The most important critiques, which we've either addressed or aim to address, are:

- **Multiple comparisons**: did we check 100's of enzymes and run many statistical tests, reporting only the most significant finding? We did not do this - we chose these enzymes a priori because of their dominance in the market for this kind of assembly, and we separated our assessment of the outlying nature of SARS-CoV-2 from later estimates of the probability of meeting various criteria required for a reverse genetic system.

- **Type IIS sites aren't retained in the genome**. This isn't true. It stems from a miscommunication on my part - I referred to this assembly procedure as "golden gate assembly" in my tweet (we avoided that term in our manuscript in favor if "*in vitro* genome assembly" or IVGA). While it's possible to assemble genomes and not leave type IIS restriction enzymes in place, the common practice amongst those making infectious clones of coronaviruses pre-COVID was to leave the type IIS sites in place. This was the protocol developed and recommended for the creation of "efficient reverse genetic system", as leaving type IIS sites in place allows further modifications of the infectious clone. With conserved type II sites across genomes (whether IIS or IIG), one is also able to make chimeric viruses and study the functions of new genotypes found in novel coronaviruses. We ran a meta-analysis of infectious clones of coronaviruses made with type IIS enzymes over the period from 2000-2019, and almost all of them retained the type IIS sites as recommended for efficient reverse genetic systems. There are different methods used by different researchers and across different fields and over different time periods, so we focused on the most common method for making infectious clones in CoVs pre-COVID.

- **These sites are found in other genomes and could be explained by recombination**. It is true that recombination is common in RNA viruses. For that reason, we studied a wide range of coronaviruses that were collected methodically for good coverage of the many clades of coronaviruses. Contrary to this critique, our paper points out that these sites are found in other coronaviruses, however no other coronavirus had such a regular-spacing of sites. Other sequences being shared appear to have similar sites as well, but, for those we've examined thus far, these additional sequences lack the regular spacing of type II restriction sites that we identified as a fingerprint of an efficient reverse genetic system. Consequently, recombination has played a role in all other CoV genomes and it has not produced such a regular spacing of type II restriction sites permitting IVGA - SARS-CoV-2 remains an outlier, and our follow up analyses finding a high concentration of silent mutations in these sites still hold.