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# Case report for BioIT innovations in Medicine and Health: How can we handle major threats to our health and survival rationally?

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# Global challenges

To face current and future global health challenges, we need solutions that converge at the interface of life sciences and information technology (BioIT), as well as systematic methods that allow us to rationally evaluate these potential routes forward. In the following, I will describe two major medical challenges: (1) Covid-19 and future pandemics, and (2) the general problem of truly personalising the choice of the individually optimal therapy and prevention measures, initially in oncology, but ultimately in all areas of medicine, disease prevention, and lifestyle choices. For both problems, logically convincing (BioIT-type) solutions have been proposed, but, unexpectedly, have not been seriously considered.

## Challenge 1: The Covid-19 pandemic

SARS-CoV-2, the virus causing Covid-19, has changed our world beyond recognition. The death toll continues to increase, edging its way closer to the one million mark (currently close to 850,000, but rapidly increasing). It causes immense human suffering and trillions of euros in economic damage, leaving some with the choice of dying by the virus or by hunger (or both).

Logically, there are two main ways out of this situation: (1) the development of an effective vaccine, and (2) a dramatic increase in testing (ideally a few cycles of synchronised, population-wide tests) to identify ALL infected on a national or supranational basis and to quarantine them until they stop being infectious.

To date, all hopes of extinguishing Covid-19 are resting on option 1 – vaccine development, supported by very large amounts of public and private funding. However, there is no guarantee that a safe and effective vaccine can be developed (after decades, the anticipated HIV vaccine is still not available), that it will be 100% effective (the US Food and Drug Administration's Covid-19 vaccine approval guidelines state it should prevent or reduce severe disease in at least 50 % of people who get it [1]) and how long we have to wait for it.

It would therefore seem critical to complement this by a similar effort on the obvious alternative, which could theoretically rapidly eliminate SARS-CoV-2 from Germany, Europe, and potentially most of the world. Population-wide tests on the national or supranational level will obviously constitute a significant logistical challenge (it will be difficult to get enough test tubes for such a large number of tests, but it is not going to be easy to get enough vials for vaccination either); however, compared to other challenges that we have successfully navigated (e.g. landing on the Moon), it seems far less demanding (and maybe even more important for humanity).

Early in the pandemic, the World Health Organisation (WHO) head Tedros Adhanom Ghebreyesus emphasised the importance of escalating testing, isolation and contact tracing, seeing this as the "backbone" of the global response. However, despite growing media interest and discussions on how this could be implemented [2] for repeated and synchronised population-scale testing, there has been no obvious systematic evaluation of this concept? What do we need to trigger this critically overdue discussion?

It is clear that the current 'gold standard' for SARS-CoV-2 tests, the individual analysis of every sample by real-time PCR, is far too expensive and capital- and work intensive to be scalable to synchronised testing of large populations. One solution, however, is to leverage the power of next generation sequencing (NGS) to enable co-ordinated and repeated massive parallel testing across a population, in combination with the ongoing development of contact-tracing IT-based technologies.

Since the publication of the initial proposal for this strategy [2] in collaboration with George Church at Harvard University, I have been working with colleagues at Alacris Theranostics (www.alacris.de) in Berlin (an individualised medicine company I co-founded in 2008) to develop scalable implementation solutions, focused on the crucial logistical and technical bottlenecks. Leveraging recent progress in next generation sequencing (NGS) technologies and industrial automation capabilities, we aim to develop a scalable and cost-efficient approach for repetitive population-scale testing, suitable for rapid implementation and compatible with existing quarantine and contact tracing efforts. For example, in Germany, with a population of ~83 million, we would need an almost two order of magnitude scaleup from the current test capacity (~1.1 million tests per week) in order to reach this coverage. For this, we need to solve four main challenges:

**1. Upstream logistics: Receipt and handling of hundreds of thousands of samples for processing.**
Solution: Samples are collected at local sample collection centres (e.g. pharmacies) in small plastic tubes containing a bar code identifier. The collected tubes are sent via couriers to processing centres. Saliva samples are used to provide ease of collection and a reduction in use of resources (i.e. no swab kits required).

**2. Sample processing: Pooling of samples to enable higher throughput.**
Solution: Automation approaches are used to ensure that samples can be swiftly processed, including handling of sample tubes, pooling of samples and sample tracking via automated bar code readers that link sample tubes to individuals (and their smartphones).

**3. Sample testing: requires a modified version of the current RT-PCR-based protocols to ensure rapid throughput.**
Solution: A modified massively parallel RT-PCR approach without a separate RNA extraction stage, using high-throughput PCR machines (e.g. waterbath PCR), instead of expensive, low throughput qPCR systems. If NGS is later used to read out the results, primers containing unique DNA sequences (molecular barcodes) are used, to indicate which tube the sample derives (if virus positive).

**4. Test readout: allowing a high throughput of samples**
Solution: Here we have two solutions: We can use high throughput optical readouts on PCRs run to an endpoint (all samples containing SARS-CoV-2 RNA amplify to the same value) or we can generate quantitative data by pooling the appropriately barcoded reactions, using NGS as a rapid and high throughput readout, in principle capable of generating 20 billion sequences in a day, enough to read out the test results of all Europeans in a single sequencing run.

The optimisation of each of these stages will provide the necessary capacity for weekly cycles of population-wide tests, leading to the potential elimination of the virus, at a cost orders of magnitude below the current testing strategies, and with the potential to guard against possible future pandemics, possibly even more devastating than Covid-19. This 'container-based', globally scalable solution for high-throughput repetitive testing for SARS-CoV-2 and other respiratory viruses, represents a key advancement in the establishment of a rapid response infrastructure for current and future viral threats.

## Challenge 2: Unnecessary suffering, death and costs due to insufficient personalisation of therapy choice, prevention and lifestyle choices

We are all different. We have different genomes, suffer different diseases, live in different environments, behave differently, and often have molecularly very different, but superficially similar diseases. It is no surprise, therefore, that we often react very differently to drug therapies, and drug-based prevention, a problem that contributes to many deaths (almost 200,000 Europeans die every year from adverse drug reactions [3]), to delays in the use of the optimal therapy optimal for the individual, and to the enormous costs of the health care systems (4.5 billion euros every day within the EU [4], a significant fraction for drugs that do not help the individual patient they are prescribed for, and downstream costs of treating the effects of using the wrong drug).

As the tools to characterise individual patients molecularly have increased in power enormously (both sequencing costs and costs for computing power have dropped roughly a million-fold over the last 20 years), it is now increasingly possible to follow the (very successful) example of how we handle similar problems in other areas: when faced with complex problems, we cannot avoid making mistakes, but in essentially all areas except medicine, we have learned to make those mistakes safely, cheaply and quickly on computer models. We build cars or planes first as computer models, test their safety by virtual crash tests, train pilots on flight simulators rather than on real planes full of passengers, and predict the weather by computer models, rather than being surprised by life threatening tropical storms.

In a future, truly personalised medicine, we should similarly be able to carry out a deep molecular analysis on every patient (and, in fact, on any individual wanting to interact rationally with his/her own biology, irrespective of whether this concerns the optimal therapy choice in a life threatening disease, or the individually optimal program in a fitness studio). Based on this detailed information, we should be able to establish a 'digital twin', a personal computer model optimised to predict the response of the individual to possible interventions (therefore the digital twin of the same person for selecting a cancer therapy will be very different from one designed to predict the effect of specific training schedules).

We are obviously not there yet, but the development of analogous simulation systems for virtual crash tests for cars or maintenance scheduled for jet engines also took time and money to develop. We already have much of the basic technologies we need. The critical point is really to prioritise where we want to be at the end - a truly personalised medicine, prevention and lifestyle selection - rather than simply improving the technologies incrementally, without having a final goal in mind.

We are, however, very close in specific areas. Deep molecular analysis (an essential part of precision medicine) is already facilitating the selection of drugs in oncology, helping to pinpoint those drugs a particular tumour and patient are much more likely to respond to (www.alacris.de). To simulate the effect of drugs on our individual cellular (tumour or normal) biological networks, we have established detailed reference computer models combining well-known cancer relevant pathways. These models can be personalised with detailed molecular information from an individual tumour and patient (e.g. gene expression changes etc.). To predict the behaviour of the tumour (e.g. its response to a specific drug), we have to convert the model into equations which can be solved numerically, if (and only if) we provide values for the currently unknown parameters (e.g. kinetic or equilibrium constants) in these equations. While the structure of the model is typically well defined, based on the results of basic research over many decades (and billions of funding), we still know very little about these parameters within the complex environment of cells (and organisms in general), critical for generating accurate predictions. For this, 'parameter

optimisation' approaches are used, based on minimising the differences between model predictions and experimental data used as a training set, followed by validation on independent test data. In our view, identification of these parameters represents a crucial step forward towards accurate predictions of an individual's response to targeted cancer drugs, allowing direct use of personalised computational models for helping to determine the optimal therapy choice - the data and model-driven personalised medicine of the future - but also key to in-silico clinical trials and other steps to accelerate and de-risk the development of new drugs.

We are currently very close to solving this bottleneck, with current models already generating good predictions of how a tumour will behave when treated with specific drugs.

We should not have to be dragged kicking and screaming into a new age of truly personalised therapies, made possible (and soon even relatively cheap) through the enormous progress of BioIT-based technologies. We should not insist on treating hundreds of thousands of cancer patients first with chemotherapy, with its associated side effects, rather than finding out which therapy would actually be optimal for an individual patient, via a deep molecular analysis of both patient and tumour (which could very well be the chemotherapy they might have received otherwise). We should use the full power of the technologies we already have available (and will have available over the next years) to start implementing true personalisation in medicine, rather than continue on the (obviously wrong) model that everybody is likely to react the same. We pay lip service by bending, where unavoidable, to the overwhelming evidence that we can react very differently, using (often not very powerful) biomarkers to stratify patients into groups; a process, which seems conceptually similar to the increasing complexity of different instalments of the Ptolemean view of the world, adjusted, where absolutely necessary, by an increasing number of epicycles. We need to shift to a 'Copernican' view of medicine in which everybody is likely to be different and has to be treated, as much as possible, as an individual, based on the molecular and clinical data available for them.

# Why BioIT?

We ultimately exist on the basis of biological processes carried out by components directly or indirectly encoded by a digital medium, our genome, forming organisms of a complexity that can only be characterised by the full power of the digital revolution we are currently part of. Ultimately, it is these biological processes that determine if we are healthy or sick, and if we live or die. Understanding and, where necessary, controlling these processes is therefore key to our survival, not only as individuals but also as species, a fact that we have been forcefully reminded of by Covid-19, a pandemic that has shaken human societies to their core.

The importance of understanding and analysing biological processes in great detail, in order to mitigate, treat or prevent disease has, however, not always been recognised sufficiently in the priorities of governments. For example, it is remarkable that the ~1.1 billion euros per year allocated to health via the 'Global Challenges' Pillar within the European Union's (EU) forthcoming Research and Development Framework programme Horizon Europe, is similar to what the EU is now spending every few hours to mitigate the catastrophic effects of Covid-19; a pandemic we have been ill prepared for. Tens of millions of euros in preparation could have saved millions of lives and trillions of euros, if we had taken the threat seriously.

We are still not reacting sufficiently rationally to the very real threats that face us as societies. Rather than systematically analysing all possible options, we pick one and ignore another, without robustly determining the chances of success. Even in mortal danger, we are not guided by logic, but by a complex interplay of factors, causing us as societies to suffer (and pay) a heavy price. If our economies and our societies are destroyed by a virus, if we starve, because our key crops are killed by diseases, and if our environment becomes uninhabitable because of global warming, we as societies are forced to focus on what is really essential - our health and survival.

# How should we evaluate possible solutions to our problems?

Few possible solutions to problems guarantee success (or if they do, they typically come with unacceptable costs). Any proposal comes with uncertainties, typically larger in '*out of the box*' solutions, but such risks can often be compensated for by having a much larger potential impact than the 'safe' solutions usually chosen in practice. It is, however, theoretically relatively straightforward to assign approximate cost-benefit ratios to different courses of action, enabling us to identify potential solutions that are worth pursuing (or not).

As a very rough approximation, we can define the cost/benefit ratio for any course of action by the following:
(impact if successful) *(probability of success)/cost

defining whether a particular course of action will, on average, generate more or less in benefits to an individual or to society than it will cost to implement. For example, a potential 'out of the box' solution with a relatively low chance of success (e.g. 10%) could cost billions of euros, but have the potential to save trillions of euros (ignoring, for the moment, human suffering and death).

Amazingly, such criteria do not seem to be used in many decisions with sometimes drastic consequences to our lives. Decisions seem to be made based on 'gut feeling' (often based on ignoring the probabilities involved, by redefining them as 'likely' and 'unlikely'), and a massive preference for changing current systems as little as possible (maybe reflecting the political influence of individuals and organisations benefitting from it?).

## Choosing the 'best' solution(s) — a transparent solution-led approach

It is useful to remember that solutions to problems can come from unexpected sources. Take, for example, the approach used by many large companies in Japan where they have a dedicated channel for soliciting suggestions for improvements (for known and unknown problems), with a guarantee that all suggestions will be considered on their merit, and only turned down with a written justification ('the Toyota way'). Maybe we need government support for innovation without compromise: not an automatic priority of supporting 'what is', rather than 'what could be'. If we are facing lethal dangers, for which no obvious 'in the box' solutions exist, it is not unlikely that interdisciplinary 'out of the box' solutions can be found, but often these run the risk of being ignored.

Governments and administrations are often much better equipped to understand and explore legal, political or social solutions to problems rather than technology-based ones. Thus, there is a tendency for governments to react to problems once they are pressured to do so, either from the general public or influential heads of companies or major organisations; the latter often influenced by the interests of their companies or members.

When dangers appear or even seen as a possibility (scientists had been highlighting the threat of a pandemic for many years prior to Covid-19), it is the duty of governments to prepare by finding solutions. As experts in relevant fields are often not very well equipped to appreciate the effect rapid changes in other fields can have on providing solutions to our problems, the use of extensive, independent interdisciplinary panels on serious issues who can offer alternative solutions should be seen as standard. This has to be complemented by a legal duty of governments to solicit solutions from a range of sources, maybe even with financial rewards, and, importantly, to make sure that any solution proposed is fairly evaluated, in critical cases by public meetings, and not simply ignored or turned down without a careful evaluation.

If a solution passes this test, governments should have the duty to fund, with the highest priority, implementation steps (e.g. initial pilot projects), to objectively evaluate the proposal, and, if appropriate success and cost- effectiveness are reached, a full implementation. No other solution will work quickly enough.

In situations in which millions of lives and trillions of taxpayer's money can be at stake, we simply cannot continue to rely on governments making decisions without systematically considering all options (in a process that also involves the originators of alternative concepts). We can (occasionally) afford to make suboptimal decisions, but not in questions of such overriding importance. Criminal cases are based on the criterion of '*beyond a reasonable doubt*'. The same criterion should apply when we decide between actions that could, in a single country, avoid thousands of deaths or cost billions of our money, a criterion obviously not fulfilled when reasonable and potentially better alternatives have never been considered.

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