A CALL TO ARMS: WE CAN ERADICATE SARS-CoV-2 NOW

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Introduction

Enormous progress in next generation sequencing techniques has opened the way for repetitive population-wide testing for SARS-CoV-2, the only strategy guaranteed to rapidly end the current uneasy trade-off between death by disease versus death by poverty.

The COVID-19 pandemic, now a few months old, has changed the world beyond recognition. Millions have been infected, hundreds of thousands have died, livelihoods have been destroyed, and the global economy is now experiencing its deepest recession in almost a century.

In response, nations across the globe have deployed a range of different policies to stem the tide of infections, from initial containment attempts and global 'social distancing' approaches, supported by varying amounts of testing and contact tracing, to the hope for herd immunity and/or vaccines. The importance of testing has been stressed by many, however, the fact that in a disease with a majority of carriers with no or minimal symptoms the appropriate metric of success is not the fraction tested, but the fraction untested, has maybe not been sufficiently considered. This has brought us to an uneasy compromise, combining unnecessary suffering and death with similarly unnecessary economic costs and restrictions on our freedom. The search for a conclusive solution to this global pandemic is intensifying, with major efforts focused on the development of a vaccine; however, we still have a long journey ahead of us and no guarantees, possibly condemning us to a long continuation of variants of the current situation.

This is not necessary. We already have the tools at hand to end this intolerable situation now, based on repetitive population-wide screening, made possible by the enormous progress in Next Generation Sequencing (NGS) techniques, in combination with intelligent contact tracing approaches. To make this reality, and to guard against future similar pandemics guaranteed to arise, we need to establish country-wide (and ultimately world-wide) infrastructures, with the capacity to screen entire populations at multiple time points.

Since SARS-CoV-2 is absolutely dependent on new infections for its survival, identifying and quarantining ALL infected individuals will rapidly drive the virus to extinction. In contrast to the hope for a vaccine, which may or may not be available anytime soon (or ever), this strategy is guaranteed to work given what we already know about the biology of SARS-CoV-2, and can be used now to eliminate this virus within one to two infection cycles, once the necessary infrastructure is in place.

NGS-based parallel sequencing en masse

Similar to the promise for truly personalised medicine, based on techniques allowing us to generate more molecular information about an individual patient than we had on all of human biology before, this new option leverages and builds upon the technological developments triggered by the Human Genome Project. We now have access to powerful sequencing technologies that enable massive parallel sequencing at ever decreasing costs, illustrated most dramatically by the cost reductions for sequencing a human genome from billions to maybe $100 by the end of this year.

We can use this enormous sequencing power to identify (and quarantine) the virus in each individual. By identifying the virus, we can pin-point ALL infected individuals in a country, a continent, or the world, by processing and analysing millions (maybe billions) of samples in parallel, ensuring that the individual sequences generated can be linked to an individual's infection status, using unique identifiers.

Every individual can provide samples, similar to the way it is currently done. The only difference is that everyone can provide the samples by themselves. For this, the health care facilities will need to distribute one or more sample tubes [1] marked by a machine-readable identifier (e.g. barcode). Depending on the overall procedure used, it can also already contain oligonucleotides encoding a second, sequence-based barcode, which will be incorporated into the preparation of sequencing templates, uniquely defining the sample it came from (see e.g. refs 2-5).

At the appropriate time, the individual spits into the tube [6,7], closes it, scans the barcode using their smartphone, and returns the tube to a designated analysis centre (in a pre-addressed return envelope, via the doctor's surgery or through a pharmacy etc.). At the processing centre, the templates for sequencing are prepared, which either already contain a unique DNA sequence identifying the sample or alternatively, a unique barcode is introduced into the sequencing template at this stage [3], and linked to the barcode on the tube identifying the sample. Templates are then pooled, and analysed by NGS.

Sample tracking

To be able to contact the infected individuals, different systems can be chosen:

1) A top-down system, in which a central organisation keeps track of the specific sample tube (and barcode) that has been provided to an individual. This makes it relatively straightforward to contact the infected individuals, to rule out further infection through quarantine, and to provide information to contact tracing apps.

2) A bottom-up approach, centred on the link between the sample barcode and the individual smartphone, established by scanning the barcode of the sample tubes before sending them to analysis centres. Through an appropriate app, the smartphone can identify the infection status of the sample, provide information on necessary quarantine measures to the infected individual, and trigger the contact tracing apps on other smartphones, which have recently been in close proximity to the infected person. This option would help to avoid data protection issues.

Cost-effective and feasible?

Implementation of the approach on a mass scale is of course a big question, and there has been much discussion of the challenges facing any large-scale testing approaches. However, a number of the elements required for this strategy - technology, capacity, experience and willingness - are already being put in place. Resources, mass production and distribution of kits requires the support of local authorities and compliance needs the willingness of citizens to participate. Big players such as Google and Apple have pledged their support in tracking the virus [8], (there are already a number of contact tracing apps), and we have the sequencing technology available. The roadmap for testing on this scale is being detailed [5] and we are ready to move forward, but we need the resources to make this reality.

With regards to costs, we expect the price tag for this program to be equivalent to a few euros/dollars per sample; a trivial amount considering the enormous economic loss already accumulated due to the need for social distancing. The actual sequencing costs are estimated at 1 cent per (infected) sample, for DNA fragments of approx. 300 bp, 3000 reads per sample and $10 per Gigabase sequencing cost.

We also have the technical capacity to do this. The highest throughput sequencing machines, NovaSeq 6000 from Illumina and DNBSEQ-T7 from MGI Tech, can generate approximately 20 billion reads in less than 2 days. Since sequencing templates will only be generated if

SARS-CoV-2 sequences are present, a single run will easily analyse all 500 million samples from Europe (given, that less than 4% of the samples are likely to be positive for this virus).

Breaking the infection chain

The goal of testing on this scale is obviously to identify infected individuals and their close contacts and be able to rapidly deploy quarantine measures, all in a bid to break the infection chain. If we can use this approach to interrupt the transfer from ALL infected individuals, the virus could be eliminated from a country within very short time. Even if the system (like all systems designed by humans) is not perfect, we should at least be able to dramatically reduce the number of infected individuals to a level that can be handled by contact tracing. To enhance compliance, a system of incentives could be beneficial, which would enable individuals deemed as 'low risk' to regain freedom of movement more quickly. For example, an individual Bayesian risk score could be calculated using a smartphone app, based on a combination of test outcomes (including other tests conducted, e.g. antibody tests), contacts tested positively, potentially mobility patterns and population parameters, with low risk individuals facing no or minimal restrictions, leading to a gradual re-opening of society on its path back to normality.

For this, for other infectious diseases, and for future pandemics we urgently need national or supranational infrastructures with the capacity to carry out repetitive population wide testing/contact tracing and use it to drive SARS-CoV-2 and maybe other infectious diseases into extinction, a different type of 'fire brigade' ready to spring into action, whenever we face this type of threat. And we need them now, more than ever, in view of the very high fraction of infected but symptomless individuals in this disease, as well as the increasing tensions in society.

References

1. https://www.scientificamerican.com/article/at-home-coronavirus-sample-collection-kits-arent-perfect-but-could-help-fill-testing-gap/
2. https://hms.harvard.edu/news/soup-nuts
3. https://www.notion.so/Octant-SwabSeq-Testing-9eb80e793d7e46348038aa80a5a901fd
4. Schmid-Burgk JL, Li D, Feldman D et al. LAMP-Seq: Population-Scale COVID-19 Diagnostics Using a Compressed Barcode Space BioRxiv doi: https://doi.org/10.1101/2020.04.06.025635
5. Esbin Mn, Whitney ON, Chong S, Maurer A et al., Overcoming the bottleneck to widespread testing: A rapid review of nucleic acid testing approaches for COVID-19 detection. RNA 2020, Published in Advance May 1, 2020, doi: 10.1261/rna.076232.120
6. Biocensus White Paper: https://docs.google.com/document/d/1jbZP1pU685YCcncxF0a2HZhgZgojZcGzrKcz4RK_3eU/edit#heading=h.ouyzwymuswy1
7. Wylie A, Fournier J, Casanovas-Massana A et al., Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs. medRxiv doi: https://doi.org/10.1101/2020.04.16.20067835
8. https://www.popsci.com/story/technology/google-apple-coronavirus-app/