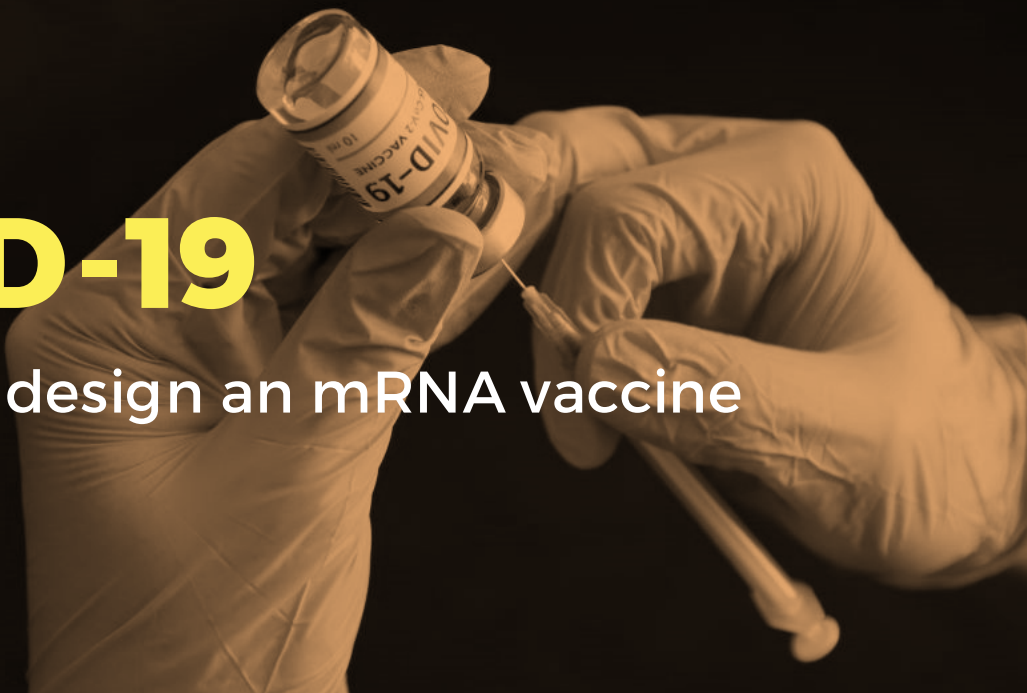




# COVID-19

## Using DSI to design an mRNA vaccine



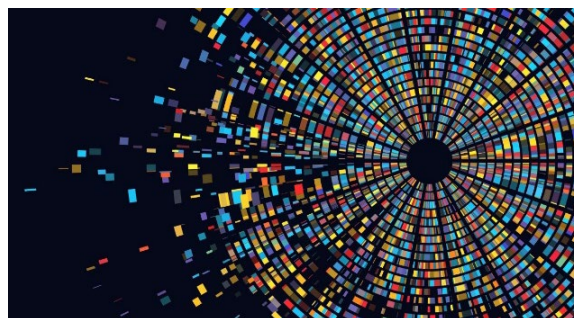
### Using digital sequence information (DSI) to design a vaccine for COVID-19

mRNA vaccines against COVID-19 produced by Moderna, and Pfizer/BioNTech were among the first to be approved in the United States and Europe and are among the most widely used and effective. mRNA vaccines introduce mRNA molecules into human cells, which use the mRNA to create a harmless viral protein that is unique to the SARS-CoV-2 coronavirus. This trains the immune system to “recognize” the protein and produce antibodies against it, which protects against severe infection.

Although rapid by historical standards, the process of developing vaccines for COVID-19 was still a lengthy and complex process, dependent on global scientific collaboration and open access to DSI. It involved vast amounts of resources and large numbers of people working across multiple phases of research, development, and testing. However, to illustrate the intricacies of working with DSI and some of the challenges scientists and

policymakers could face with regard to benefit-sharing from DSI, this case study will focus on a specific part of the work done by Moderna - the filing of patent US-10702600-B1: “betacoronavirus mRNA vaccine”<sup>1</sup>.

This patent was filed in February 2020, just two months after the pandemic started. It describes a general method for generating an mRNA vaccine for respiratory viruses, and in particular for betacoronaviruses (the genera that includes SARS-CoV-2, which causes COVID-19, as well as SARS-CoV-1 and MERS-CoV).



<sup>1</sup> <https://assets.modernatx.com/m/6fa93a4f95208572/original/US10702600.pdf>





## How should the benefits arising from a vaccine be shared?

---

A benefit-sharing system that needs to know what DSI was used in the development of a particular product in order to identify which countries are entitled to receive benefits from its sale and/or use, would likely rely on publicly available documents such as a patent application. For mRNA vaccines, the final product is essentially a single, relatively short nucleotide sequence. It may seem like a one-to-one relationship between the natural sequence and the vaccine sequence should exist, making it straightforward to assign benefits to a country of origin. Consideration of patent US-10702600-B1 demonstrates why this is not the case.

In this patent, no SARS-CoV-2 sequences were used, so countries sharing information related to COVID-19 would not be entitled to benefit-sharing from this patent. Instead, the patent draws on publicly available DSI and references 176 genetic sequences from several different respiratory viruses, drawn from a large range of countries, including Saudi Arabia, the UK, the UAE, Jordan, France, the USA, Qatar, Thailand, Oman, and China. In addition, the patent discloses 96 new sequences, which were submitted to public DSI databases alongside the patent. Some are similar or identical to existing

public sequences, others represent engineered or modified versions of sequences already referenced elsewhere in the patent document. Many are labelled simply as “Artificial Sequence” and therefore do not have a country of origin that can be traced (Fig. 1).

This means that a system for tracking and tracing the origin and use of individual sequences would have provided negligible benefit-sharing and none of the countries providing SARS-CoV-2 DSI would necessarily have benefited. The large variety of sequences used and the omission of SARS-CoV-2 sequences also demonstrates that Moderna was free to decide which sequences to include in the patent document. No single sequence was vital to its work. So, if such a system were to be adopted by only some countries, and not by all of them, Moderna could simply avoid using sequences from countries that enforced benefit-sharing (“forum shopping”).





## What about benefit-sharing for a specific sequence?

The challenges above relate only to a small part of the vaccine development process. One might suggest that instead of looking at the various sequences used in the process of developing a vaccine and listed in the patent, the process could be simplified by instead only dealing with the final sequence present in the vaccine itself. However, that sequence is impossible to link to any specific natural sequence. The final result was an artificial sequence that does not match any sample that could have been collected “in the wild” and therefore traced to a country of origin.

Indeed, the actual sequence used in the Moderna vaccine was originally protected by trade secret (a legal protection that would be very hard to compel via benefit-sharing laws) and shares only about 70% of its make-up with naturally occurring strains of SARS-CoV-2 (Fig. 2). It is the culmination of a long process of research that must identify which proteins serve as good vaccine targets, how they vary, how they’re structured, and how they can be engineered for greater stability. All of this research requires a diversity of sequences beyond the virus of interest. Furthermore, some of this research happens in the academic research domain and, therefore, may not be

fully reflected in corporate documents or patents.

In the cases of both the patent and the vaccine itself, a benefit-sharing system relying on tracking and tracing individual sequences risks being ineffectual and would not reward all of those contributing data to public DSI systems. On the other hand, public researchers conducting crucial epidemiological research often depend on large publicly accessible DSI databases, whose value depends on their size and openness. Any system that would disincentivize the use and sharing of DSI would risk hindering them.

There has been much public debate about the unequal distribution of COVID-19 vaccines around the world, and the lack of direct benefits for countries that have shared relevant sequence information but have not been able to afford to buy them in the necessary quantities. A benefit-sharing system for pathogen DSI should compel vaccine sharing linked to access to viruses and DSI. All actors must be committed to such a system and avoidance or non-participation must have far-reaching consequences.



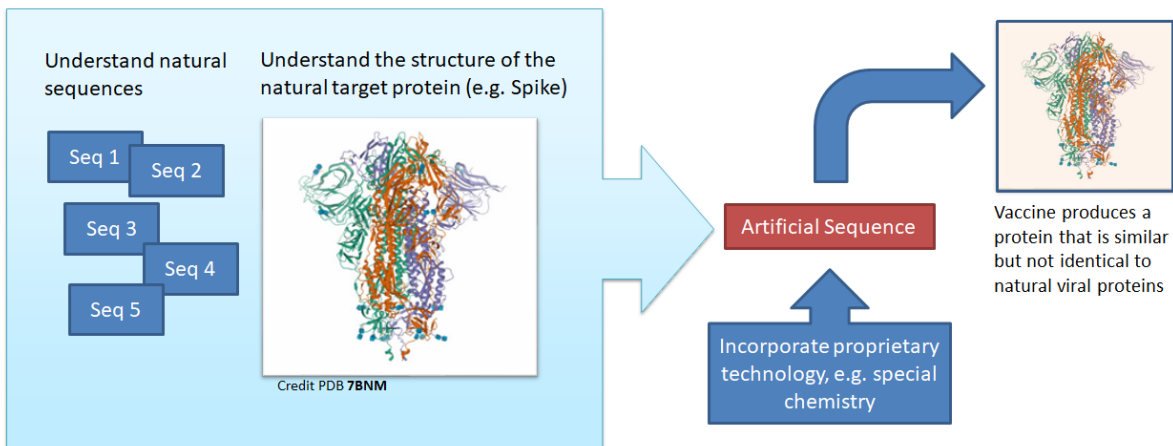




## Key takeaways

- **Open access to DSI** provides non-monetary benefits by enabling the rapid development of vaccines, medical treatments and diagnostic tools, and supporting epidemiological monitoring to guide public health response. A trigger point for monetary benefit sharing could be at the aggregate level such as defined sectoral commitments, levies, and percentage of the revenue from retail sales. In-kind contributions that ensure equitable distribution of vaccines around the world should also be part of the equation of benefit-sharing.
- Even though the end product was a single nucleic acid, the Moderna vaccine mRNA sequence was only 70% identical to a natural sequence. Further, research that uses DSI routinely compares and selects among millions of sequences, and often merges or edits them, which means **specific products can often not be attributed to any single sequence**. In addition, there are many nearly identical sequences from different countries in the databases and it is not possible to prove which ones were used to develop commercial products. Thus, **benefit-sharing based on the geographical origin of sequences is not feasible**.
- Multiple combined options or bilateral exceptions to any DSI multilateral mechanism will add complexity, incompatibility, and avoidance behaviour. It is necessary to have a single, global and predictable set of rules for benefit sharing.





**Fig. 1.** Simplified process for designing an mRNA vaccine.  
© Dr Andrew Hufton

```
>Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/CA-CDPH-
2000014286/2020, complete genome
Sequence ID: OK653344.1 Length: 29872
Range 1: 21557 to 25377

Score:1496 bits(1658), Expect:0.0,
Identities:2629/3825(69%), Gaps:8/3825(0%), Strand: Plus/Plus

Query 55 ACCATGTTCTGTTCTTCTGGTGCTGCTGCCCTGGTGAGCAGCCAGTGCCTGAACCTGACC 114
      || ||||| || || || || | |||| || || || || ||||| || || || || ||
Sbjct 21557 ACAATGTTTGTGTTTTCTTGTTTTATTGCCACTAGTCTCTAGTCAGTGTGTTAATCTTACA 21616
```

**Fig. 2.** A portion of a BLAST hit between the vaccine sequence and a natural SARS-CoV-2 sequence. The sequence used in the Moderna vaccine is only about 70% identical to natural SARS-CoV-2 sequences, a country of origin therefore cannot be inferred