were ready in as little as one month. If the MVP accuracy was sufficient for the use case, the team deployed and integrated the model into business workflows. If beneficial and possible, the team then iterated on the model to improve accuracy and performance. In spring 2020, Moderna had about 20 algorithms in production with another 20 in development and testing.

One example of a use case for algorithms was Sanger sequencing, a method for determining the nucleotide sequence of DNA. This was a critical part of Moderna's process to quality-check their DNA templates. As a single nucleotide change could result in a nonfunctioning protein, proper quality checks were vital. While an off-the-shelf solution for this existed, it was typically unable to perform certain more in-depth analyses, which mean that trained operators had to manually review specific sequence stretches, introducing the risk of human error. Moderna developed a convolutional neural network[f] to predict operator response with superhuman accuracy, saving countless hours of manual review. Johnson's team often pursued this approach: using existing algorithms published elsewhere and tweaking them to perform better, or building onto them.

While the use cases and corresponding development, testing and deployment strategies were manifold, Johnson saw one universal truth. "For us—and any company, really—to be able to be an AI company, it takes sponsorship at the highest company level," he said. He added, "Working on tangible real-world problems rather than lofty moonshots, and being able to demonstrate proof-of-concept to the organization is key in instilling AI at every level of any organization on the path to becoming the first truly digital biotech company."

[f] A convolutional neural network was a type of artificial neural network that relied on deep learning to analyze visual imagery. Designed to process pixel data, convolutional neural networks were often applied in image recognition and classification, including medical image analysis.

Making Manufacturing Digital

Along with committing to a digital and, where possible, AI spirit throughout the various stages of drug development and testing, Bancel decided early on that digital would also have to permeate the manufacturing process. He hired Juan Andres, with whom he had worked at Eli Lilly, as Moderna's chief technical operation and quality officer, in charge of its production processes. With 18 years at Lilly and 12 years at Novartis leading manufacturing and global operations, Andres had a clear view of what the role of manufacturing was in traditional pharma companies and what it needed to be at Moderna. "Manufacturing in big pharma is a commodity. Its role is to translate the uncertainty of pharma research and development and drug approval into certainty of supply. It serves to neutralize variability," he noted, adding, "At Moderna, manufacturing is almost a source of revenue. It's a completely different game because of the platform nature of things. mRNA as a new class of medicines allows manufacturing to assume a different role than in recombinant biology."

Andres shared Bancel's vision for digitization. "Turning things digital allows fast growth and learning, ensures quality, and makes replication and standardization possible. It's impossible to learn—and learn reliably—if you need to work with manual data. Because we have an obsession to learn, we needed to turn things digital, including in manufacturing," Andres explained.

Moderna's manufacturing process early on was scattered around the globe but over time the company started to internalize this capability. "The best reason to outsource is when you don't know something well and you need to rely on others who are better," Andres said. "But the platform nature of our operations was so novel to others that outsourcing was not really warranted. Also, a supply chain that's all over the place may work for one- to two-product companies but not if you have a pipeline of products like we do."

Moderna still had not commercialized any drugs and had no revenues. (See **Exhibit 6** and **Exhibit 7** for financials.) Nonetheless, Bancel, Afeyan and Andres decided to build a state-of-the-art plant and integrate everything they needed into it. At the time, the investment was pegged at about $125 million (or about 10% of 2016 year-end cash balance). "You need great conviction that your platform is going to be successful to make that kind of an investment with investor money. It's not normal to invest so much into manufacturing rather than R&D when you're a young biotech," Andres noted.

They decided to build a plant for pre-clinical and clinical research as well as their personalized cancer vaccine unit in Norwood, Massachusetts, about a 45-minute drive from Moderna's headquarters. Vertical integration of manufacturing would give them more control and allow them to produce drugs faster than with the previous globally dispersed supply chain, while saving manufacturing costs.

Though it was a highly digitized plant, Andres noted, its integration set Norwood apart from big pharma manufacturing sites. He said, "I could easily say we have the best digital technologies at Moderna. But the truth is big pharma has great stuff, too. What's more important than having sophisticated digital tools or algorithms, is integration at all levels. The way things come together is what matters about technology, not the technology itself. You make medicine by cross-functional integration." Norwood housed essentially three manufacturing engines: pre-clinical R&D, personalized cancer vaccine, and the clinical area. While all three were completely independent, Andres acknowledged, "From a digital learning point of view, they are extremely connected. It's easy to transfer any learning from one to the other." He elaborated,

> For example, a scientist says 'This is the sequence. Here is the corresponding mRNA for the desired protein, with cap and tail.' She sends the sequence over to Norwood. It

> goes into the machine and in 30 days, they can turn it back as a manufactured molecule. But each instance provides new information, and it's all available and shared. So the scientist can look at it and say, 'Based on the past 25,000 iterations, let's tweak it this way or that to improve the cap or the tail, etc.'

Moderna in Early 2020

By early 2020, Moderna was running 23 programs for various drugs, of which 11 were in Phase 1, and one was in Phase 2. The programs included 11 vaccines, including nine prophylactic vaccines and two cancer vaccines. The latest addition of vaccines included one against the novel coronavirus, though other vaccines had been in the pipeline for much longer. Besides vaccines, Moderna also had several therapeutics, including against cancer, autoimmune disorders and heart failure. (See **Exhibit 8** for the pipeline of Moderna's drugs.) None of Moderna's drugs had so far hit the market.

Moderna frequently published papers sharing its approach and findings, and Moore was excited about uncovering new things in applied and basic science. "We are pushing up against the boundaries of human science with our approach and we are overturning several dogmas along the way. With our research, we are extending the basic knowledge on how the human body works," she said.

Solving for COVID-19

It was late December 2019 when the local government of Wuhan, China, confirmed that health authorities were treating cases of an unusual type of pneumonia caused by a virus, initially nicknamed "2019 novel coronavirus." Said to have surfaced at a Chinese poultry and seafood market,[10] the virus—part of the family of Coronaviruses—was later named SARS-CoV-2, in reference to its SARS-CoV-1 predecessor responsible for the SARS outbreak in 2003.[11] It was not until January 11, 2020, that reports of the first death from the illness caused by the virus appeared. The illness, named COVID-19 (short for coronavirus disease), later spread across all continents and developed into a full-fledged pandemic, killing several hundreds of thousands of people globally in a matter of months.[12]

Moderna shifted into high gear when the first death was announced. Over the weekend of January 11 and 12, the Chinese authorities posted the genome sequence of the virus online for everybody to access. Given his deep experience in big pharma, Andres realized quickly what the situation meant. "This is pandemic response. If we decide to pursue this, it means we need to be all in. There's no exit. You put one toe in the water and you are all in." The executive committee engaged in a lively discussion and decided that Moderna would try and develop a vaccine and be in the clinic before anyone else. "After January 13, all hands were on deck," remembered Moore. "Though designing the actual mRNA sequence only took a few hours, manufacturing the vaccine and performing all the necessary testing was an around-the-clock-effort. It really brought out the best in people. There was a clear goal and an urgent threat at the same time. We knew we had to act fast and everyone was invested in this."

By February 7, the team at Moderna had manufactured the first clinical batch for the vaccine, on which they then ran quality control. On February 24—a mere 42 days after first getting access to the virus genome sequence—they sent their vaccine to the NIH. On March 16, the first inoculation happened: the first dose of Moderna's vaccine was injected into a human volunteer in Seattle, Washington. This meant the company had moved from the viral genome sequence to a human trial in just over two months. "Doing all of this in a mere two months was groundbreaking," said Bancel.

Moderna's unique mRNA approach, paired with a proven track record in vaccines, played a role. "We don't just have the science, or the technology. We have both. mRNA as a platform allows us to

develop a vaccine much faster than recombinant biology would. Also, this isn't our first vaccine, but our tenth. We had already generated learnings from our previous nine vaccines that allowed us to move into the clinic quickly now." It was not Moderna's first time working on a coronavirus—nor with Dr. Fauci, luminary immunologist and head of the U.S. Administration's Coronavirus Task Force.

Bancel himself had more than two decades of experience in infectious diseases, including during his time at bioMérieux's when H1N1 (the Swine Flu) hit. "I wanted Moderna to be ready for a pandemic vaccine. And we were ready for COVID when it came," Bancel said. He had invested in building relationships with key entities and personalities, like Fauci. In addition to NIAID, Moderna had also built relationships with entities such as the Gates Foundation, the Defense Advanced Research Projects Agency (DARPA) and Biomedical Advanced Research and Development Authority (BARDA). In 2016, BARDA had awarded Moderna a grant of $126 million for the development of a Zika vaccine.

Moderna had already developed a vaccine for MERS with the NIH. "We worked with Dr. Fauci's team on MERS for two years, providing them with our mRNA," said Bancel. "And Dr. Fauci's team visited our Norwood plant in November 2019." So when news of a new infectious disease agent in China spread in early January 2020, Bancel emailed Fauci's team directly, asking for more information.

Moving from the genome sequence to a vaccine ready for trial in 42 days highlighted Moderna's advantages. Moore elaborated:

> We had already invested years of fundamental research to find the best algorithms for designing mRNA. But we didn't just do the basic science on mRNA; we are a delivery company too. So, we had also done much research to find the best lipids to deliver mRNA once in the body. The final piece of the puzzle was knowing which viral protein to make. Our Infectious Disease group had also been working for years with colleagues at NIAID on coronavirus coat proteins, so they knew exactly what variant of the 'spike' protein would produce a potent immune response. The combined know-how from mRNA science, research on LNPs to deliver mRNA, and knowing which protein we needed the body to make allowed us to act fast when the Chinese researchers published the sequence on January 11. We knew we could design the RNA that encoded the right viral protein, and that we could do it fast.

Bancel noted, "Manufacturing was also a key enabler. If you have great science but cannot make a product, there's no business. We invested in our own plant in Norwood, which gave us full control over the manufacturing process." Bancel deemed this a superior strategy over working with contract manufacturers. "We'd have had no chance to go this fast, had we relied on contract manufacturers."

Race to Defeat COVID-19 Through a Vaccine

On April 16, 2020, BARDA announced that it had awarded Moderna a $483 million grant to accelerate development and manufacturing of its COVID-19 vaccine. This amounted to about half of the federal agency's total grant money awarded to date, with Johnson & Johnson receiving $456 million and Sanofi receiving $30 million.[13] Moderna caught the attention of the public and the media. Its share price started to rise dramatically—from $37.25 on April 15 to $80 on May 18, 2020. On July 26, one day before the launch of Phase 3 testing, BARDA committed an additional $472 million to support Moderna's late-stage clinical development efforts, including the upcoming Phase 3 trial.[14]

"COVID really catapulted us onto the world stage. We got so much press and investor interest from it," Talukdar explained. "People are working super hard. There's a sense of responsibility and urgency

that requires unparalleled tenacity in this race against the virus. We want to prove our technology and demonstrate that it can make a difference," she continued.

The field developing a vaccine quickly became crowded. By July 2020, more than two dozen companies had candidate vaccines in clinical trials, following a variety of approaches.[15] (See **Exhibit 9**.) Promising candidates included Oxford University's and Swedish-British drug maker AstraZeneca's partnership efforts, China's CanSino Biologics's vaccine, and U.S. pharma giant Pfizer's and German biotech BioNTech's joint venture effort.[16] As the world eagerly watched and made bets on who would come up with a commercialization-ready vaccine first, Moderna was bullish about its chances and timelines, but also encouraging of other pharma companies' efforts. "We believe our technology works, and it allows us to be much faster than others. But we're rooting for everyone. The reality is multiple vaccines will be needed because no one company can supply the whole world," Moore said.

As big pharma companies were grappling with the speed required under the circumstances of an unprecedented pandemic, developing a COVID-19 vaccine was somewhat business as usual for Moderna. "This was a routine endeavor for us," said Johnson. "Generating an mRNA sequence was nothing unusual for us. We leveraged processes we had already built and tested before." Bancel added, "It was easy for us to do because we had a fully digital facility and because of our digital platform model. We basically designed the vaccine on the computer. Our factory is paperless. Everything is digital. All machines are directly connected to our digital manufacturing systems." As just one example of many in Moderna's drug development process, integrated electronic batch records saved time and money across equipment use, testing and release. These helped Moderna's operators select, manage and track raw materials through real-time integration with SAP. They facilitated all testing steps, including labeling, information-sharing, audit trails and security controls, ensuring accuracy and speed. They captured all batch record exceptions digitally, enabling real-time review and quality assurance, significantly reducing cycle time, converting stacks of paper reports and manual updating into a fully digital system that was continually updated.

By the end of July 2020, only six months after getting access to the genome sequence, Moderna's vaccine was in Phase 3 of development. Phase 1, which Moderna had launched with the first inoculation in mid-March, had encompassed testing its vaccine in human clinical trials on 45 healthy adults. It had aimed to understand the safety and dosage of the vaccine. Phase 2 tested the efficacy and side effects of the drug on about 600 volunteers. Andres explained, "In any product development process, the goal is to de-risk in Phase 1 before moving on to Phase 2. This is especially important for vaccines, where you are treating healthy human volunteers. It needs to be absolutely safe if it is to advance to a human trial." Phase 3 moved to testing the vaccine on an even larger number of people, to understand its efficacy and any adverse reactions to it.[17] Conducted in collaboration with the NIAID and BARDA, the randomized, placebo-controlled study expected to include approximately 30,000 volunteer participants in the U.S.[18]

Though Andres was excited about the opportunities that lay ahead, he was also aware of the challenges. "We basically have to go from an early adolescent company to a full adult company, skipping all of late adolescence. This rapid evolution is painful. But we cannot reject the opportunity. It's like we are in the Champions League now, and we have to play like we are going to win." He attributed Moderna's rapid rise to its digital infrastructure and culture, giving it tremendous leverage and a clear advantage over incumbent players. But Moderna had yet to prove its license to play, never having brought a product to market. "Even though we have not done this as of yet, we have to demonstrate that we can play in the League," Andres concluded.

Partnering for Scale

Once its vaccine was ready, the Moderna team knew they needed extra support in manufacturing the vaccine. It would mean leveraging a global network of manufacturing and delivery capabilities; the scale of vaccinating a global population of over 7 billion was immense. And, early research over efficacy and immunity had yet to clarify if a single vaccination was enough, or if multiple doses would be needed. "People think in linear terms," Bancel said. "But we needed to start thinking in 10x dimensions. I challenged my team to think big rather than to think incrementally." The team knew that Moderna's production capacities were too limited even if other vaccines made it to market, so Bancel began to consider manufacturing partners to gain scale. He wanted to find someone who could host Moderna's process but also match its digital capabilities.

Andres was also astutely aware that Moderna was not going to be able to do this alone. He said, "If we are successful in developing that vaccine, demand will exceed supply. Enormously! Everybody is going to want this vaccine. And we will only be taken seriously as a company if we are able to produce that." Bancel, Andres, and the board quickly decided to outsource part of their vaccine manufacturing.

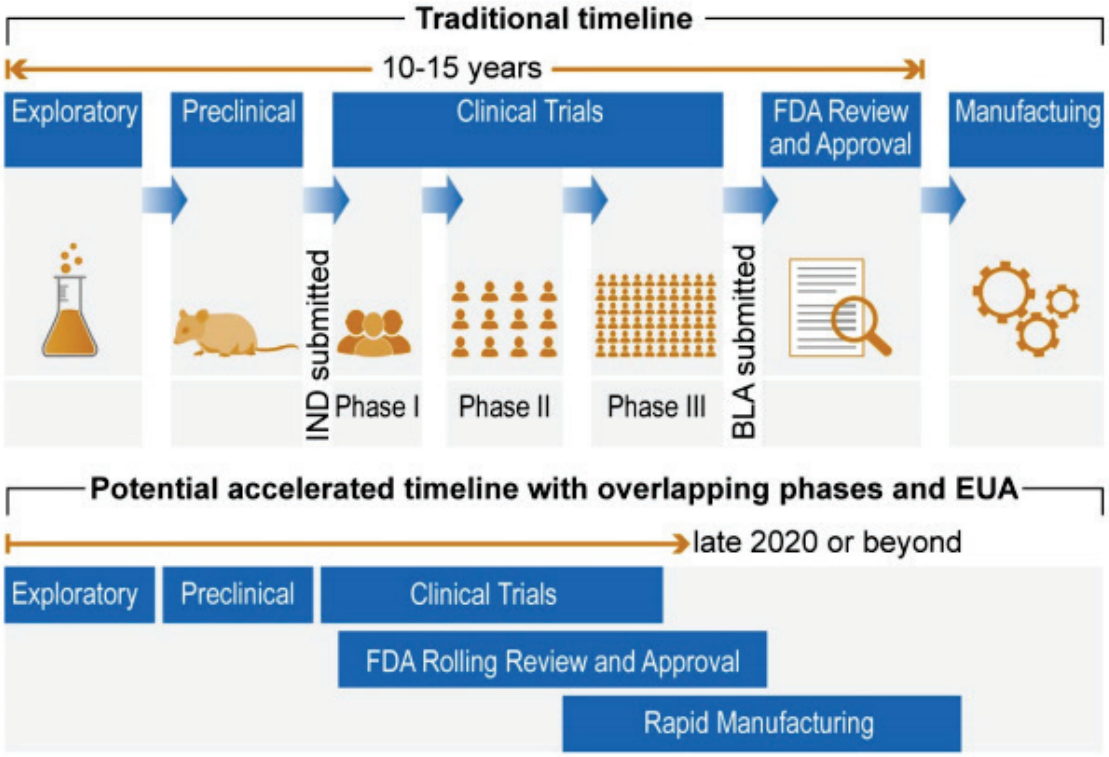
Given Moderna's accelerated maturation as a company, Andres thought Moderna would be well advised to partner with an experienced organization that could also serve as a mentor to the company. Swiss-based chemicals and biotech company Lonza quickly caught their eye. "Lonza scored high on basically all evaluation criteria," Bancel explained. It had a U.S. factory only one hour from Norwood, which would make cooperation in the U.S. easy. It also had an extra production facility outside the U.S., in Visp, Switzerland, which could serve as the basis for supplying the European market. Andres had worked with Lonza in the past, prior to joining Moderna, and knew he could rely on a trust-based relationship and shared values with the Lonza team. "Lonza can produce at scale, and they are a highly digital company—two things we needed," Andres said. They announced an agreement in early May. The partners were looking to finalize the technology transfer by July, allowing them to start production in less than three months—a process that would usually take two to three years.

The partnership with Lonza, just as Moderna's general progress in the development of the vaccine, was widely covered by the media, giving Moderna even more of a public platform. Talukdar summarized her feelings about the race for a COVID-19 vaccine, "COVID-19 put us on the map and helped us gain a lot of traction. While we don't want to become known as *the* COVID company, it has allowed us to tell our story. We want to stand for more as well but we realize we—and the public—are rightfully devoting a lot of attention to the COVID-19 vaccine development."

Next Frontiers for Moderna

As much of the world struggled to contain the virus and plan for the fall, Afeyan and Bancel reflected on how far Moderna had come and what was next. Given the unprecedented impact and scale of the virus, and by extension any vaccine for it, would a separate organization enable a team to focus exclusively on the pandemic? Spinning off a stand-alone organization might allow Moderna to act even faster, enabling it to be more agile and nimble than if operations continued to be embedded within Moderna. A "coronavirus unit" could always be repurposed to deal with future pandemic responses. They were, however, wary of creating silos—something they had been determined to avoid from the outset with Moderna's digital structure, having seen the detrimental effects of such organizational structures in big pharma organizations. Moderna's competitive advantage came exactly from a shared understanding and shared data across all departments and teams. Was spinning off a separate unit counterintuitive?

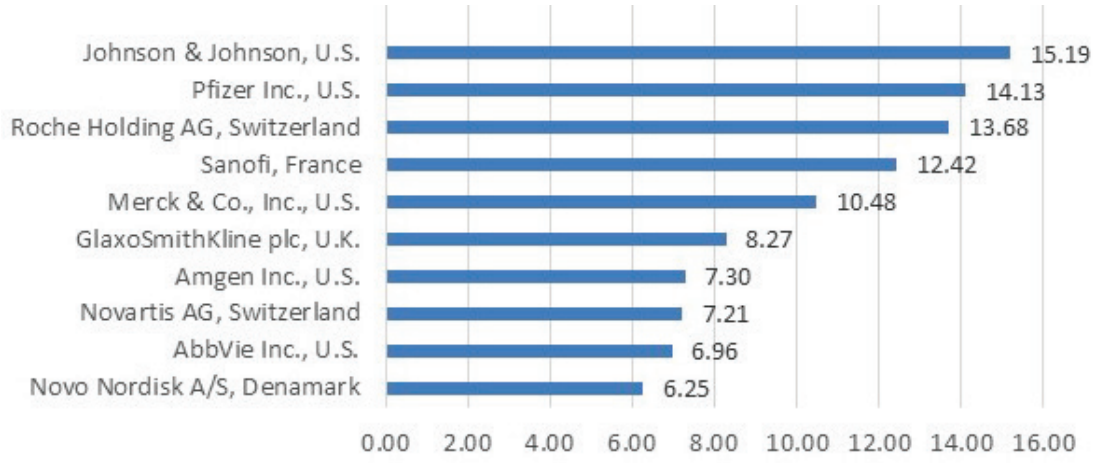
Exhibit 1 Vaccine Development Timeline (May 2020)



Source: U.S. Government Accountability Office, "COVID-19 Vaccine Development," May 2020, https://www.gao.gov/assets/710/707152.pdf, accessed October 2020.

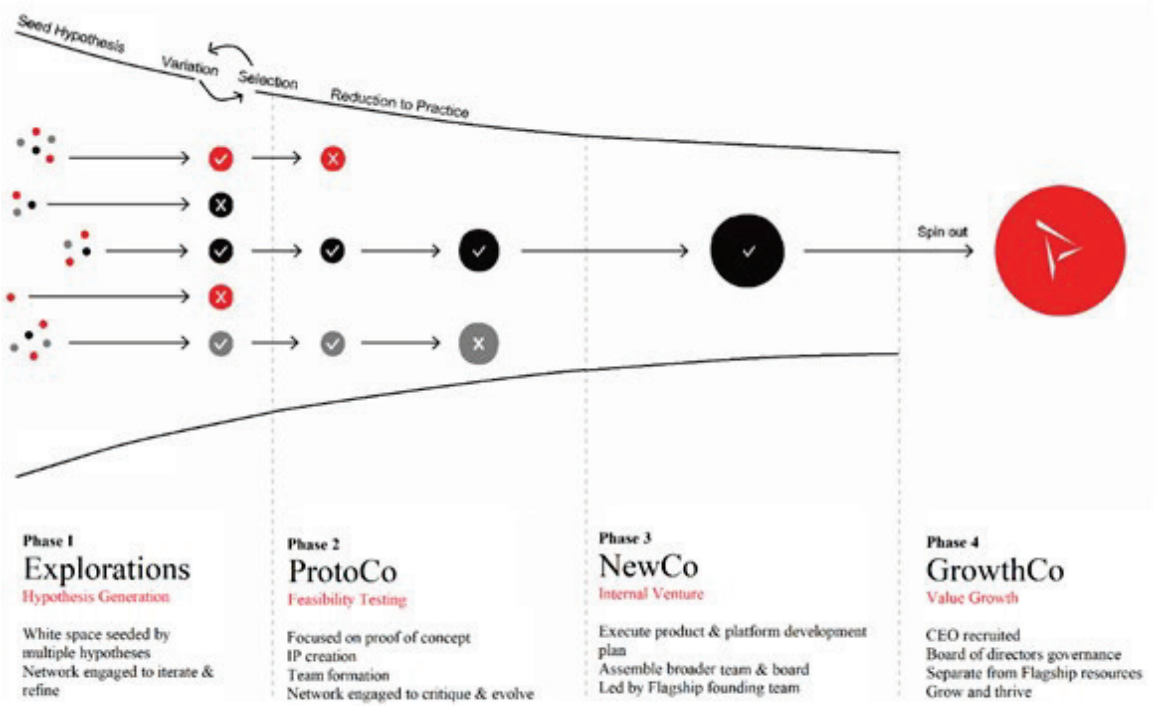
Notes: IND = Investigational New Drug; BLA = Biologics License Application; EUA = Emergency Use Authorization.

Exhibit 2 Top Pharmaceutical Companies, 2020, by Net Income, in $ billions



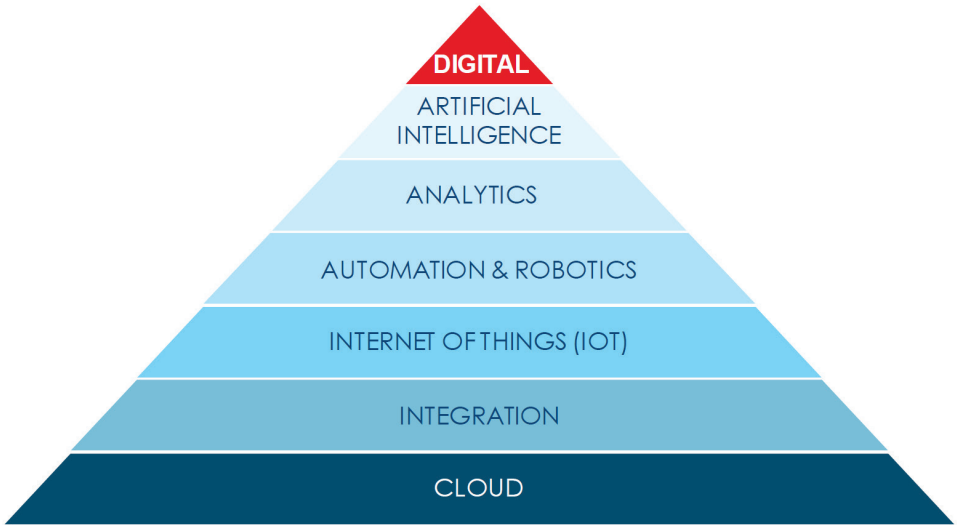
Source: Casewriter, compiled from Capital IQ, accessed July 2021.

Exhibit 3 Flagship's Process for Pioneering



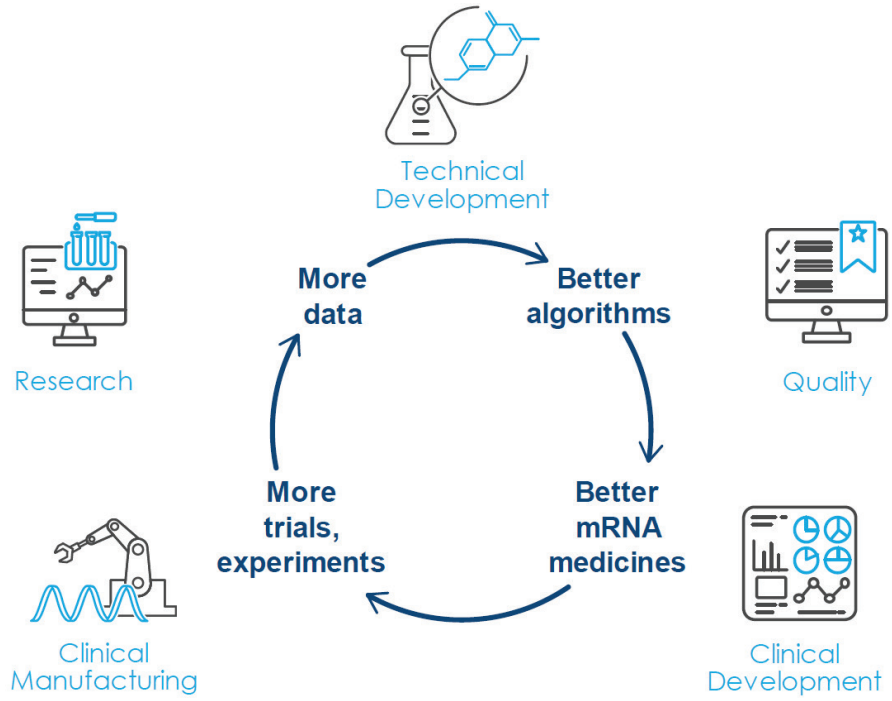
Source: Company documents.

Exhibit 4 Moderna's Digitization Building Blocks



Source: Company documents

Exhibit 5 Digital Integration at Moderna



Source: Company documents.

Exhibit 6 Moderna's Balance Sheet and Statement of Cash Flows, 2018-2019 ($000s)

	December 31	
	2018	**2019**
Cash, cash equivalents and investments	1,694,417	1,262,987
Total assets	1,962,149	1,598,422
Total liabilities	431,908	414,612
Total stockholders' equity	1,530,241	1,174,810
Net cash used in operating activities	(330,865)	(458,968)
Cash used for purchases of property and equipment[1]	(105,766)	(31,554)

Source: Company documents.

Note: 1. Includes $14.6 million and $94.5 million for the years ended December 31, 2019 and 2018, respectively, related to our Moderna Technology Center manufacturing facility.

Exhibit 7 Moderna's Profit and Loss Statement, 2018-2019 ($000s except shares)

	Three Months Ended, December 31		Years Ended December 31	
	2018	**2019**	**2018**	**2019**
Collaboration revenue	32,816	10,553	122,512	48,036
Grant revenue	2,605	3,502	12,556	12,173
Total revenue	**35,421**	**14,055**	**135,068**	**60,209**
Research and development	150,429	118,754	454,082	496,309
General and administrative	38,023	25,857	94,252	109,620
Total operating expenses	**188,452**	**144,611**	**548,334**	**605,929**
Loss from operations	(153,031)	(130,556)	(413,266)	(545,720)
Interest income	8,894	7,984	27,023	38,530
Other (expense) income, net	2,879	(1,837)	1,835	(7,526)
Loss before (benefit from) provision for income taxes	(141,258)	(124,409)	(384,408)	(514,716)
(Benefit from) provision for income taxes	168	(169)	326	(695)
Net loss	(141,426)	(124,240)	(384,734)	(514,021)
Net loss attributable to common stockholders	(144,099)	(124,240)	(401,857)	(514,021)
Net loss per share attributable to common stockholders, basic and diluted	(1.14)	(0.37)	(4.95)	(1.55)
Weighted average common shares used in net loss per share attributable to common stockholders, basic and diluted	126,298,266	334,392,128	81,114,183	330,802,136

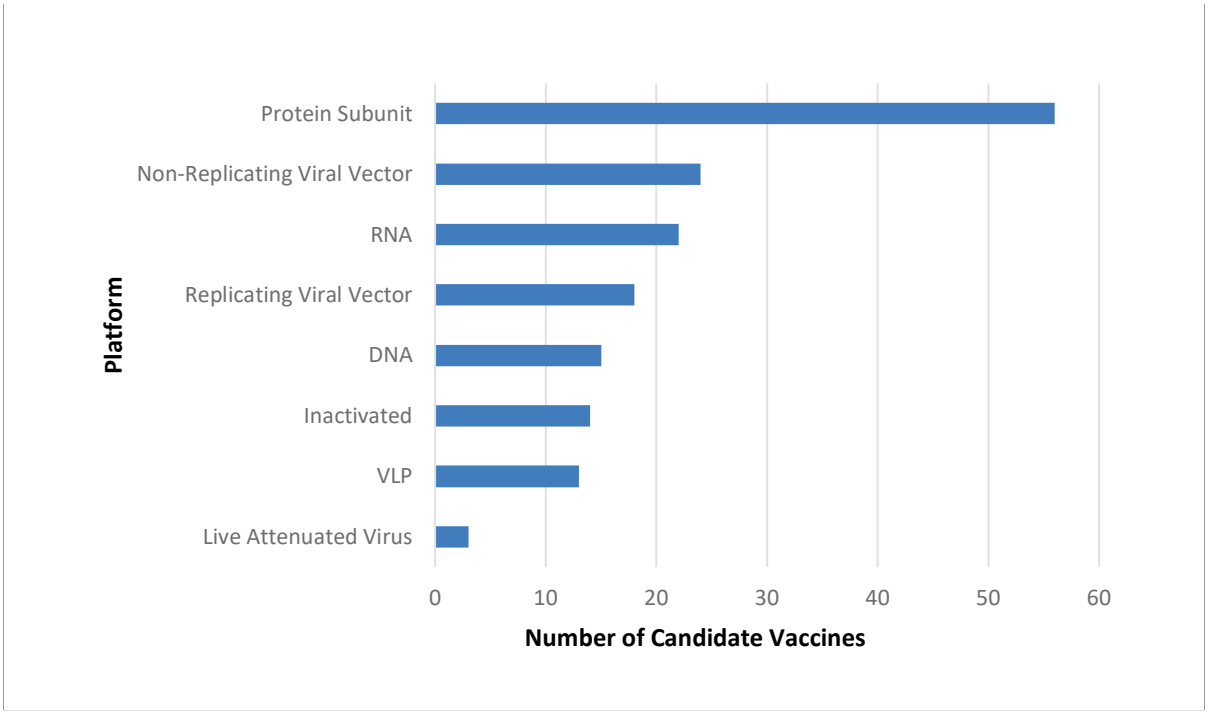
Source: Company documents.

Exhibit 8 Moderna's Drug Pipeline, 2020

Modality	Program Number	Program Information
Core Modalities		
Prophylactic Vaccines	mRNA-1273	Novel coronavirus (SARS-CoV-2 vaccine)
	mRNA-1647	Cytomegalovirus (CMV) vaccine
	mRNA-1653	Human metapneumovirus and parainfluenza virus (hMPV/PIV3) vaccine
	mRNA-1172; mRNA-1777	Respiratory syncytial virus (RSV) vaccine
	mRNA-1893	Zika vaccine
	mRNA-1345	Pediatric respiratory syncytial virus (RSV) vaccine (*Future respiratory combo)*
	mRNA-1189	Epstein-Barr virus (EBV) vaccine
	mRNA-1851	Influenza H7N9 vaccine
Systemic Secreted & Cell Surface Therapeutics	mRNA-1944	Antibody against Chikungunya virus
	AZD7970	Relaxin (*Heart failure)*
	mRNA-6981	PD-L1 (*Autoimmune hepatitis)*
	mRNA-6231	IL-2 (*Autoimmune disorders)*
Exploratory Modalities		
Cancer Vaccines	mRNA-4157	Personalized Cancer Vaccine (PCV) (*Solid tumors)*
	mRNA-5671	KRAS vaccine (*CRC, NSCLC, pancreatic cancer)*
Intratumoral Immuno-Oncology	mRNA-2416	OX40L (*Solid tumors/lymphoma, advanced ovarian carcinoma)*
	mRNA-2752	OX40L/IL-24/IL-36γ (*Solid tumors/lymphoma)*
	MEDI1191	IL-12 (*Solid tumors)*
Localized Regenerative Therapeutics	AZD8601	VEGF-A (*Myocardial ischemia)*
Systemic Intracellular Therapeutics	mRNA-3704	MUT (*Methylmalonic academia (MMA))*
	mRNA-3927	PCCA/PCCB (*Propionic academia (PA))*
	mRNA-3283	PAH (*Phenylketonuria (PKU))*
	mRNA-3745	G6Pase (*Glycogen storage disorder type 1a (GSD1a))*

Source: Company documents.

Exhibit 9 Pipeline of COVID-19 Vaccines (July 2020)



Source: Casewriter compiled from World Health Organization "Draft Landscape of COVID-19 candidate vaccines – 31 July 2020," July 2020, https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines, accessed October 2020.

Note: The totals include vaccine candidates in both clinical and preclinical evaluation. As of July 31, 2020, there were 26 candidates in clinical evaluation and 139 candidates in preclinical evaluation.

Endnotes

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[16] "Three Coronavirus Vaccine Developers Report Promising Initial Results," *The New York Times*, July 20, 2020, https://www.nytimes.com/2020/07/20/world/covid-coronavirus-vaccine.html, accessed August 2020.

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