

Genome Sequencing – Chasing the Virus and Changing the Dynamics of Pandemic

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Two things that can be said to have changed the curve of the COVID-19 Pandemic are Genome Sequencing and Vaccines. The story of vaccines is well-known to one and all. But the foundation of vaccine development is based on Genome sequencing. Genome sequencing is the process of recording a virus' genetic code. To be more precise, it is the way of finding out gene sequences in the RNA (or DNA) of any organism and comparing the sequence to previous records. Gene sequencing allows researchers to understand if the Virus is new to the human population. Genome Sequence is essential for developing modern vaccines based on newer platforms like mRNA or vector-based vaccines. Most frequently used vaccines during the Pandemic, like the mRNA vaccine from Pfizer and Vector based Vaccine from Serum Institute of India, could be developed in record time because of the availability of Viral Genome, which was decoded as early as 11th January 2020, even before the Virus had reached to many parts of the world.

Sequencing is not new. It has a history going back to 1977, when the first complete DNA genome of bacteriophage was sequenced. Since then, the scientific community has been putting in continuous efforts, but reliable results started pouring only in the last decade. If the Pandemic had happened more than ten years ago, there is no doubt that the Virus could have caused much more damage with few vaccines and fewer doses. Fortunately, Genome Sequencing has come a long way. For example, the initial Human Genome Project (HGP) was completed in about 13 years at an astronomical cost of nearly three billion US Dollars. However, using the next-generation sequencing (NGS) technologies of today, the entire HGP could be done in less than two weeks and at the cost of just around €1,000. Not only has the cost come down, but also the size of the testing equipment, which is now no bigger than a handheld stapler.

Owing to the easy availability of equipment, the genetic structure of variants of COVID-19 has been tested worldwide at an unprecedented scale, designating COVID-19 as one of the most highly tested pandemics ever. This information helps us in two ways – firstly, we can track how different forms of the Virus are evolving and spreading locally, nationally & internationally and secondly, how the particular subset of mutations can affect the spike protein of the Virus and hence alter its behaviour in terms of transmission and virulence.

During the early days of 2022, the Pandemic was driven by two variants, Delta and Omicron. Unfortunately, most doctors could not determine which variant of the coronavirus a patient was harbouring, a distinction that could change the line of management and mean the difference between life and death those days because high-risk patients carrying the Delta variant could benefit significantly from the monoclonal antibody treatments available then. These treatments could reduce hospitalization and death in cases of Delta infection but would mostly do nothing for patients with Omicron, who would only respond to a different antibody treatment, Sotrovimab, developed by GSK. Since both had different prognoses and treatments, patients also wanted to remain informed of the Virus they were harbouring. Omicron, a more benign variant, would instill a sense of relaxation and hope for quick recovery. It was Genome sequencing that helped us reveal the emergence of the Alpha variant in 2020, the Delta variant in early 2021 and Omicron in late 2021 and early 2022 and multiple sub-variants of Omicron like BA.1, BA.1.1, BA.2, BA.2.75, BA.3, BA.4, BA.5, BQ.1, BQ.1.1, XBB, XBB.1, XBB.1.5, BF.7 [1].

Omicron is now a family of more than 650 variants. The evolution pattern of the Virus can be clearly outlined and followed. In the initial eighteen months of the Pandemic, there was little immunity in the population exposed to neither natural infection nor vaccination.

Since the population's immune environment dictates the evolution of the Virus, during the early days, there was little selective pressure on SARS-CoV-2 to mutate in the absence of herd immunity. Therefore, the same Virus prevailed over different regions of the world, sequentially moving from one region to another.

Today, with the larger population of the world infected and more than 70 per cent of the world population fully vaccinated, the landscape of circulation virosphere of SARS-CoV-2 is different in different regions of the world.

Moreover, the Variants that do not cause a major outbreak in the region of their evolution may continue to move around the world in search of the immune naïve population, causing steep waves (e.g., BF.7 in China). And thereby, the Virus may continue to evolve further, including through recombination with other variants [2].

Despite the availability of advanced technologies and expertise, India is not performing well in sequencing the samples. It has sequenced only 2.06% (305766 samples sequenced as per INSACOG bulletin 9th Jan2023) and shared just 1.5% of all cases, according to the GISAID (Global Initiative on Sharing Avian Influenza Data), the world's largest database of novel coronavirus genome sequences. Since the emergence of SARS-CoV-2, a total of 14,818,161 sequences have been shared with GISAID globally as of the last GISAID update on 27 Jan 2023, of which India has shared 225840 till the last week of Jan 2023. The reason behind this low number of sequenced samples is because of strict control of the Government over genome sequencing. Initially, NIV and ICMR were responsible for sequencing samples of international passengers from countries with a surge in cases. In December 2020, the Indian Government established a multi-agency consortium, the Indian SARS-CoV-2 Genomics Consortium (INSACOG), to track SARS-CoV-2 variants within the country. INSACOG is a Pan-India network of 54 laboratories, among which 10 private laboratories were added in early 2022 due to a surge in omicron cases worldwide.

In comparison, New Zealand has conducted genome sequencing for more than 39 % of its total cases and is one of the best-performing countries. Meanwhile, the United Kingdom has conducted genome sequencing for 10% of its total cases, and the United States has done so for 3.35%.

INSACOG was set up to sequence at least 5% of COVID-19 samples. But only 1% has been achieved yet, reasons for which could be many, including an exponential rise in the number of cases during the Pandemic. If we look at the capacity augmentation for COVID-19 testing, we find that we did less than 100 COVID-19 tests per day at the onset of the COVID-19 pandemic in January 2020. Still, India phenomenally increased its diagnostic capability in a few months and reached a capacity of more than 17 lakh tests per day at the peak of the Pandemic. The same was possible with the involvement of the Public-Private Partnership model, with govt acting as an apex regulatory and monitoring body. Similarly, Public-Private Partnership is the only plausible way to meet the rising demand for Genome Testing. Govt should permit Genome testing in Private Labs with result sharing on a commercial basis. Genome testing setups are already available in many corporate hospitals. Many of them are allowed to do genetic analysis for research purposes but are not permitted to issue reports on a commercial basis. Once allowed commercially, more business houses would be ready to invest, mainly when genome testing equipment is available from \$ 1,000 to >\$ 50,000. The Pandemic has provided the opportunity to popularise the test as the ongoing demand for the test is likely to break even the initial investment costs, leading to comfortable future modelling.

Genome sequencing may have been popularized by Covid-19, but it has a significant role to play in the future of healthcare. For example, it can diagnose rare genetic disorders, help make personalized medicine decisions, and monitor the ever-increasing threat of drug resistance.

Opponents may always argue about the risks involved with Genome testing. There are a lot of fears and concerns. For example,

routine genome sequencing could overwhelm doctors and patients with confusing and sometimes alarming information, leading to anxiety, stress, and expensive and sometimes dangerous follow-up testing. In addition, infringing on privacy concerns may lead to the opening of the pandora's box, threatening the fabric of familial networks.

But Governments can always exercise control through legislation and strict punishments. Various potentially risky but beneficial programmes like organ transportation, IVF, child surrogacy, pre-natal diagnostic ultrasounds and genetics have shown how responsible citizen behaviour and strict legislative control can yield good results while protecting society from the misuse of scientific advancements.

During the Pandemic, tests like IL-6 descended from research labs to next-door street laboratories. RTPCR became a familiar name. Similarly, expanding the Gene Testing Network for the nation could be a Golden Opportunity. Labs set up today will unlock unseen frontiers in the future and benefit humanity. Let it not become an opportunity lost.

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