Aptamers for Detection and Diagnostics (ADD): Proposed mobile app acquiring optical data from aptamers conjugated with quantum nanodots may detect harmful molecules as well as SARS-CoV-2

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ABSTRACT

Engineering a biomedical device as a low-cost, non-invasive, detection, and diagnostic platform for surveillance of infections in humans, and animals. The system embraces the IoT *"digital by design"* metaphor by incorporating elements of connectivity, data sharing and (secure) information arbitrage. Using an array of aptamers to bind viral targets may help in detection, diagnostics, and potentially prevention in case of SARS-CoV-2. The ADD tool may become part of a broader platform approach.

1. ADD for SARS-CoV-2

The scale of mortality and morbidity due to SARS-CoV-2 evokes us to explore unconventional approaches to mitigate the risks presented by pandemics. Scientists may be less aware of the discovery of aptamers thirty years ago but the "fit" of aptamers with respect to the molecular biology of the current problem makes it worthwhile to propose new tools. Innovation may arise from the combination of chemistry and molecular biology with sensor engineering and opportunity for data dissemination[1] to benefit public health[2] by integrating the principle[3] of internet of things[4] (IoT[5] as a design metaphor).

	Emergence	Cases	Fatality Rate	Transmissibility
SARS	2003	8,098	11%	+
MERS	2011	2,519	34%	+
SARS-CoV-2	2019	> 40 million	0.5-1% Est	+++
SARS-CoV-3?	??	??	??	??
SARS-CoV-4?	??	??	??	??

Table 1: Is the eight[6] year interval between SARS, MERS and COVID-19 just an unrelated coincidence?

2. Aptamers for Detection and Diagnostics (ADD)

Single stranded (ss) DNA aptamers (ssRNA[7] are equally useful[8] but susceptible to degradation by ribonuclease) bind with specificity to SARS-CoV-2[9] proteins (Nucleocapsid, Spike, Nsp1). Aptamers are conjugated with carbon or cadmium quantum (QT) nano-dots. If there are viruses (1, 10, 100, 1000) in a sample (sputum, saliva) at a detectable level, then it triggers QT.DNA (QTD) conjugated complex to transmit optical property change (EIS or electrochemical impedance spectroscopy is another option for signal transduction). An optical signal transduction mechanism may offer low cost data acquisition, enabling billions of people to use ADD (detection tool) *at home or anywhere* (AHA). The end-user must have access to the **"QTD"** conjugate (distributed by health departments in hamlets, towns and cities). QTD (product) may be a slurry in a tube labeled as **"CoV-2-DETECTION & DIAGNOSIS" (C2DD).** It remains to be investigated if inclusion of endo-b-N-acetylglucosaminidases (ENGases[10]) in the slurry may be necessary to expose the binding sites by partially removing the N-glycan coat if the viral Spike protein is the target (Figure 20). Imagine **C2DD** as a tube of lip balm or similar form factor. For supply chain and logistics, it will reduce operational cost of distribution if **C2DD** may be shipped as a tamper-proof sterile vial without the need for cold supply chain or special storage to extend shelf-life.

First, the end-user uses her ***smartphone holo-lens*** **"QTD" app** (may not be limited to Microsoft, others who can/may develop are Apple, Google, Baidu, Tencent) to take an image of the C2DD vial/tube ***without*** sample (no virus). Priming (tuning) step is **critical** to establish a baseline for signal transduction and app-embedded data analytics engine to set the system to "without virus" ground state to obtain an optical "ground zero" (baseline will be different for EIS). Open question for instrumentation is the need for UV activation (for traditional nanodots) to record the shift (valence electron transfer). Can the app be configured to *perform the activation* and record the photoluminescence change? Using visible light to activate and coupling activation/quenching with the app needs innovative chemical/device engineering.

Second, the end-user spits (or adds a small volume saliva or sputum using a swab/spoon) in the test tube (vial). *There is room for controversy in this step but it is the easiest non-invasive procedure.*

Third, end-user uses her smartphone holo-lens **"QTD" app** to record optical change (as soon as possible after adding saliva/sputum). Perhaps similar to bar code or EPC or QR code scanning.

Fourth, end-user uses her smartphone holo-lens **"QTD" app** to record optical changes every 5 minutes for 30 min (from the time of adding the sample). There will be questions about ENGase activity, binding kinetics of the aptamer, signal to noise ratio ([filtering algorithms (Kalman[11] filter), error correction], activation/quenching issues, damping of signals due to interference from host proteins, salinity and **pH** of mucus-mucin/saliva/sputum sample (any or all could jeopardize binding and signal).

3. ADD Digital Data Design

Baseline versus change over time will appear as a plot in the app (analytics, Figure 1, uses basic machine learning (ML) tools, for example, SVM or support vector machine). Fool-proof visualization by generating a **"traffic signal" visual** [green oval (NO virus detected); red oval (virus detected); yellow oval (inconclusive/ambiguous)]. Data gathered by the smartphone app (if enabled by user) to be transmitted to national centers of epidemiology (eg CDC in USA, ECDC in EU) and local hospitals (the choice will be user-dependent). Allowing collection of anonymized data may be one alternative (without recording IPv6/IPv4 addresses) but pros/cons to be considered for the greater good, public safety and privacy[12].

This app is a "frontline" detection tool which may be used **everyday** or each week, At Home or Anywhere (AHA), by individual users. The **"C2DD"** vial has no therapeutic value. Positive results (red oval - virus detected) may have to be re-confirmed using lab tests (PCR, mAbs) in a clinic or hospital. **C2DD** *PRODUCT and* ***associated*** *SERVICE* **"QTD"** app if combined, are ***data-informed tools.*** It does not offer or guarantee further testing or treatment. Distribution and pricing of the hypothetical **C2DD** product and proposed pay-per-use (**PAPPU**[13]) service for **QTD** will be debated by corporations. Free distribution of C2DD and a **micro-payment** model (pay-per-use) for the **"QTD"** app is ***advocated.***

Users may hide or selectively control data/information sharing as well as access to surveillance data (data from daily screening for infection by the infectious agent in question). Secure sharing of surveillance data by users (**citizen science**) is recommended to generate a robust and representative status of the community or infected demographics in the region in terms of **molecular epidemiology**.

In general, data from molecular epidemiology is critical for resource-constrained healthcare supply chains to optimize planning (humanitarian logistics), allocate human resources (medical professionals) and organize transportation of materials to the geographic areas where assistance is needed, the most.

Citizen science[14] efforts are germane for the efficacy of healthcare systems in case of widespread infections (epidemics/pandemics). The tools which makes citizen science possible and effective may be viewed as global public goods. Similar systems for **animal surveillance** (farms, cattle, poultry, meat) are necessary to reduce infection in domestic animals (pets) and from crippling the food supply chain.

Components of the ADD system (QTD, C2DD) including mobile data collection, information arbitrage and public health applications are not limited to SARS-CoV-2 but is a **platform approach** which includes digital design elements illustrated[15] in Figure 1. Citizen science supported public health may immensely benefit from detection of viruses, bacteria, fungi, prions or ***any infections agent*** as long as an aptamer (oligonucleotide based on the idea[16] of an "anti-sense" approach[17]) may bind a small molecule or a macromolecule (peptides or proteins) with sufficient specificity, sensitivity and selectivity to generate credible data which may be *distributed* in real-time to inform and initiate subsequent steps.

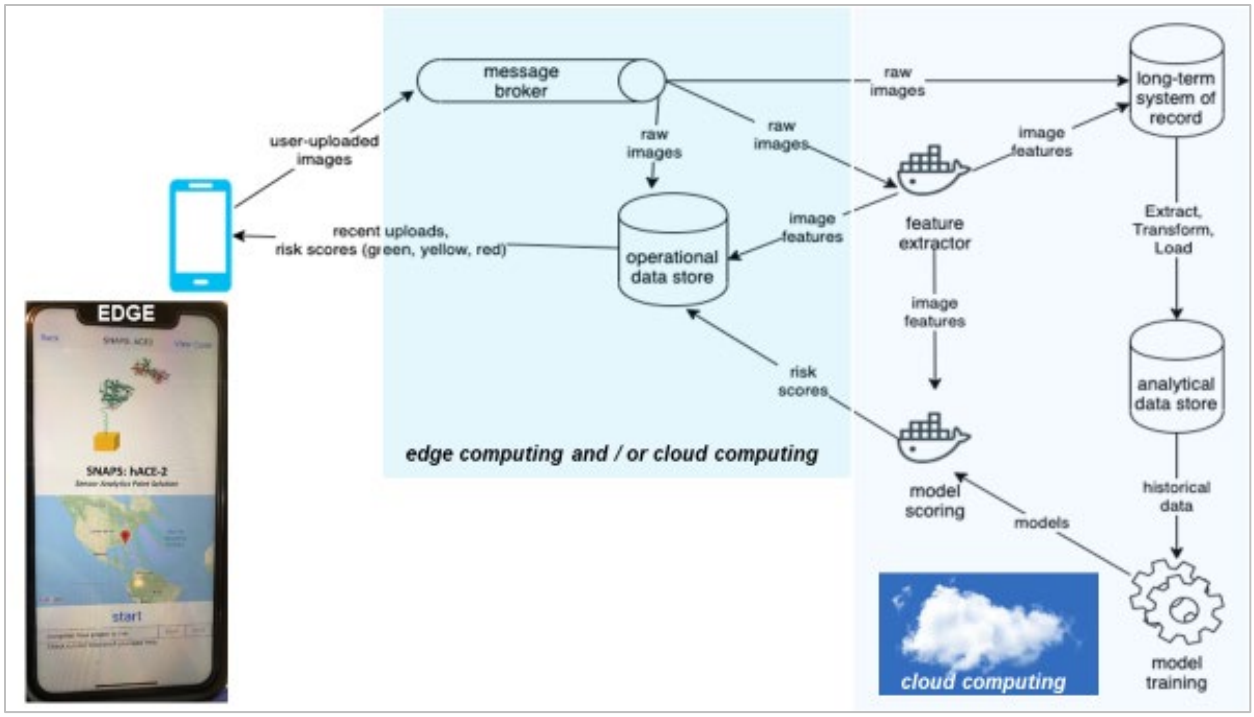


Figure 1: ADD system also includes data acquisition, analytics and data distribution which includes elements of the concept referred to as internet of things (IoT) which is a "digital[18] by design" metaphor. Cartoon shows the potential path of raw data from the hypothetical binding between a sensor and a target[19] molecule. Raw data from signal transduction due to binding activity is transmitted and acquired at the "edge" by the smartphone. The raw data is "processed" using tools either at the edge (embedded operations in the smartphone) or data may be uploaded to the cloud. Post-cloud computing analytics is returned to the edge device for display within an ADD application portal on the smartphone. The choice between edge versus cloud computing is a function of infrastructure (availability of wireless bandwidth, at the edge). The user may observe a difference in the time that it takes to process the data and display information (delayed visualization due to latency, function of bandwidth and speed).

Data scoring and processing is recommended due to variability of systems. ADD proposes the use of aptamers but other alternative arrays (see section 6) which may use the general approach (above) may "weigh" the information based on probability of false positive / false negative outcomes from tests[20] (separate from false positives / false negatives in machine learning[21] models). Assigning weighted risk to data and running other analytics can be performed on the mobile device (smartphone) or in the cloud, depending on access to and quality of telecommunications infrastructure. Cloud computing could add latency[22] between upload and display of information or prediction, depending on availability, reliability and connectivity to the internet. Several regions of the world still lack sufficient access to the internet[23].

Scoring, processing and assigning risk within the analytical engine may benefit from machine learning (ML) tools to create a set of models or rules, to be described by and agreed on by experts. The system may scan and screen the image or data from the holo lens app (optical signal) to compare with these models or rules. Assigning an "image risk score" (IRS) may influence the presentation of the raw data where the "traffic signal" "red" may be provided with a sub-text containing a confidence score or include a qualitative comment (***likely*** presence of virus) associated with a Likert-type[24] indicator/scale.

In any procedure, enabling the IRS to influence the raw data must be stringently controlled. Models or rules must be agreed by global experts whose credibility may be above question. Hence, these models and rules must stay outside the realm of testing services or labs or groups that are involved with creating systems, for example, ADD. It is preferable if model scoring (assigning risk score to an upload) runs on a platform which is not influenced by the local operator or the mobile user. The smartphone uploading the data may use a "tool" that applies the IRS engine residing in a secure infrastructure in a public cloud (FDA, NIH, NSF, CDC, ECDC) using appreciable level of cybersecurity (eg. Microsoft Azure, Amazon AWS). The smartphone must have the permission and physical availability to wireless internet or mobile data network to remotely access analytical tools in the cloud, such as, the IRS engine.

One alternative is to install (and update) the data scoring models/rules (IRS engine) in the ODS (operational data store, see Figure 1). The 'message broker' receives uploads and sends them to the ODS, which serves "hot" data to the app. ODS database is tuned for rapid reads, and serves requests made by the mobile app (only recent uploads and metadata about those uploads, including "risk scores").

Risk scores are generated from models which are trained from historical data relevant to the test in question (using aptamer or antibody or other molecules, for example, hACE2). There must be access to sufficient statistical data from each type of test to create a credible risk score. If the model is based on bad data (garbage in), the risk score and IRS engine will spew bad information (garbage out). The model's responsibility to assign "risk score" impacts the "traffic signal" and could alter the outcome. Model training[25] requires vast quantities of historical data, curated and pooled across multiple users who used the test and ***verified*** their outcome. If the binding was positive it must be corroborated by PCR[26] or another test with even higher specificity to confirm the result from the binding test using ADD tool.

Model-building is an iterative exercise that requires lab data from testing to be evaluated by credible scientists before data scientists can use it (curate?) to train ML models, which are error prone[27]. In model scoring, a model (in the IRS engine) is called to act on the uploaded (input) data. This analysis generates a prediction, displayed on the smartphone as information or recommendation for the user. The outcome the user views depends on the ***design choices*** made in ML model[28] training. It is absolutely central that model scoring requires ***"features"*** (characteristics germane to model/analysis). Creating features[29] is the task of a ***team*** of specialists (scientists collaborating with data experts). Harvesting

feature vectors and data relevant to the feature is the task of feature extractors. It may be provided by humans or we may use automated[30] feature[31] selection/extraction[32] to generate features from raw data.

4. Beyond ADD

Scientific and engineering challenges to design ADD must embrace trans-disciplinary activities. But, no new physics is necessary. ADD may be available to **billions**, as a low-cost mobile AHA (at-home) ***product*** linked to IoT-type ***service*** app. The user experience is related to the service, not the product. The convergence of hardware and software with science and engineering as well as analytics and machine learning to ***meaningfully*** ascend the DIKW pyramid (data, information, knowledge, wisdom) is key to creating any detection **platform** where other tools and devices may upload data using open data APIs and standards-compliant data interoperability (DDS[33]) tools to aggregate or explore cumulative analytics, integrated with other systems, for example, geographic information systems[34] or GIS.

In the broader spectrum, ADD is an embryonic element of a potential ***global health surveillance platform*** (GSP) which may be pivotal as an early warning signal for humans and animal farms. Lessons from tsunami detection are sorely missing from public health policy discussions. Implementation of GSPs are neither a part of any local public health strategy nor on the agenda of precision population health management organizations (CDC, ECDC, WHO).

An important element of the ***global health surveillance platform*** (GSP) may include data from non-invasive profiling, referred to as *"pay-per-pee"* healthcare, which may be instrumental in molecular profiling for longitudinal studies on health and wellness[35]. GSPs may try not to dwell on genomics[36] (DNA) and expression[37] (RNA[38]) in imprecision[39] medicine but include proteomics because gene expression is insufficient unless the ***functions*** are ***implemented*** by proteins. Aptamers[40] in proteomic profiling (GWAS[41], metabolomics) and other applications[42] including ADD may benefit from synergistic integration to help predict status of health (collected papers[43] provide select applications of aptamer).

Genomics is a "snapshot" (static structure of the infrastructure) and transcriptomics (RNA, GTEx) is an indicator of expression, which is data, but data may not (always) contain information. Proteins bind[44] in a myriad of ways[45] and translates *data to usable information* to maintain standard dynamic operating procedures (physiology, homeostasis, metabolomics).

Proteomics is a "time series" but its analysis over time may be interrupted due to feasibility and logistics of implementing programs like *pay-per-pee* healthcare, not to mention the complexity involved in extracting sense, often cryptic, from thousands of protein profiles, *over time*. Static protein profiles using NMR and mass spec[46] tools only capture *snapshots*. Can proteomics make sense[47] of a cytokine storm as markers of counter-anti-inflammatory response[48] even before the infectious agent is detected? Perhaps it is utopian to expect proteomic profiling as a daily practice in healthcare and home-health.

A woman spits into a tube so that her saliva can be tested for the presence of the novel coronavirus.

COVID-19

Spit shines for easier coronavirus testing

Tests using saliva are cheaper and faster than those with nasal swabs—and can be just as accurate

Figure 2: (Top) *Pay-per-pee* healthcare may provide time series data for precision medicine. (Left) "*Collection of saliva samples by patients themselves negates the need for direct interaction between health care workers and patients. This interaction is a source of major testing bottlenecks and presents a risk of nosocomial infection. Collection of saliva samples by patients themselves also alleviates demands for supplies of swabs and personal protective equipment. Given the growing need for testing, our findings*[49] *provide support for the potential of saliva specimens in the diagnosis of SARS-CoV-2 infection.*"

5. Prevention follows Detection and Diagnostics

If viewed[50] as non-classical antibodies[51] then the role of aptamers vastly exceeds that of detection. It spills over into prevention, perhaps as an alt-vaccine, albeit non-immunogenic. Identifying aptamers that can detect viral proteins in saliva implies that the aptamers may also bind the same protein (albeit with altered kinetics[52]) if administered topically (nasal spray, throat spray, soft-mist inhaler). Protecting the naso-pharyngeal area by saturating it with aptamers which binds (irreversibly?) to proteins from respiratory viruses (SARS) may be a preventative measure. Asymptomatic[53], pausi-symptomatic and COVID-19 patients clearly expressing symptoms associated with SARS-CoV-2 may continue application of the aptamer cocktail to reduce the spread of infection by disabling (?) nascent virions. Aptamers preventing the spike protein (S1 RBD) of SARS virion from ***attaching*** to the ACE-2[54] viral receptor protein of uninfected cells may slow down the infection and development of COVID-19.

It follows that aptamers can also bind to any or all viral proteins not only in the extracellular space but also *inside* the cell. Delivering a portfolio of functional aptamers inside the cytosol must face the challenges posed by bio-availability and toxicity due to the potential for perturbing functions of essential[55] cellular proteins. Creating aptamers as ***alt-vaccines*** for ***any*** infecting organism (virus, bacteria, fungi, prion) which uses a protein in its lifecycle may be an (~30 year) old idea. Will the use of aptamers gain greater prominence in global public health practices, as a low-cost ***global public goods tool*** to contain the current and future epidemics and/or pandemics, worldwide, in humans and animals?

Single stranded RNA or ssDNA aptamers are not linear "tapes" but 3-dimensional ***shapes*** as illustrated by the discovery of tRNA[56] by Paul Zamecnik, Mary Louise Stephenson and colleagues at MGH, HMS. Publication of the discovery of tRNA by Zamecnik in 1958 catalyzed an array of milestones including the discovery of mRNA by Brenner[57] and Gros[58] as well as the *lac operon* model of feedback inhibition by Jacob and Monod[59], all three published in 1961. The role of proteins in regulation[60] emerged as central to physiology and metabolism. In transcription, translation and replication[61] the binding between proteins and nucleic acids acted as a "switch" (mechanism of action). The notion[62] of aptamers[63] germinated[64] in 1990 but it drew on knowledge from binding between oligonucleotides and proteins. Aptamers may be 20-60[65] oligonucleotides or more. Binding specificity[66] of an enriched pool may be orders of magnitude different (K_d) between a nearest neighbor or an analog. Sequential steps[67] are necessary from a starting sample (for example, 9×10^{14} ssDNA oligonucleotides) to arrive at an enriched pool of aptamers (19 ssDNA aptamers). The process has evolved[68] in complexity[69] and unique structures may be involved[70] in conferring specificity. In many applications[71] of aptamers[72] the debate also involves issues pertaining to trust and doubts[73] due to the constant demand for increasing accuracy and precision with respect to sensitivity, selectivity and specificity, in detection and diagnostics.

Current and future[74] application[75] of aptamers include chemistry[76], chemotherapy[77], food[78] safety, diagnostics[79], antibodies[80], alt-vaccines[81], imaging[82] and different[83] types[84] of biosensors[85]. ADD as a detection tool for SARS-CoV-2 proposes aptamer-based sensors (aptasensors) to detect SARS-CoV-2 proteins. When an aptamer binds with the target, the signal (data) will be transduced and captured by a mobile device. Analytical tools will process data and display information on smartphones (Fig 1). Data dissemination will follow according to user preferences, to inform public health authorities or hospitals.

Optimism for aptamers as detection tools[86] extend to SARS-CoV-2 due to the detection of SARS-CoV (etiologic agent of 2008 SARS epidemic) C-terminal of N (nucleocapsid) protein at a concentration as low as 2 picograms/mL using a RNA[87] aptamer in a nanoarray. Tests using saliva[88] may be unsuitable for RNA[89] aptamers due to presence of ribonuclease[90] (RNase). DNA aptamers previously shown to bind to the N protein of SARS-CoV (K_d 4.93±0.3nM[91]) also[92] binds to the N protein of SARS-CoV-2. The N protein[93] of SARS-CoV-2 shares 91% sequence homology with the N protein[94] of SARS-CoV but is less similar (16% - 38%) with N protein from the other 5 known human coronaviruses. Thus, detection[95] of N protein in saliva using an aptamer-based ADD aptasensor is *possible*. Aptamer-based technologies[96] directed toward SARS-CoV-2 Spike protein are gaining[97] momentum[98]. Blocking[99] the S protein from attaching to hACE-2 may perturb viral entry and prevent[100] the spread of infection. Aptamers created against the S1 RBD[101] may block binding to hACE-2 (internally) or serve as a detection tool (external ADD aptasensor) to test saliva/sputum for SARS-CoV-2. Other[102] SARS-CoV-2 targets[103] including Nsp1[104] may be less accessible in saliva because they are synthesized after viral entry. But, during the burst cycle, when new virions are released, viral proteins inside the host cell may be exposed. The targets are not limited to external viral proteins (spike, nucleocapsid, envelope proteins; Figure 4).

Signal transduction and *data acquisition* follows detection. In addition to EIS (electrochemical impedance spectroscopy[105]) signals, optical signals are preferred because data acquisition using cameras and apps in smartphones are feasible in locations where resources may be limiting. Protein[106] detection[107] by conjugating aptamers with quantum dots[108] is a tried[109] and true[110] process[111] which may be the optical signal (data) for this ***system***. Changes in optical characteristics due to binding may be captured by cameras on mobile phones or HoloLens[112] app in smartphones may scan the saliva sample (think barcode or QR[113] code scan). Cameras (sensors) associated with the holo-lens (Kinect[114]) can scan the "field" and collects data to create a digital geometry[115] (digital model, 3D image). For ADD, HoloLens tools required for holographic functions[116] may be unnecessary, for example, accelerometer (speed of movement), gyroscope (tilt, orientation) and magnetometer (compass). Optical data captured from saliva containing testing vials will be analyzed (machine learning tools; see Figure 1) followed by visualization of information on the mobile device and (secure) information arbitrage, if authorized.

6. Alternative Arrays

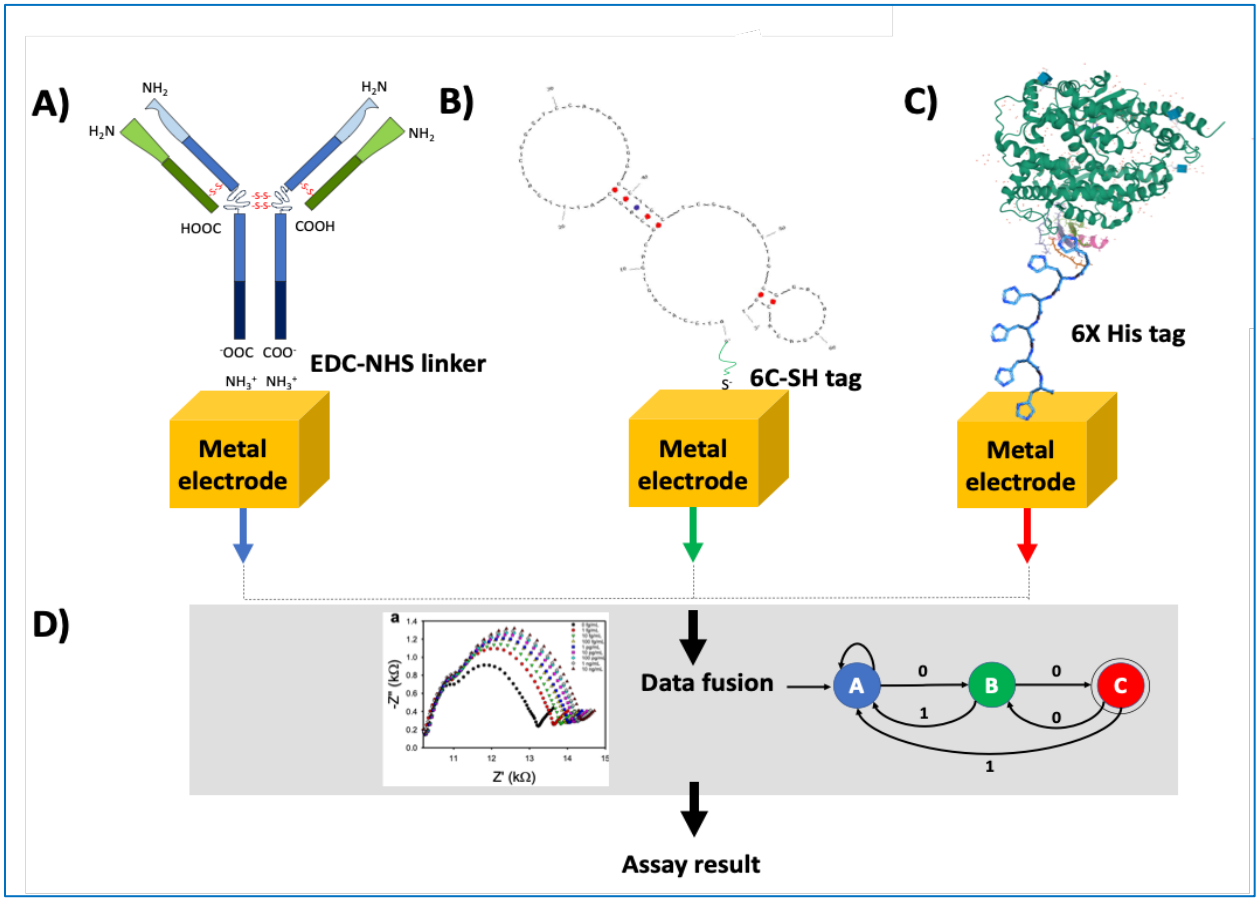


Figure 3: **Multiplexed**[117] **Detection Tool for SARS-CoV-2.** Upper panel presents potential recognition and detection chemistries. The data (fusion, middle panel) will be analyzed and assay results displayed (bottom). The data and information will be displayed on a mobile device (see cartoon in Figure 1). Three distinct binding targets for SARS-CoV-2 spike protein RBD are presented in sections A, B (ADD) and C. In (A) RBD-antibody (SARS-CoV-2 strain specificity) is functionalized with EDC-NHS chemistry to metal (gold, Au) nanoparticles (or may be attached/adsorped on laser inscribed graphene, LIG). In (B) single-stranded DNA aptamers with thiol linker is adsorbed to metallized LIG (ADD aptasensor). In (C) histidine-tagged human ACE2 is adsorbed to metallized LIG. (D) Binding elicits signal (EIS, impedance spectroscopy) which is transduced to a mobile device. Data acquisition is followed by "hot" data upload to embedded tiny database (tinyDB[118]) in the device (ODS in Figure 1). Analytics may be executed on the device (embedded logic, machine learning tools) or uploaded to cloud server. The data fusion (model scoring) step may be necessary to make sense of the data, *in combination*, to provide not only raw data (results from A, B and C) but information, extracted from data and processed according to a simple SNAPS[119] paradigm to convey the ***meaning of the outcome,*** to inform the non-expert end-user.

Interpretation of data may be necessary due to the caveats of target binding and recognition. The specificity of the antibody used in the tool may not bind or bind with lower affinity (K_d) with viral target protein (Spike protein) due to mutations in the epitope which generated the immunoglobulin (IgG). Lack of binding or lower affinity of binding can interfere with signal generation and failure to log signal over noise. Thus, individuals carrying SARS-CoV-2 may fail to test positive (false negative) if the viral variant possesses mutations preventing the antibody (A) to bind with the mutated Spike protein. Other factors (temperature, pH, salinity) may also interfere with signal (see "model scoring" in Appendix).

In (B), binding with the aptamer is highly specific but it depends on precisely which oligonucleotide (sequence of the ssDNA from an enriched pool) binds to which part of the Spike protein. For ADD, one aptamer may bind to the RBD (receptor binding domain) of the SARS-CoV-2 Spike protein. The length of the RBD (primary sequence) used in screening and enriching for the aptamer(s) may influence the shape (structure) of the RBD during selection phase. The complementarity of the shape of the RBD and the secondary/tertiary structure of the ssDNA *complex* is key to the binding specificity and affinity. If the test sample contains the whole Spike protein (includes RBD) as well as fragments (peptides with different lengths of amino acid sequence) which may or may not contain the RBD then the binding to the aptamer may fluctuate (widely) because the primary sequence of the protein may influence the secondary and tertiary structural outcome. The latter may change the configuration of the RBD in a given fragment and prevent binding to the aptamer, generating a false negative. If a sample contains other proteins and peptides, it is possible that the 3D configuration of an arbitrary protein or protein fragment could mimic or compete, albeit partially, with the RBD, and elicit a signal by binding with the aptamer, even if the binding is ephemeral due to reduced affinity (false positive result).

Binding of the Spike protein RBD to the immobilized hACE2 protein target (C) is probably the weakest link in this tripartite approach. Presence of mutations, dynamic or modified configuration and the effect of the environment (temperature, pH, salinity) may perturb binding and corrupt the signal.

Error correction and data curation may be necessary to prevent data corruption (false negative, false positive, limit of detection) to improve the information and recommendation for end-users. If the confidence in the raw data from each element is high, then the data may be responsibly combined (*after data scoring, image risk score*) to display the information with an assigned degree of confidence which may be more than the sum of the parts (positive, negative, false positive, false negative). The strategy from data acquisition and display vs information and recommendation must reduce risk, optimize level of precision and accuracy to maximize the value of the information for the user and/or the community. Of greater concern is the *accumulation* of errors, which when aggregated (time series data from ADD used as a surveillance tool), may generate spurious results with respect to the status of the population.

7. Array of Targets

The ADD approach for detection of infectious agents is based on targets identified from the biology and/or lifecycle of the organism and its interaction with the host (humans, animals). The RBD (receptor binding domain) of the Spike protein from SARS-CoV-2 and the human ACE2 cellular receptor (in bats, rats, pangolins and related animals in the phylogenetic tree; reviewed in reference 9) are under intense scrutiny. But, exploring the biology of SARS-CoV-2 reveals other equally potent targets. Developing drugs, antibodies and aptamers may benefit from a brief review of the viral biology. For SARS-CoV-2 detection alone, there are at least two other external proteins which may serve as targets for binding to aptamers, the M protein and the E protein in addition to S protein (Figure 4).

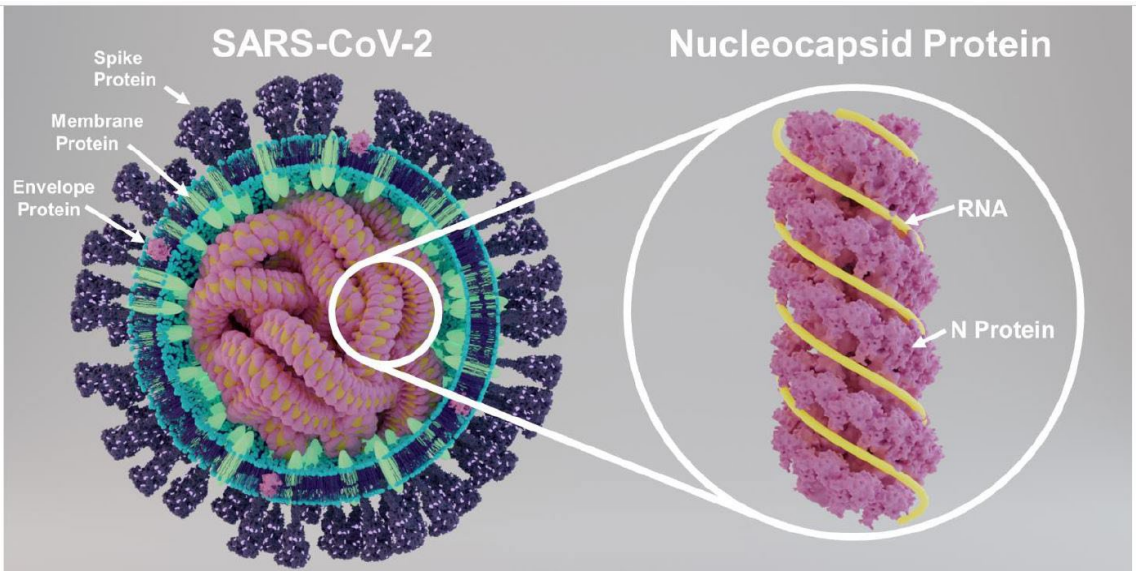


Figure 4: ssRNA genome of SARS-CoV-2 is longer compared to other RNA viruses (HIV, Influenza, Zika, Ebola; see Figure 16). It is encased in a nucleocapsid core (N protein[120]) and resides inside the virus. External surface of the virus is studded with S (spike), M (membrane) and E (envelope) proteins.

The receptor binding domain (RBD) of the Spike protein appears to make the first contact with the human cellular receptor ACE2 (angiotensin converting enzyme 2). Disrupting this event is the Holy Grail for preventing the virus from entering the cell. The mechanism by which Spike protein facilitates viral entry is not merely due to the recognition (between RBD and ACE2) but a cascade of events that begins after successful binding. The events that follow result in ***fusion*** of the viral envelope with the cell membrane, thereby allowing the viral genetic material (+ssRNA) to be delivered inside the cell in order to create progeny viruses. *Fusion* is mediated by the *fusion machinery* and *fusion peptide* sub-segments of Spike S2 protein which includes a step resembling a "jack-in-the-box" toy[121]. These segments of the Spike protein are *better conserved* and occupy a distinctly different part of the Spike protein (Figure 5).

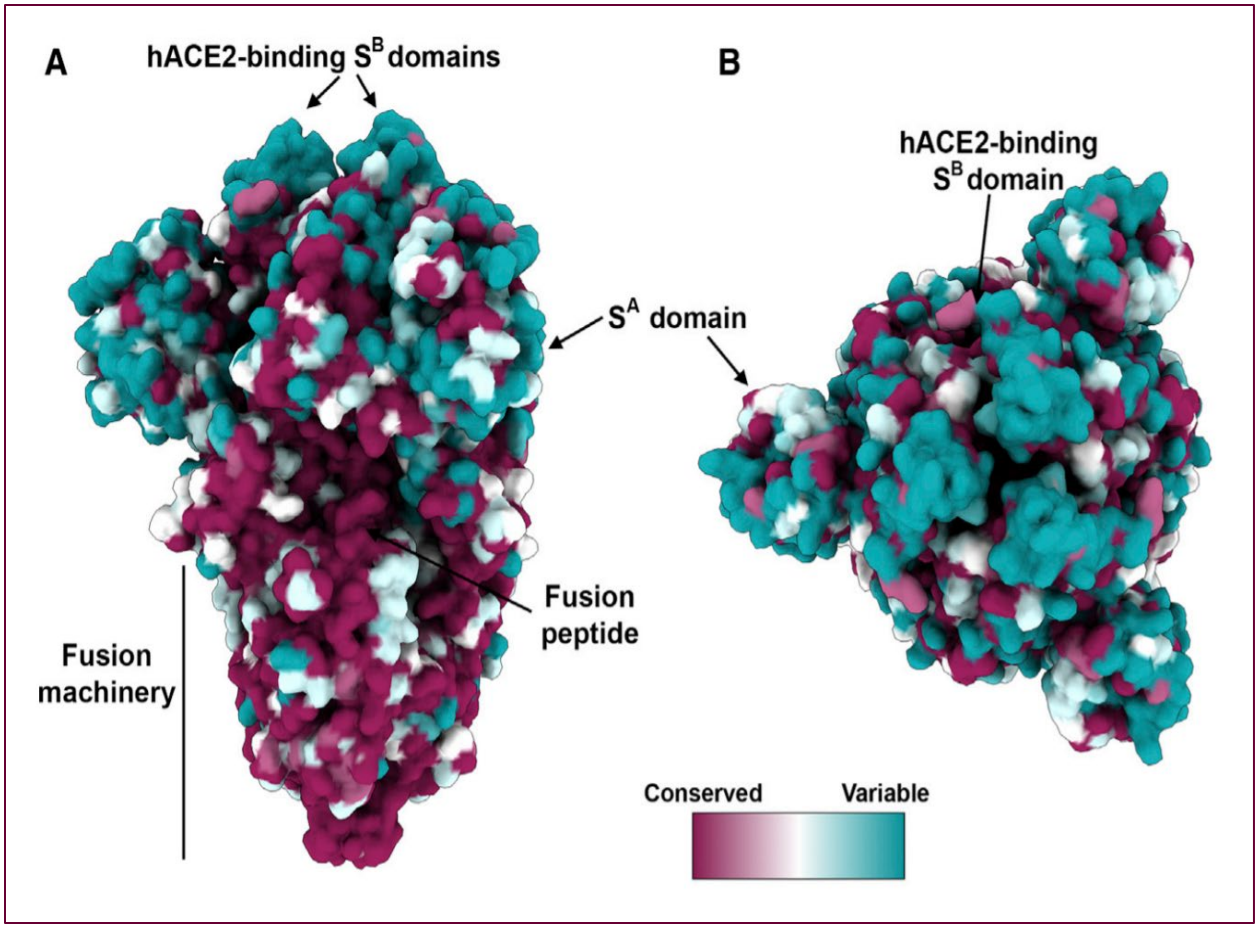


Figure 5: Sequence conservation[122] of sarbecovirus S glycoproteins plotted on the SARS-CoV-2 Spike protein structure [viewed from the side (A) and top (B)]. The receptor binding domain (RBD S1) is separate from the region of the Spike S2 protein necessary to initiate viral entry. The latter is better conserved (fusion machinery, fusion peptide) and perhaps better targets for ADD aptasensors.

The better conserved segment of the Spike protein may offer valuable epitopes[123] and potential binding sites for aptamers (unless glycan moieties interfere). In addition to the RBD (which appears to be more variable), the conserved portions of the S2 subunit responsible for fusion (fusion machinery, fusion peptide) are likely targets for aptamer binding. It remains to be seen if reagents (monoclonal antibodies, aptamers) aimed at the fusion specific domain of the S protein can disrupt viral entry and serve as tools for detection *as well as* prevention.

Interfering[124] with the human cellular proteins ACE2 and TMPRSS2 (which are viral targets) to prevent viral binding may not be prudent. Reagents directed against proteases, usually non-specific, may perturb physiological functions essential for homeostasis. The events which follow after the viral Spike protein docks with the human ACE2 protein are illustrated (Fig 6 copied from Scientific American[125]).

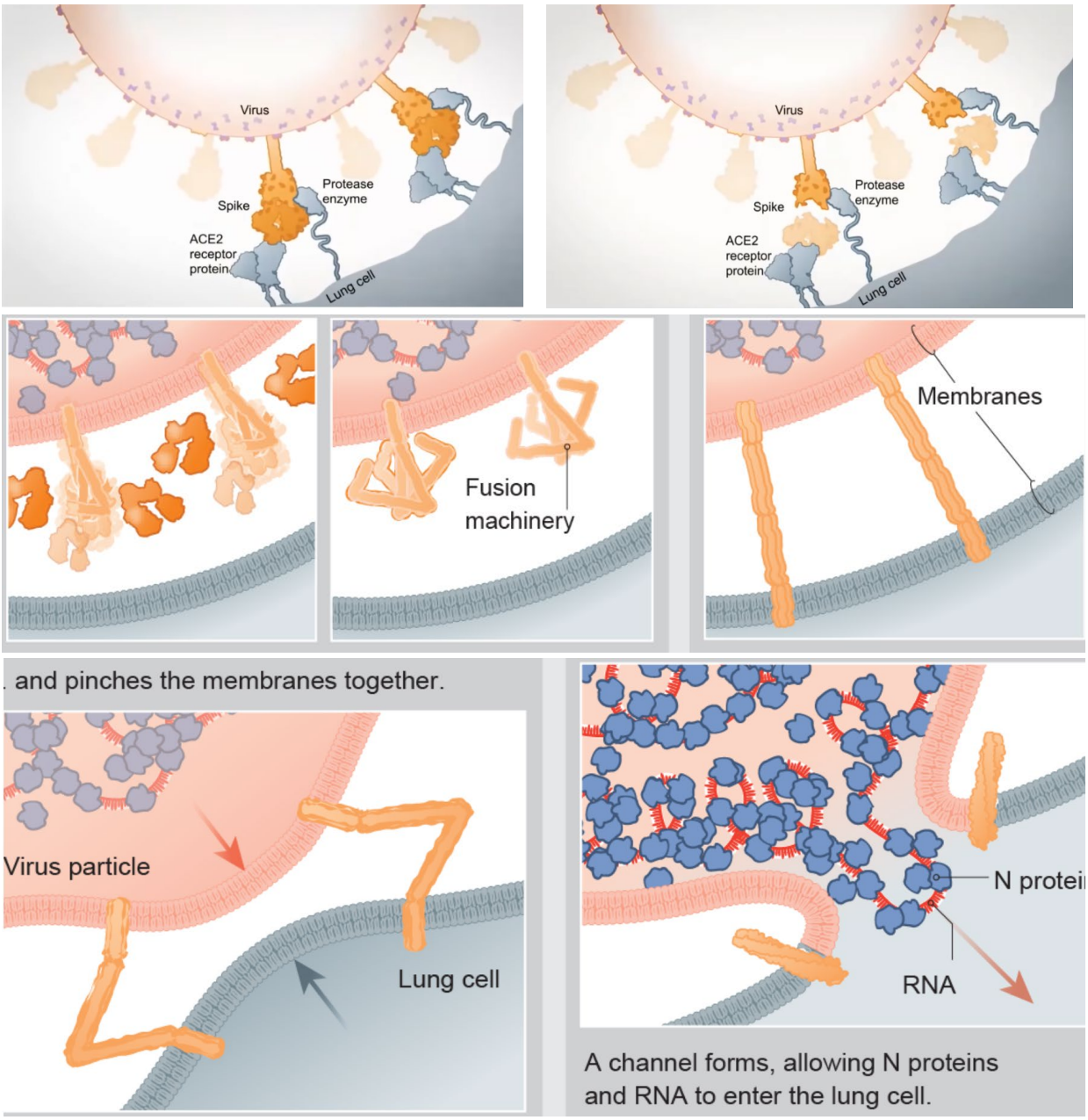


Figure 6: Cascade of events[126] leading to viral entry into host lung cell identifies the *"jack-in-the-box"* mechanism as a pivotal tool used by the fusion machinery of the Spike protein to deliver the viral RNA inside the host cell. Selectively disabling the fusion machinery of the Spike protein is an attractive target for aptamers and other reagents. If available, the latter may not only detect and diagnose but prevent infection, even if virus particles may have already reached the human apical surface[127] area. Superior region of the lungs are more vulnerable to infection due to higher number of hACE2 receptors. The number of hACE2 decreases from superior to inferior. Lower part of the lungs have less ACE2 and TMPRSS2 proteins, corroborated by the observation that these genes are expressed at a higher level in upper nasal epithelial tissue compared with bronchial and small airway epithelial brushings[128].

The +ssRNA of SARS-CoV-2 (positive strand serves as mRNA) generates at least 27 or more viral proteins by creatively manipulating the host translational machinery. Theoretically, any or all viral proteins could serve as targets for anti-viral[129] strategies. Virus-encoded proteases[130] are distinct[131] from cellular proteases and may serve as good[132] targets. The viral protease[133] 3-chymotrypsin-like protease[134] or 3CLpro[135] aka M^{pro} is encoded by Nsp5 and appears[136] to cleave (see "scissors" in Figure 7) essential viral proteins from "polyproteins" generated from translation of open reading frame (ORF) 1a and 1b (Fig 7). Papain-like protease[137] PLpro (ORF 1a, Nsp3[138]), cleaves[139] proteinaceous post-translational (ref 131) modifications on host proteins to evade host anti-viral immune responses. Nsp1[140] suppresses host translation by cleaving cell mRNAs[141] and competes[142] with mRNAs for binding to human 40S ribosomal mRNA channel[143] (as well as 43S, 80S subunits). Type 1[144] interferon[145] (IFN-1) response[146] is modulated by Nsp1, Nsp 6 and Nsp13, which interferes indirectly with IFN-1 by suppressing the phosphorylation and/or nuclear translocation of other cellular molecules[147] involved in catalyzing the IFN-1 response.

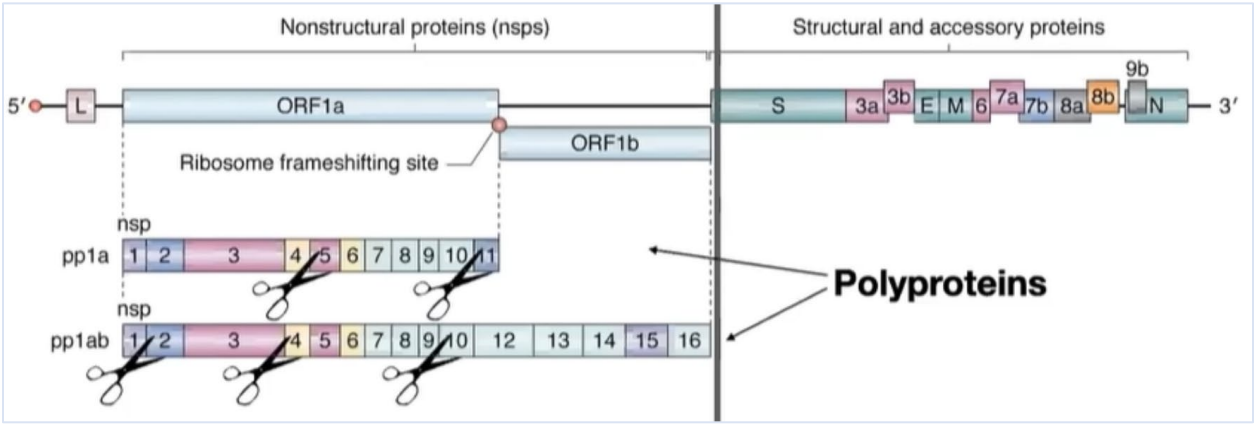
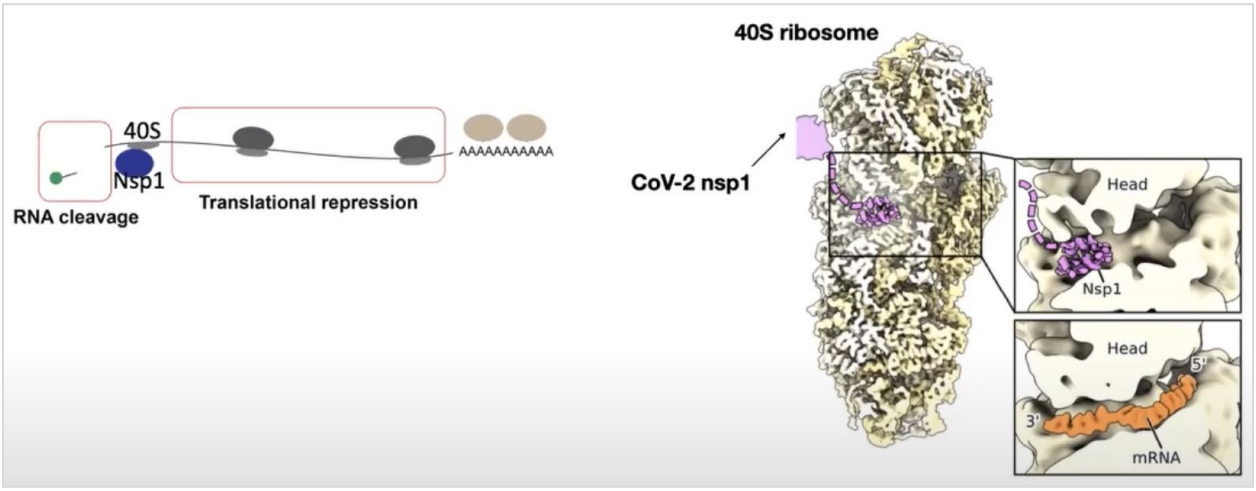


Figure 7: (Top) SARS-CoV-2 genome[148] encodes nonstructural proteins (nsp), structural and accessory proteins. Nsps are encoded by ORF1a & ORF1b generating pp1a (nsps 1-11) or pp1ab (nsps 12-16). The structural and accessory proteins are synthesized by translation of their respective sub-genomic mRNAs. (Bottom) Translational repression (Kamitani *et al*) and binding to 40S ribosome (Thoms *et al*) by Nsp1.



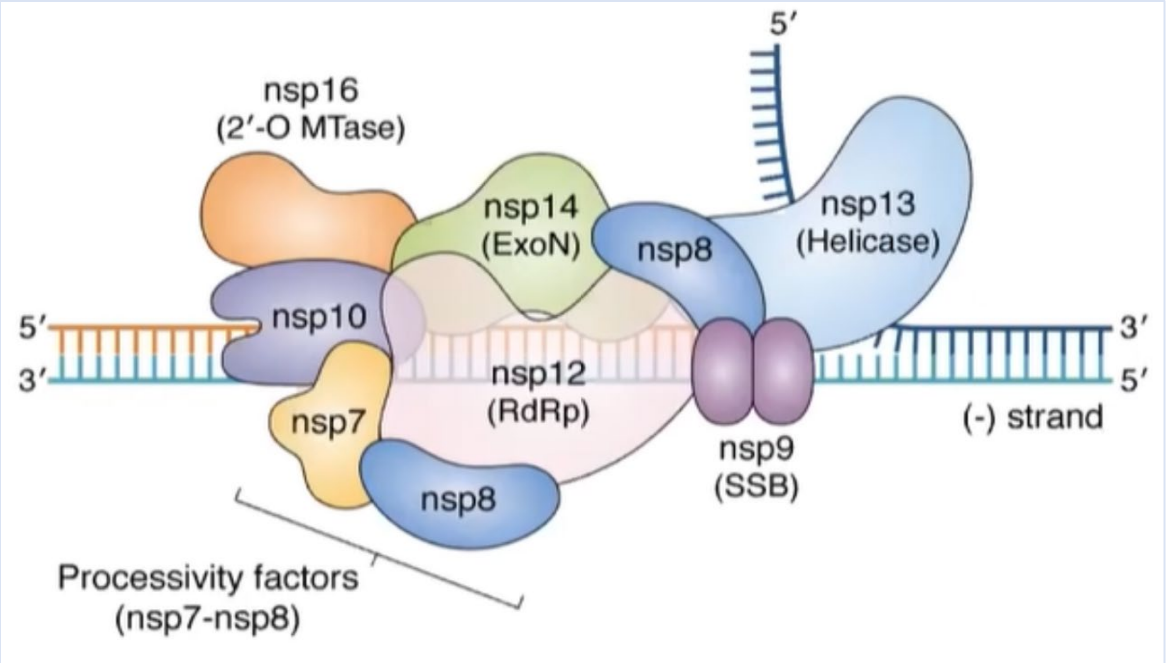


Figure 8: The positive sense (+ss) RNA genome is translated by the host translation machinery to make polyproteins that are co-translationally cleaved by proteases (PLpro/Nsp3 and 3CLpro/Nsp5) encoded in the polyprotein to generate components of RdRp or RNA dependent RNA polymerase (Hartenian and Nandakumar *et al*). The RdRp complex uses the genome as a template to generate negative sense subgenome and genome length RNAs, which are in turn used as templates for synthesis of positive sense full length progeny genomes and subgenomic mRNAs. Each and/or any protein factor in this complex may be a target for anti-viral reagents, for example, aptamers, antibodies, small molecules and inhibitors.

The conundrum and complexity presented by an abundance of anti-viral targets, a variety of strategies and potentially many cell types susceptible to infection, adds to the pharmaceutical dilemma where the problems of bio-availability, cross-reactivity and toxicity may force a solution to extinction. Viral proteins are distinct but structural homologies and overlapping functional issues are non-trivial.

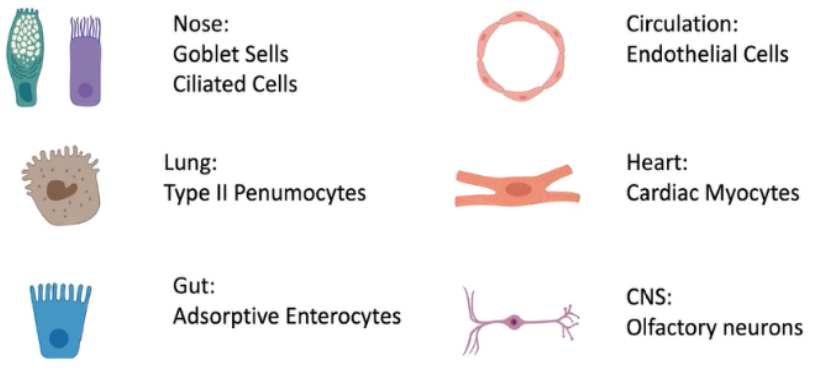


Figure 9: Identification of ACE2 receptors on many other cells (humans). The SARS-CoV-2 virus is not only a respiratory virus or results only in pneumonia. It is causing systemic diseases presenting a vast array of symptoms and acuity.

The medical chaos due to our lack of understanding of the biological minutiae of SARS-CoV-2 is not completely without a silver lining, albeit bleak. The ray of "hope" emanates from ExoN (Figure 8) the protein produced from Nsp14 segment of ORF1b (see Figure 7). It appears that SARS-CoV with inactivated ExoN is growth impaired and mutates at a much higher level (>20-fold[149] higher, see right panel in Figure 10). SARS-CoV with one of the longest genomes (see Figure 16) among common RNA viruses (HIV, Influenza, Rhino, Ebola) abhors errors[150] in replication (not corrected in other common RNA viruses with low fidelity RNA replication). High fidelity replication has enabled SARS-CoV to maximize its genome size (see Figure 16) using RNA-dependent proof reading system, repair and error correction implemented by Nsp14-ExoN (there are Nsp14 homologs in other viruses). Lack of error correction in humans[151] may result in disease, dysfunction and death, even due to point mutations.

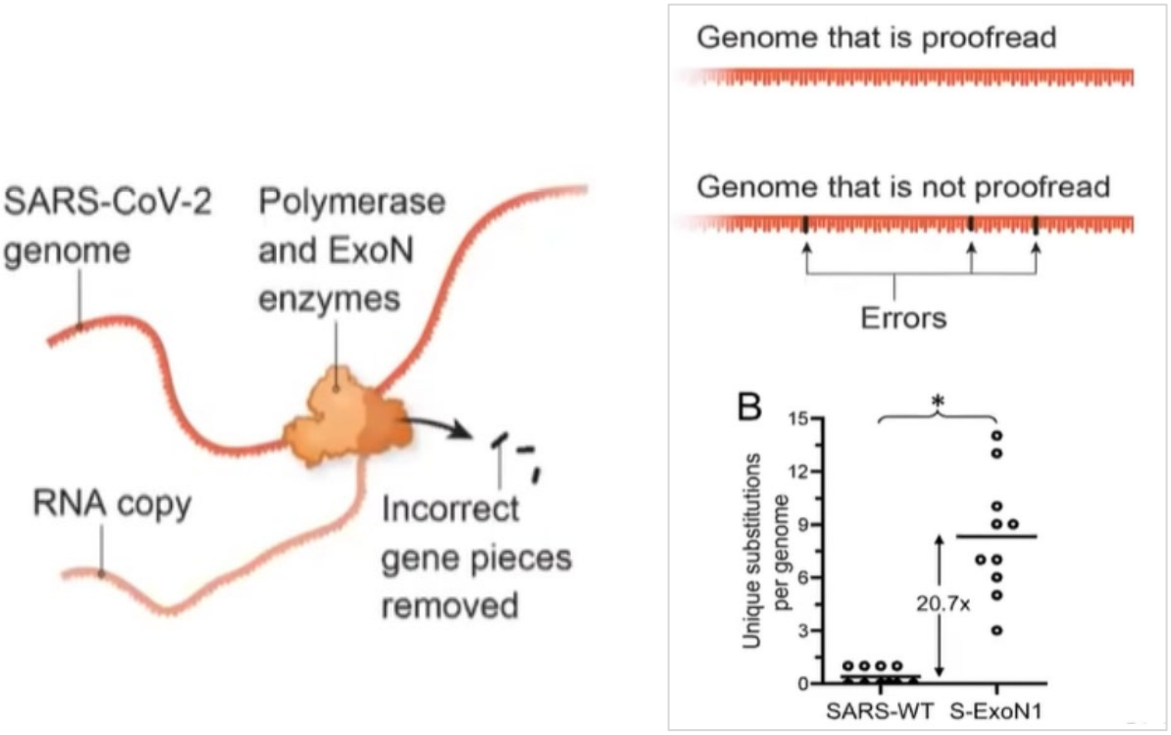


Figure 10: Mutated or inactivated Nsp14-ExoN results in >20-fold increase (Eckerle *et al* 2010) in genomic errors (B, right panel). ExoN in RdRp of SARS-CoV-2 enables error correction (left panel).

Error correction in SARS-CoV-2 may have implications for optimizing target selection for anti-viral strategies. The choice of the receptor binding domain in subunit 1 (S1 RBD) of the SARS-CoV-2 Spike protein, therefore, may be incomplete as a target (Figure 3). It appears that the fusion machinery and the fusion peptide (FP) region of the Spike protein (subunit 2) is better conserved and will ***continue*** to *remain* better conserved due to the error correction mechanism (see Figure 10). Hence, sub-segments within subunit S2 of S protein may be better targets. The obvious caveat in this discussion is whether the chosen sub-segments in S2 may be sufficiently exposed or available to bind with the anti-viral molecules.

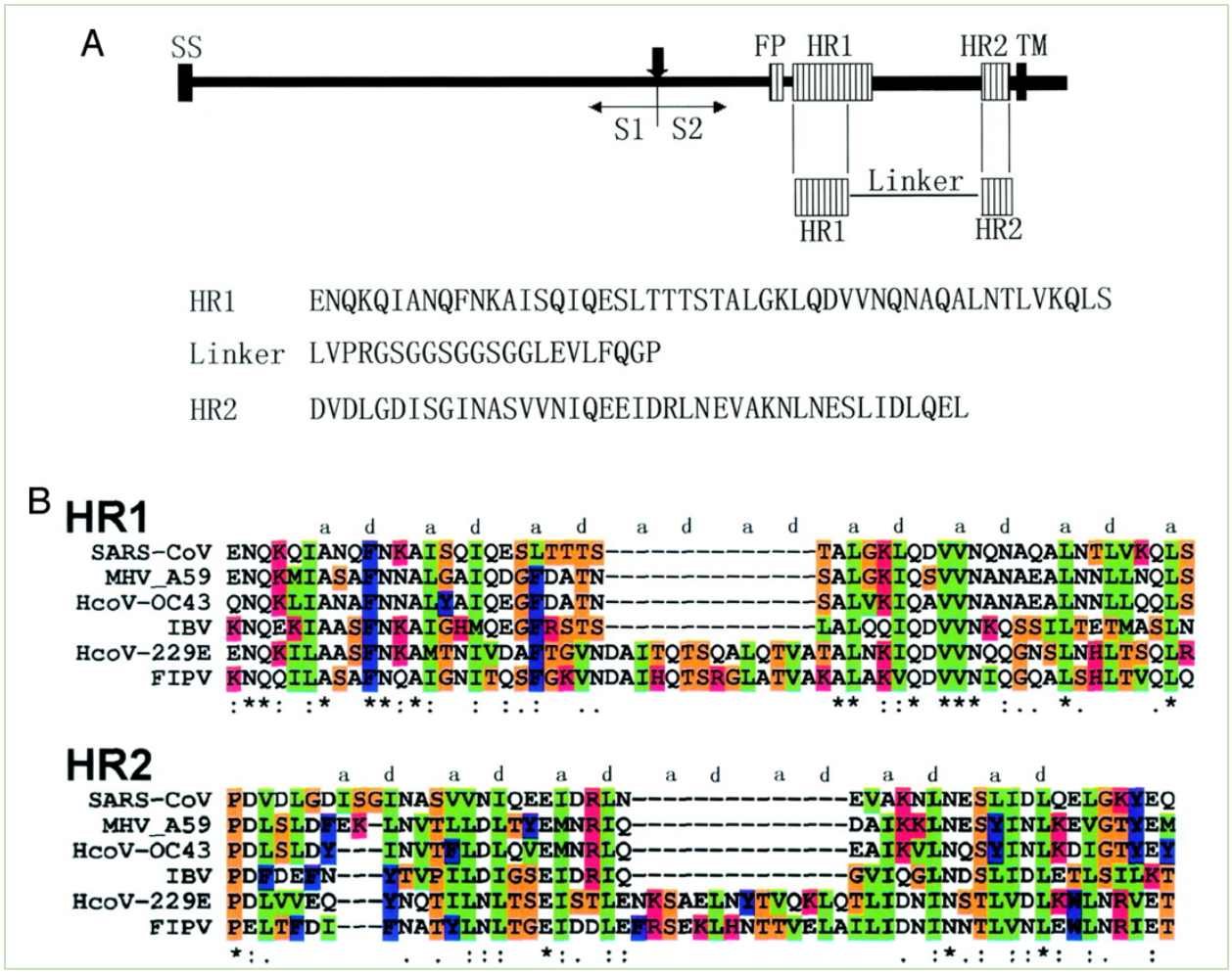


Figure 11: S protein (trimer) consists of 2 structurally noncovalently linked domains, S1, contains RBD (receptor binding domain) and S2 contains the fusion machinery and the **fusion peptide**[152] **(FP)**. Site of proteolytic cleavage → vertical arrow. S2 contains 2 HR (heptad repeat)[153] regions HR1 (898 –1005) and HR2 (1145–1184) connected by 22-amino acid linker (LVPRGSGGSGGSGGLEVLFQGP). Hydrophobic residues (a and d positions in heptad repeat regions) are conserved. SS (N-terminal signal sequence), TM (transmembrane domain, C terminus), **FP (fusion peptide, bottom**[154]), IBV (infectious bronchitis virus), FIPV (feline infectious peritonitis virus), MHV (murine hepatitis virus - murine coronavirus).

8. Discussion

Could we detect SARS-CoV-2 in saliva, prevent[155] membrane fusion and block viral entry[156] with the same aptamer or another type of molecule based[157] on the better conserved S2 of the SARS-CoV-2 Spike protein? Could we detect SARS-CoV-2 in saliva of asymptomatic individuals without COVID-19? ADD may use better targets for its aptasensors beyond RBD S1 and hACE2. ADD ***can*** be accomplished, as suggested by the evidence from creation of DeMEA[158] (but it uses high cost microfluidics[159]).

Even if ADD is successfully engineered to be a low-cost biomedical device for non-invasive detection, ***dissemination*** of ADD and other systemic surveillance tools will still depend on community-specific economics of technology[160] to facilitate diffusion and adoption. Bringing data and information together to make sense and extract foresight (uncertain of the value of hindsight[161]) will be a challenge which new initiatives[162] must address. Diffusion of the tool to vulnerable communities will be restricted unless the end-to-end system is cost-effective at a level where it is sustainable for repeated use, preferably daily, as a surveillance tool for humans, pets and farm animals.

Data when transformed into ***usable*** information may deliver value for the greater good, for the greatest number. ADD is one small surveillance tool but it isn't enough. Healthcare cannot be a knee-jerk reaction to epidemics and pandemics. Continuous monitoring (even for high risk individuals) may remain a mirage in view of the disproportionate socio-economic imbalance. While we must ADD up to address the crisis[163] at hand, we must also utilize this disaster as an opportunity to deploy profiling as a healthcare staple. Other tools, for example, wastewater[164] analysis[165] may offer transparency[166] and guide public health strategies regarding elements the community must address, in advance, to prevent melt-down of health services. When an emergency presents itself we must not disintegrate into quagmire.

Precision medicine and precision public health may benefit if we probe the broader question of physiological status as expressed by proteins but further complicated by our microbiomes[167]. Isolated snapshots of data may be rate-limiting for communities under economic constraints. But, convergence of data from ADD along with multiple levels of profiling[168] (DNA, RNA, protein, RDW[169]) as well as environmental[170] and wastewater[171] data[172], if included[173], may augment the value of information, which could be catalytic for medicine[174], in general, if aggregated and shared between open[175] platforms.

Analytical skills necessary to deconstruct the data and reconstruct its meaning, relevant to the individual and/or the community, may pose a rather insurmountable barrier in terms of tools and/or human resources. The ill-informed inclination is to hastily pursue a "quick and dirty" version (perhaps shoddy, yet masquerading as good enough) without a long term view or a vision that embraces a sense of service, science for the good of society and access to global public goods for all. It goes without saying that one shoe does not fit all. It is obvious that ADD is not enough to better prepare for the future[176].

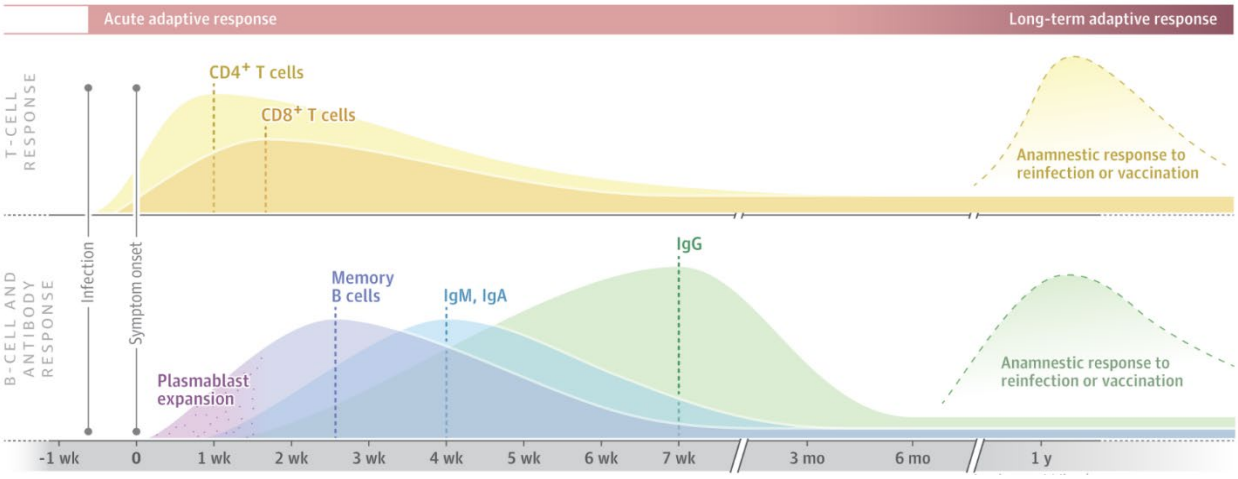
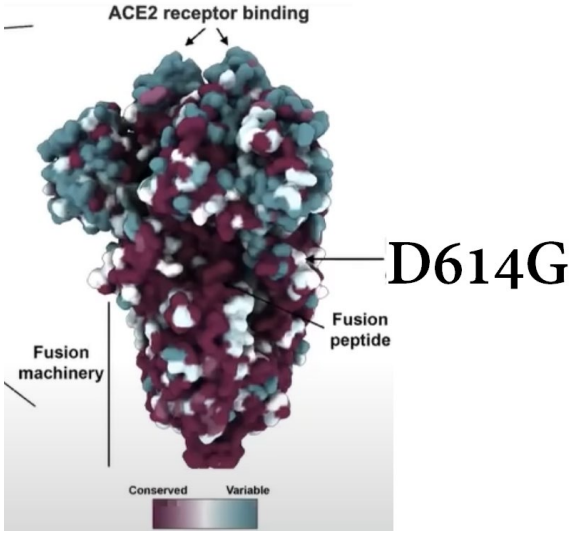
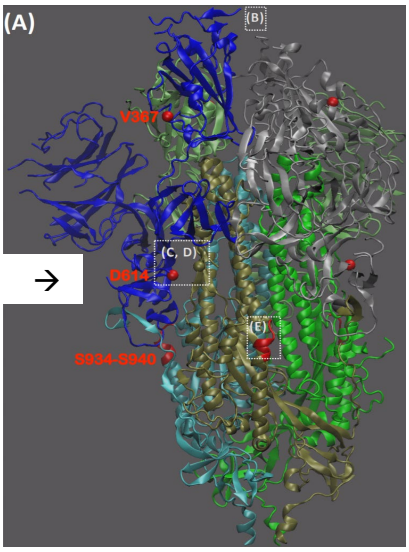
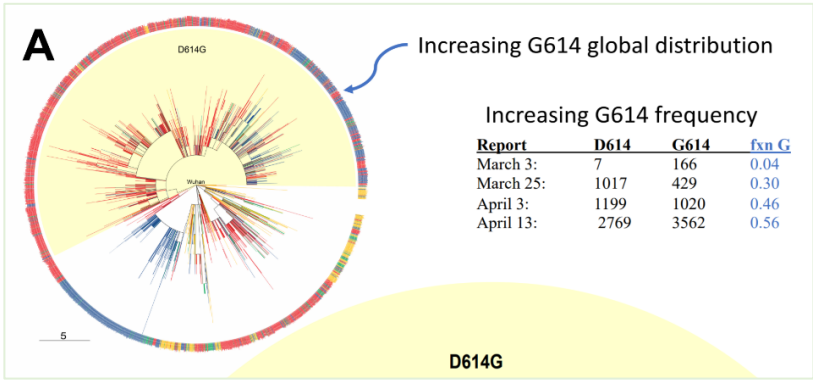


Figure 12: Serum from a significant percentage of patients (one third) recovering from COVID-19 have low viral neutralizing activity. Depending on the acuity of the infection, patients may or may not follow *standard* immune profile (top[177]). Low variation (Fig 10) in SARS-CoV-2 Spike protein is good news but mutations, D614G (middle panel and bottom) may still complicate[178] the immune response and expected anamnestic response to reinfection or use of classical[179] approaches[180] to vaccination.







If immunity from traditional vaccines are uncertain[181], can we supplement with *alt-vaccines* (which are non-immunogenic, for example, aptamers), to better prepare for low-cost and rapid[182] response to public health during future epidemics / pandemics?

9. Concluding Comments

Since 1980's the HIV epidemic has infected ~76 million people[183] (~1% of the global population) and almost half are dead (~33 million AIDS related deaths, disease caused by HIV) and currently the other half is still living or struggling with the disease. Yet, the thrust for HIV vaccine pales compared to the warp speed vaccine development collaboration[184] against SARS-CoV-2, which erupted in 2020 as the COVID-19 pandemic. Is it because SARS-CoV-2 is irreverent and indiscriminate in infecting humans?

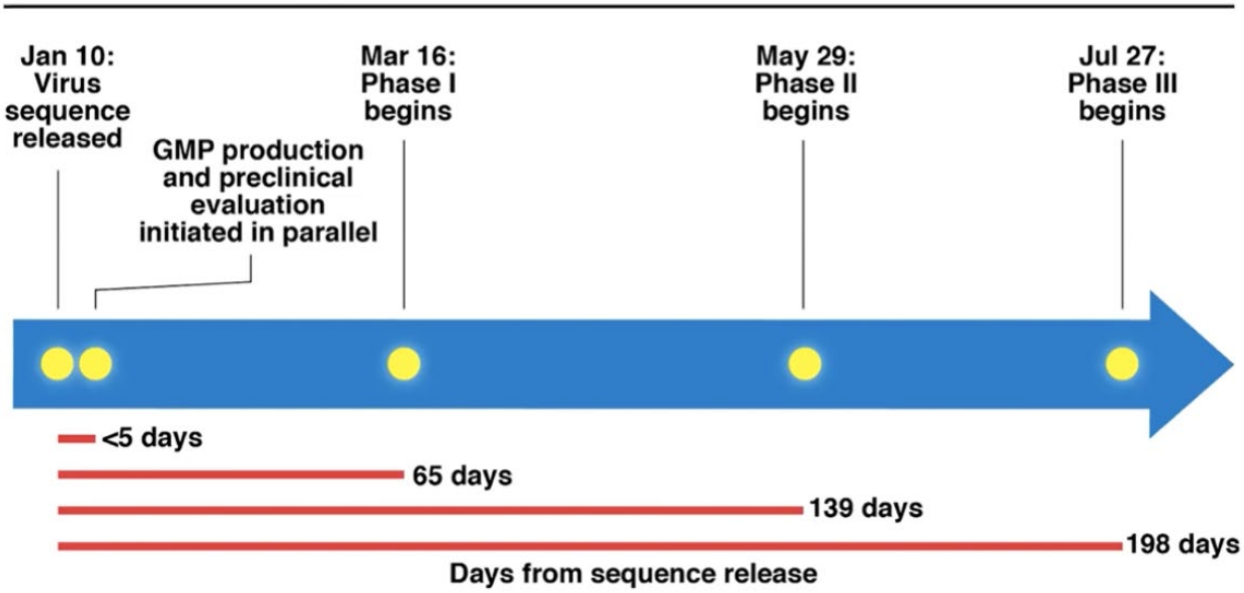


Figure 13: The timeline of SARS-CoV-2 Vaccine Development[184] (mRNA-1273 vaccine[185]) to control COVID-19 (codeveloped by NIAID, NIH and Moderna, Cambridge, MA). The mRNA encodes the SARS-CoV-2 full-length spike glycoprotein trimer, S-2P (modified to include two proline substitutions at the top of the central helix in the S2 subunit). The mRNA is encapsulated in lipid nanoparticles (0.5 mg per mL) and diluted with normal saline to achieve the final target vaccine concentrations[186].

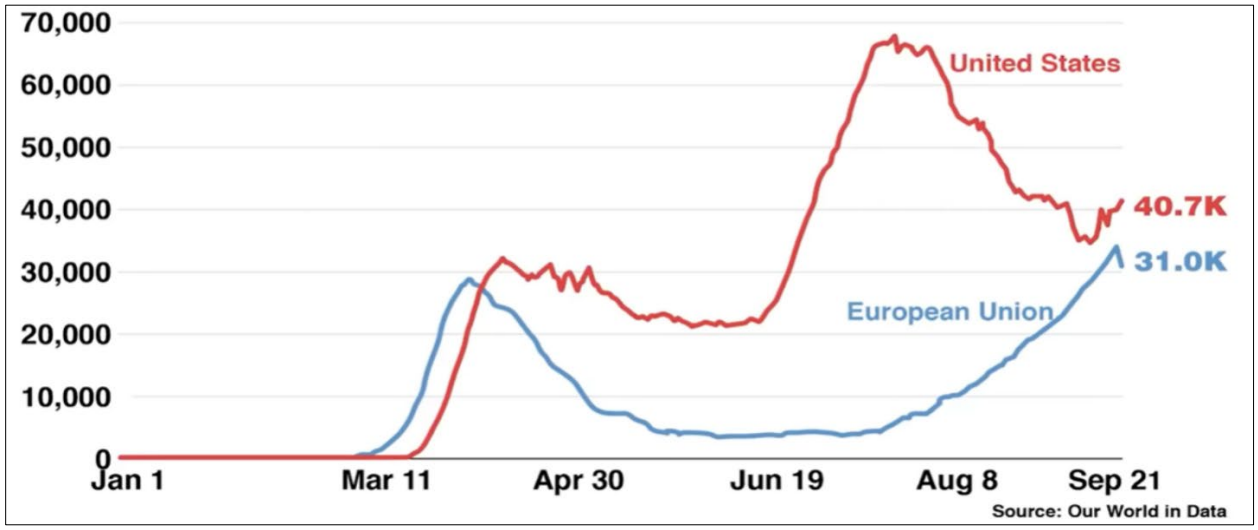


Figure 14: 7-day rolling average of new COVID-19 cases[187] from January through September 21, 2020.

Coronaviruses have long co-existed with humans and animals. Error correction (Figure 10) has made the genome of the coronavirus one of the largest among viruses (Figure 16). What does it mean? Compared to diseases[188] due to relatively unknown viruses[189], and despite the flu pandemic ~100 years ago, the coronavirus, in less than six months, has changed, perhaps permanently, global thinking, trends and technology. Tobacco Mosaic Virus (TMV) was discovered around 1890-1892[190] but after more than 100 years[191] of virus discovery, we have *just now* acknowledged the threat to global health from viruses. Understanding the molecular basis of virulence is the single most important questions in basic biology which must be investigated by the best and brightest, if we ever expect to mitigate the risk from viruses.

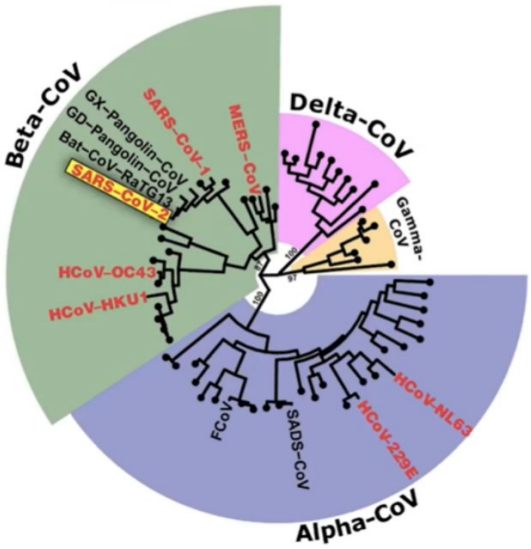


Figure 15: Coronavirus phylogenetic tree. Human coronaviruses (courtesy of S. M. Gygli, NIAID)[192]

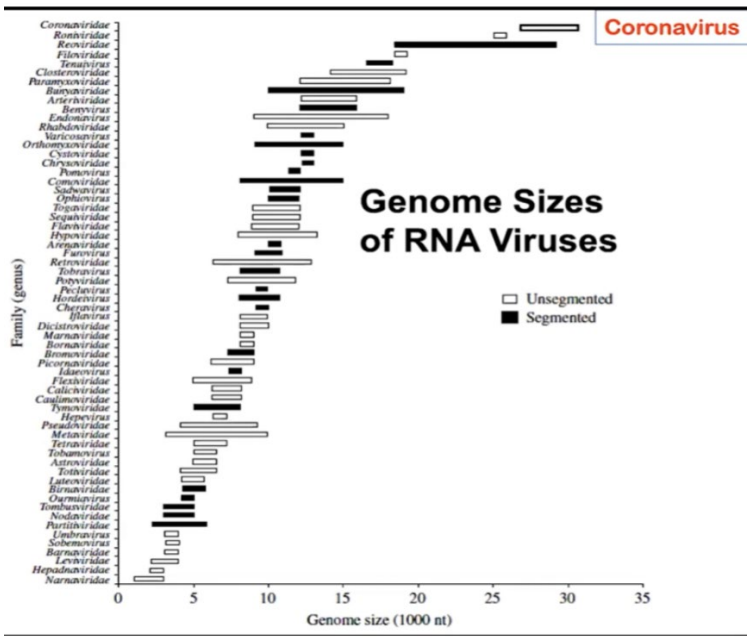


Figure 16: Coronavirus pandemic wasn't really expected[193] according to at least one global expert[194]. The coronavirus has the largest RNA genome. Is it just a coincidence or is there any bio-medical correlation?

While we remain clueless about what constitutes virulence, the genome size does not offer any solace or solution. The quagmire[195] about R0 and *k*[196] for COVID-19 defies epidemiological models[197] but prefers apocryphal Pareto[198] principles which suggests that 80% of new infections may be caused by only 20% (or even less, 10%) of the infected individuals.

Could there be one or more genetic factors that may underlie the differentiation between super-spreaders[199] vs sub-spreaders for SARS-CoV-2? If the latter is true then how valuable is *generalizing* infection dynamics[200] from communities as a prediction tool for *overall* public health, advance planning and use as early warning[201] for cautionary preparation?

In future, genomic analysis may enlighten us if there are polymorphisms[202] which may partially account for this differentiation. It may be worth digressing to note that some individuals may be more susceptible to leprosy, caused by *Mycobacterium leprae*. Genes[203] associated with leprosy include HLA (human leukocyte antigen) proteins. Analysis of eleven HLA genes in 1155 Vietnamese individuals revealed 4 leprosy-associated independent amino acid variants [HLA-DRβ1 positions 57 (D) and 13 (F), HLA-B position 63 (E) and HLA-A position 19 (K)] which comprised 2 pairs of linked genes, with one set conferring susceptibility [HLA-DRβ1 and HLA-A] and one being protective[204].

The demographics of infection by SARS-CoV-2 may be due to genetic[205] determinants[206] and individual outcomes[207] may be determined by our genes[208] as well as epigenetic factors which may be mapped to biomarkers[209]. At this point it is unclear whether the etiologic agent of this 2019 coronavirus pandemic should be referred to as SARS-CoV-2 where SARS imply severe acute respiratory syndrome.

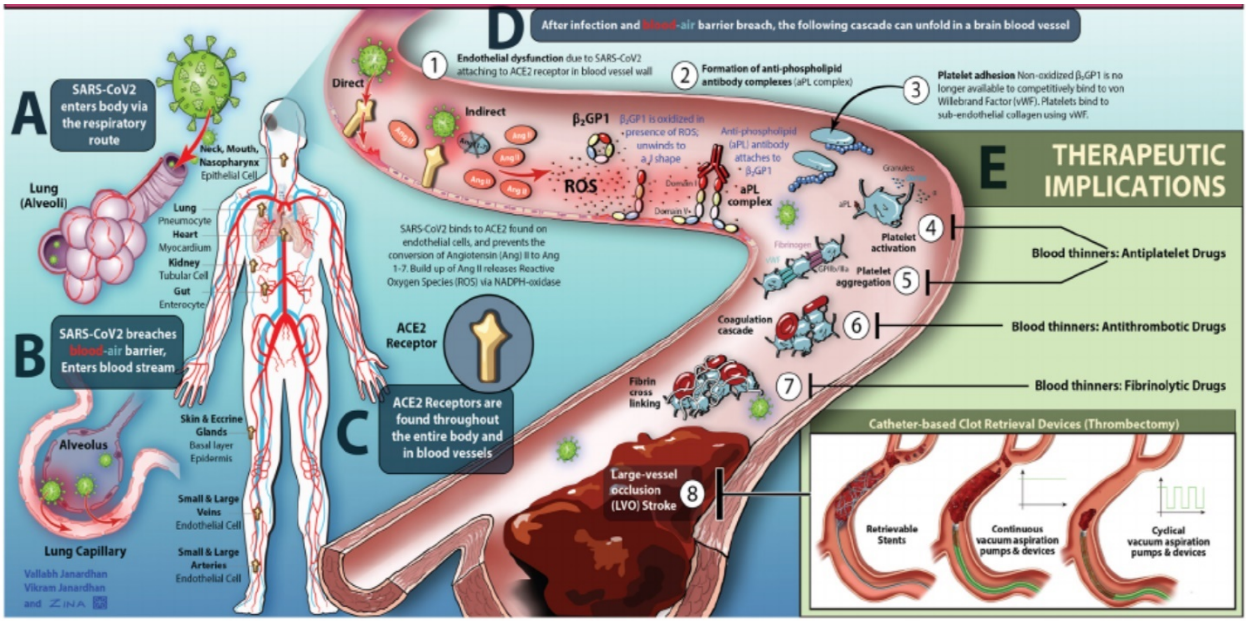


Figure 17: What is COVID-19? Respiratory illness? Blood clotting disorder[210]? Cardiovascular disease?

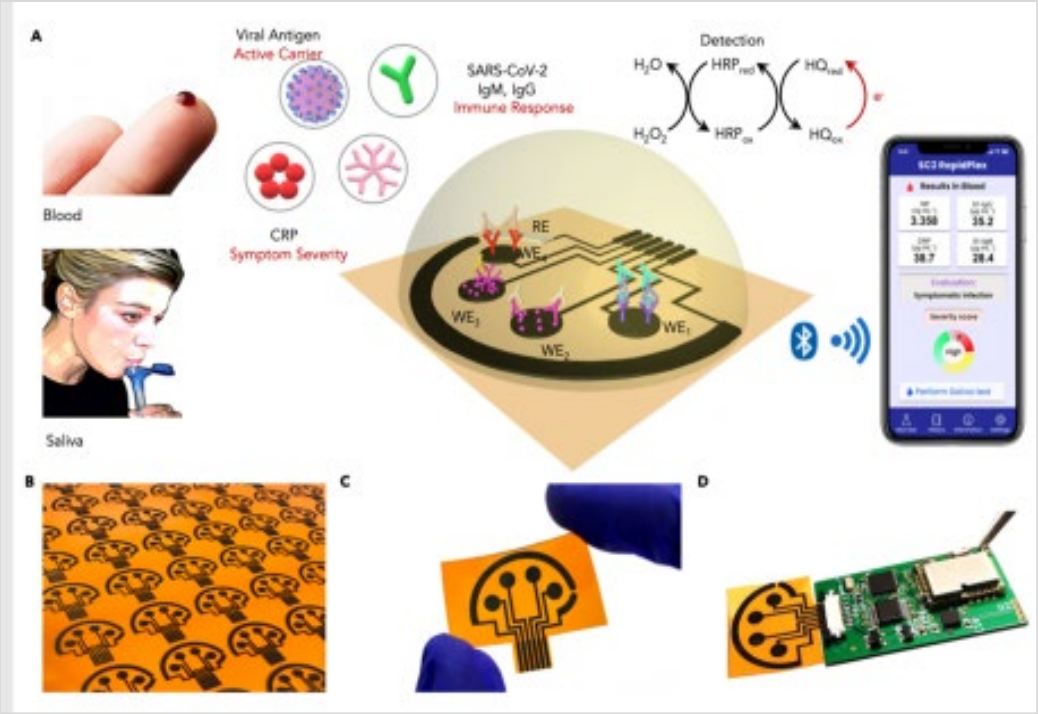


Figure 18: CalTech's hypothetical[211] 5[212] cent[213] *déjà vu* graphene sensor claims to detect SARS-CoV-2 antigens. Can it serve as a global surveillance tool (humans, animals) and bridge the chasm of inequity?

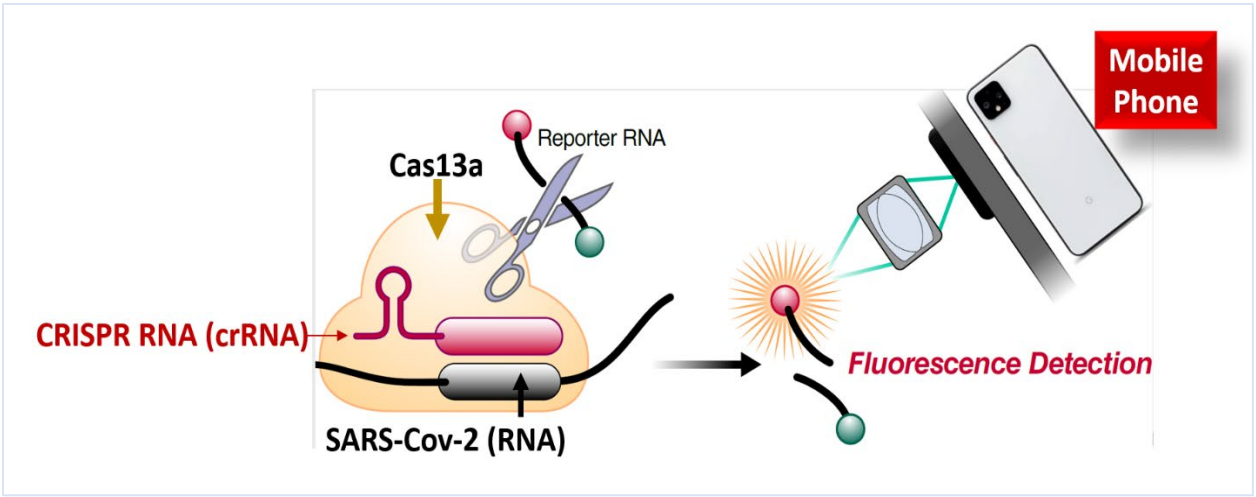


Figure 19: Detection of one copy RNA per µL (microL) from SARS-CoV-2[214] with mobile phone camera. Cas13a (C2c2) is complexed with a CRISPR RNA (crRNA) containing a programmable spacer sequence (red tube) to form a nuclease-inactive ribonucleoprotein complex (RNP). When the RNP binds to a complementary ***target*** RNA, it activates HEPN (higher eukaryotes and prokaryotes nucleotide-binding domain) motifs of Cas13a that then indiscriminately cleaves surrounding ssRNAs. Target RNA binding and subsequent Cas13 cleavage activity can therefore be detected with a fluorophore-quencher pair linked by an ssRNA, which will fluoresce after cleavage by active Cas13. Ott et al used the SARS-CoV-2 nucleocapsid (N) gene as the template (detection ***target***) to create an array of crRNA spacer (red tube).

The socio-economic fall-out from the stochastic spread of infection and non-deterministic trends affecting certain countries, select groups (race, ethnicity) and underserved clusters, may be an example of *"writing on the wall"* we are slow to acknowledge. The cost of testing 100,000 individuals in the US approximate $6 million. If 30 million tests are performed weekly it would require an additional $75 billion and adding the cost of contact tracing might bring the total to approach $100 billion[215].

The *"writing"* says that the NIAID-Moderna mRNA-1273 vaccine or any other safe and effective vaccine against SARS-CoV-2, when it may become available in 2021 or later, may still be out of reach for *billions* of people. CRISPR[216]-based tests may be promising[217] in the future (see Figure 19). BinaxNOW $5 test[218] is at hand but may not be feasible for daily use in communities under economic constraints. The case of Hepatitis-C[219] is an example how even after nearly 50 years, anti-viral drugs are not within the buying power of billions of people.

Death, destruction and the decay of civilization[220] may continue and may *continue to amplify* in certain regions of the world, long after the pandemic. ***If*** the current pandemic is substantially contained by the end of 2021, then the aggregated loss from mortality, morbidity, mental health conditions, and direct economic losses in the US alone is conservatively estimated at $16 trillion[221]. The US economy is about a quarter of the global economy[222], hence, extrapolation suggests that losses due to this pandemic may be an estimated $64 trillion, globally (about 80% of the global GDP[223]).

This mundane proposal is an elusive quest for an alternative path, albeit temporary and vastly incomplete, perhaps through the use of aptamers (or other variations based on oligonucleotides[224]) to partially bridge the chasm of inequity[225] and cushion the blow from the mortality and morbidity, yet to be witnessed. Healthcare is a pillar (**FEWSHE** - food, energy, water, sanitation, healthcare, education) of life and living but it is prudent to avoid indulging in any illusion or delusion because neither aptamers nor vaccines or CRISPR tools, irrespective of their respective efficacies, are a panacea for the restoration of civilization, even if this pandemic subsides in one or two years. The quintessential ingredients for the global rejuvenation may be credibility, magnanimity and ethical leadership.

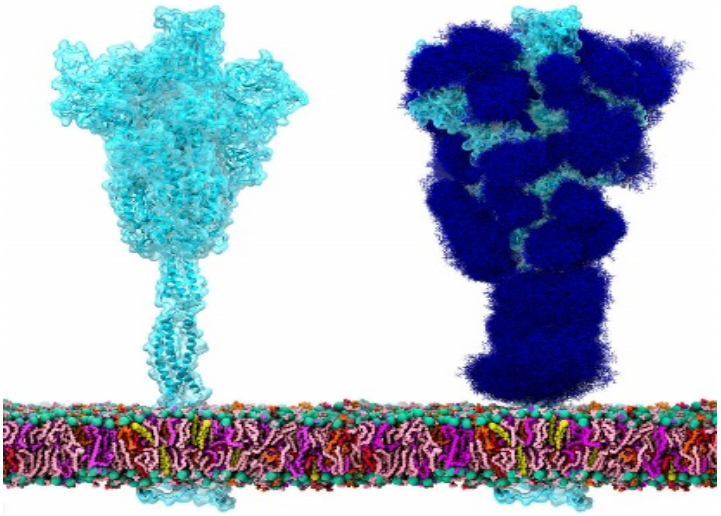
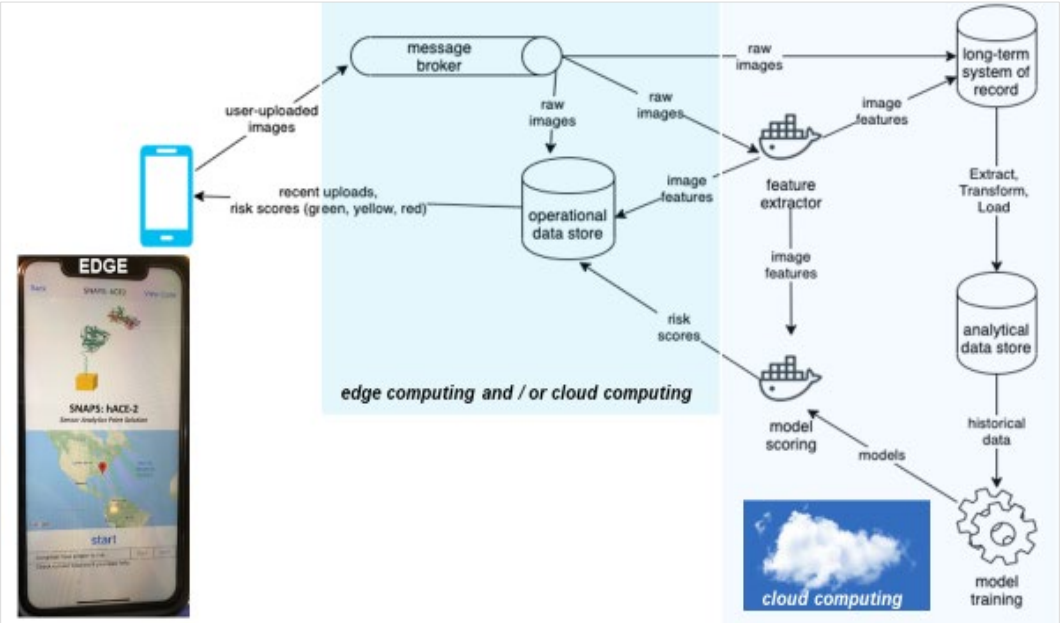


Figure 20: Similar to HIV and other viral fusion proteins, SARS-CoV-2 Spike protein uses a N-glycan shield[226] to thwart the host immune response (protective coating of N-glycans in cobalt blue, right) and makes long term immunity heterogeneous, at best. If SARS-CoV-2 becomes endemic[227], it will behoove us to explore parallel risk mitigation strategies. Oligonucleotides and aptamers may be an alternative path, suggested in this proposal.

10. APPENDIX – Brief Description of the Components[228] for ADD Decision System (Figure 1)



Message Broker

When users upload images (the data after scanning with the HoloLens app or equivalent mobile tool), the mobile application (on their phones) writes messages with the image content and other metadata to a message-broker, which may be cloud-based message queuing (MQ[229]) protocol (open source software). The message broker allows devices to quickly offload data and confirm "sent" to a user (if cloud based), thereby decoupling the user experience from the data store (even if it uses a temporary tinyDB on the device, if the network is unavailable to access the cloud in real-time at the point of use). Messages can be queued in topics and the system may enable autoscaling (as usage of the application increases, more users can be provisioned, process user uploads and get them stored). The uploads (data) are also sent by the message broker to the feature extractor and long-term storage database (may use the batch upload option when device is proximal to a high bandwidth gateway which can offer access to cloud services).

Operational Data Store

The message broker transfers uploads to ODS (Operational Data Store[230]), which may be a cloud-based managed service or part of the tinyDB on the device, if cloud is inaccessible at the point of use. ODS must be able to store image data (supports binary blog column type) alongside time-index numerical and character data. It is intended to only serve "hot" (nascent) data to the application. Older data may be evicted (batch uploaded to cloud managed facilities) to optimize on-device service and prevent data amplification. ODS is tuned for fast random reads and serves requests made by mobile app when users view recent uploads and additional metadata about those uploads, including "risk scores". ODS is optimized for fast writes and high efficiency time-series queries.

Feature Extractor

Extracts additional metadata from images/data uploaded from the mobile app (uploads it to the long-term system of record[231] which includes raw data uploaded from the application, similar to "master data" in ERP[232]). Feature Extractor may convert the uploaded image into a numeric matrix[233] or create hash table or representation of a region[234] and correct for differences in resolution (for example, variation due to pixel density of cameras on different smartphones). Feature[235] vectors[236] may be maintained in the long-term system of record. It may be written to the operational data store to enable extraction/selection[237] of incoming data (uploads from message broker) relevant to these feature vectors.

Long-term System of Record

Mobile applications may never access data directly from this data store[238]. Interactive-speed queries to this data store may not be supported. When necessary, objects stored in this "record" may be extracted and the data is loaded into an analytical data store. For object stores, this operation may be accomplished using query-over-files engines[239]. The thorniest problem that ferments within long-term data record is the inaccuracy of "accurate" data and the diabolical mayhem from "big data" if it is sourced and stored.

Analytical Data Store

Scientists and data experts will need historical data (from uploaded samples) to train task-specific[240] machine learning (ML) models to assign risk scores to samples. Analytical data store (ADS database[241]) may be populated with data from the long-term system of record using scheduled batch data uploads.

Model Training

In model training[242], a statistical model is built from historical data. Models should be serializable[243] representations of the program generated by ML training. Serialization is essential for interoperability on different platforms. It is key to create composable models where models from different groups can be deconstructed to sub-elements which can be reconstructed to compose a new model (which may be greater than the sum of parts). Serialization enables the process of translating a data structure or object state into a format that can be stored or transmitted and reconstructed. Proprietary software vendors obfuscate or encrypt serialized data to prevent access. Standard architectures such as CORBA[244] define the serialization formats in detail to enable open access.

Model Scoring

In model scoring, a model is called on input data, the model processes the input data and generates a prediction. The structure of this code depends on the ***design choices*** made during model training. For reliability of deployment, model scoring may run in a container[245] (an unit of software) which contains code (and all its dependencies) that uses a model to produce predictions on new input data. If model scoring runs in a container then the model can be arbitrary code in the developer's language[246] of choice. Model scoring requires features created previously by the feature extractor (feature selection is critical).

REFERENCES

[1] Subirana, Brian, et al. "Hi Sigma, Do I Have the Coronavirus?: Call for a New Artificial Intelligence Approach to Support Health Care Professionals Dealing With The COVID-19 Pandemic." April 2020. http://arxiv.org/abs/2004.06510 and https://arxiv.org/ftp/arxiv/papers/2004/2004.06510.pdf

[2] Massachusetts General Hospital (2020) New Tool Can Detect COVID-19 Outbreaks in US Counties. https://www.massgeneral.org/news/press-release/New-tool-can-detect-covid-19-outbreaks-in-us-counties and https://analytics-modeling.shinyapps.io/outbreakdetection/

[3] Engels, D. W., et al. "Networked Physical World: Automated Identification Architecture." *Proceedings. The Second IEEE Workshop on Internet Applications. WIAPP 2001*, IEEE Comput. Soc, 2001, pp. 76–77. doi:10.1109/WIAPP.2001.941872 https://ieeexplore.ieee.org/document/941872

[4] Sarma, Sanjay, Brock, David and Ashton, Kevin (2000) *The Networked Physical World: Proposals for Engineering the Next Generation of Computing, Commerce & Automatic-Identification.* White Paper WH-001. October 1, 2000. MIT Auto-ID Center, Massachusetts Institute of Technology. https://cocoa.ethz.ch/downloads/2014/06/None_MIT-AUTOID-WH-001.pdf

[5] Susan Symington, William Polk and Murugiah Souppaya (2020) *Internet of Things (IoT) Device Network-Layer Onboarding and Lifecycle Management.* NIST Cybersecurity White Paper (Draft). https://nvlpubs.nist.gov/nistpubs/CSWP/NIST.CSWP.09082020-draft.pdf

[6] Chinese Numerology https://en.wikipedia.org/wiki/Chinese_numerology

[7] Shambhavi Shubham, Jan Hoinka, Soma Banerjee, Emma Swanson, JacobA. Dillard, Nicholas J. Lennemann, Teresa M. Przytycka, Wendy Maury and Marit Nilsen-Hamilton (2018) A 2'FY-RNA Motif Defines an Aptamer for Ebolavirus Secreted Protein. *Nature Scientific Reports* 2018 Aug 17; 8(1):12373 doi: 10.1038/s41598-018-30590-8 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6098113/pdf/41598_2018_Article_30590.pdf

[8] Jakub Ptacek, Dong Zhang, Liming Qiu, Sven Kruspe, Lucia Motlova, Petr Kolenko, Zora Novakova, Shambhavi Shubham, Barbora Havlinova, Petra Baranova, Shi-Jie Chen, Xiaoqin Zou, Paloma Giangrande, Cyril Barinka, Structural basis of prostate-specific membrane antigen recognition by the A9g RNA aptamer, *Nucleic Acids Research*, gkaa494. https://doi.org/10.1093/nar/gkaa494

[9] Datta, Shoumen (2020) *CITCOM Paradigm* "CITCOM+" https://dspace.mit.edu/handle/1721.1/111021

[10] Fairbanks, Antony J. "The ENGases: Versatile Biocatalysts for the Production of Homogeneous N-Linked Glycopeptides and Glycoproteins." *Chemical Society Reviews*, vol. 46, no. 16, 2017, pp. 5128–46. doi:10.1039/C6CS00897F. https://pubs.rsc.org/en/content/articlepdf/2017/cs/c6cs00897f

[11] Khargonekar, Pramod P. (2020) Kalman Filtering, Sensor Fusion, and Eye Tracking https://faculty.sites.uci.edu/khargonekar/files/2020/08/KFSensorFusion_PPK.pdf

[12] NIST Differential Privacy Engineering (2018) https://www.nist.gov/itl/applied-cybersecurity/privacy-engineering/collaboration-space/focus-areas/de-id/tools#dpchallenge

[13] Victoria Morgan, Lisseth Casso-Hartman, David Bahamon-Pinzon, Kelli McCourt, Robert G. Hjort, Sahar Bahramzadeh, Irene Velez-Torres, Eric McLamore, Carmen Gomes, Evangelyn C. Alocilja, Shoumen Palit Austin Datta and Diana C. Vanegas (2019) *Sensor-as-a-Service: Convergence of Sensor Analytic Point Solutions (SNAPS) and Pay-A-Penny-Per-Use (PAPPU) Paradigm as a Catalyst for Democratization of Healthcare in Underserved Communities.* Diagnostics *2020,* 10 *(1), 22* https://doi.org/10.3390/diagnostics10010022
"SNAPS TRILOGY" MIT Libraries https://dspace.mit.edu/handle/1721.1/123983

[14] Winn, Zach (2020) Real-time data for a better response to disease outbreaks. https://news.mit.edu/2020/kinsa-health-0821

[15] Lamb, James (2020) ADD Appendix – Description of Major Components (*personal communication*) https://github.com/jameslamb

[16] Zamecnik PC, Stephenson ML.(1978) *Inhibition of Rous sarcoma virus replication and cell transformation by a specific oligodeoxynucleotide.* Proc Natl Acad Sci (US). 1978 January; 75(1):280-4. doi: 10.1073/pnas.75.1.280 www.ncbi.nlm.nih.gov/pmc/articles/PMC411230/pdf/pnas00013-0285.pdf

[17] Cohn, Danny M., et al. "Antisense Inhibition of Prekallikrein to Control Hereditary Angioedema." *New England J of Med.* vol. 383, no. 13, September 2020, pp. 1242–1247. doi:10.1056/NEJMoa1915035

[18] APPENDIX Figure 1: Description of Components https://github.com/shoumendatta/ADD-DIGITAL

[19] McLamore, Eric (2019) Surveillance Smartphone App *(personal communication)* https://abe.ufl.edu/people/faculty/eric-mclamore/ & https://emclamor.wixsite.com/mclamorelab

[20] Shmerling, Robert (2020) *Which test is best for COVID-19?* Harvard Medical School. 21 Sept 2020. https://www.health.harvard.edu/blog/which-test-is-best-for-covid-19-2020081020734

[21] Classification: True vs. False and Positive vs. Negative https://developers.google.com/machine-learning/crash-course/classification/true-false-positive-negative

[22] Candela M, Luconi V, Vecchio A. *Impact of the COVID-19 pandemic on the Internet latency: A large-scale study.* Computer Networks. 2020 December 9; 182:107495. doi: 10.1016/j.comnet.2020.107495. Epub 2020 August 20. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7439971/pdf/main.pdf

[23] World Economic Forum (2016) *4 billion people still don't have internet access.* https://www.weforum.org/agenda/2016/05/4-billion-people-still-don-t-have-internet-access-here-s-how-to-connect-them/

[24] Likert Scale https://www.sciencedirect.com/topics/psychology/likert-scale

[25] Roh, Yuji, et al. *A Survey on Data Collection for Machine Learning.* August 2019. http://arxiv.org/abs/1811.03402 and https://arxiv.org/pdf/1811.03402.pdf

[26] CDC - 2019-nCoV Real-Time RT-PCR Diagnostic Panel. www.fda.gov/media/134920/download

[27] Hutson, Matthew. "Artificial-Intelligence Tools Aim to Tame the Coronavirus Literature." *Nature*, June 2020, pp. d41586-020-01733–37. doi:10.1038/d41586-020-01733-7

[28] Kanter, James Max, et al. "Machine Learning 2.0 : Engineering Data Driven AI Products." July 2018. http://arxiv.org/abs/1807.00401 and https://arxiv.org/pdf/1807.00401.pdf

[29] Collection of scholarly articles and book on FEATURES (200MB) http://bit.ly/BOOKS-FEATURES

[30] Escalante, Hugo Jair. "Automated Machine Learning - Brief Review at the End of the Early Years." August 2020. http://arxiv.org/abs/2008.08516 and https://arxiv.org/pdf/2008.08516.pdf

[31] Kanter, James Max, and Kalyan Veeramachaneni. "Deep Feature Synthesis: Towards Automating Data Science Endeavors." *2015 IEEE International Conference on Data Science and Advanced Analytics (DSAA)*, IEEE, 2015, pp. 1–10. doi:10.1109/DSAA.2015.7344858. http://axperia-ventures.com/wp-content/uploads/2015/10/DSAA_DSM_2015.pdf

[32] Gilad Katz, Eui Chul Richard Shin and Dawn Song (2016) "ExploreKit: Automatic Feature Generation and Selection." *2016 IEEE 16th International Conference on Data Mining (ICDM)*, IEEE, 2016, pp. 979–84. doi:10.1109/ICDM.2016.0123 https://people.eecs.berkeley.edu/~dawnsong/papers/icdm-2016.pdf

[33] Data Distribution Service https://www.dds-foundation.org/what-is-dds-3/

[34] Berke EM. *Geographic Information Systems (GIS): recognizing the importance of place in primary care research and practice.* J Am Board Fam Med. 2010 Jan-Feb; 23(1):9-12. doi: 10.3122/jabfm.2010.01.090119 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3174470/pdf/nihms-323401.pdf

[35] Tebani, A., Gummesson, A., Zhong, W. *et al.* Integration of molecular profiles in a longitudinal wellness profiling cohort. *Nat Commun* **11,** 4487 (2020). https://doi.org/10.1038/s41467-020-18148-7 https://www.nature.com/articles/s41467-020-18148-7.pdf

[36] Pennisi, Elizabeth. "Massive Project Reveals Complexity of Gene Regulation." *Science*, vol. 369, no. 6509, 10 September 2020, pp. 1286–1287. doi:10.1126/science.369.6509.1286

[37] Zahn, Laura M. "Custom Transcriptome." *Science*, vol. 369, no. 6509, 10 September 2020, pp. 1316–1317. doi:10.1126/science.abe4492

[38] The GTEx Consortium. "The GTEx Consortium Atlas of Genetic Regulatory Effects across Human Tissues." *Science*, vol. 369, no. 6509, 10 September 2020, pp. 1318–1330. doi:10.1126/science.aaz1776 https://science.sciencemag.org/content/sci/369/6509/1318.full.pdf

[39] Hutchinson, L., Romero, D. Precision or imprecision medicine?. *Nat Rev Clin Oncol* **13,** 713 (2016) https://doi.org/10.1038/nrclinonc.2016.190 ▪ https://www.nature.com/articles/nrclinonc.2016.190.pdf

[40] Gold, Larry (2020) *Personal Communication* https://amzn.to/2QGSz1i

[41] Dodig-Crnković, Tea, et al. "Facets of Individual-Specific Health Signatures Determined from Longitudinal Plasma Proteome Profiling." *EBioMedicine*, vol. 57, July 2020, p. 102854. doi:10.1016/j.ebiom.2020.102854. www.thelancet.com/action/showPdf?pii=S2352-3964%2820%2930229-2

[42] https://somascandiscovery.com/publications/

[43] APTAMER (Collected Papers) https://bit.ly/APTAMER

[44] She, Richard, et al. "Comprehensive and Quantitative Mapping of RNA–Protein Interactions across a Transcribed Eukaryotic Genome." *Proceedings of the National Academy of Sciences*, vol. 114, no. 14, April 2017, pp. 3619–3624. doi:10.1073/pnas.1618370114 https://www.pnas.org/content/pnas/114/14/3619.full.pdf

[45] Pál, Gábor, et al. "Comprehensive and Quantitative Mapping of Energy Landscapes for Protein-Protein Interactions by Rapid Combinatorial Scanning." *Journal of Biological Chemistry*, vol. 281, no. 31, August 2006, pp. 22378–22385. doi:10.1074/jbc.M603826200. https://www.jbc.org/content/281/31/22378.full.pdf

[46] Petricoin, Emanuel F., et al. "Use of Proteomic Patterns in Serum to Identify Ovarian Cancer." *The Lancet*, vol. 359, no. 9306, Feb. 2002, pp. 572–77. doi:10.1016/S0140-6736(02)07746-2 http://fenyolab.org/presentations/Proteomics_Informatics_2014/pdf/02_petricoin_lancet.pdf

[47] Canna, Scott W., and Edward M. Behrens. "Making Sense of the Cytokine Storm: A Conceptual Framework for Understanding, Diagnosing, and Treating Hemophagocytic Syndromes." *Pediatric Clinics of North America*, vol. 59, no. 2, April 2012, pp. 329–44. doi:10.1016/j.pcl.2012.03.002 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3368378/pdf/nihms370318.pdf

[48] Tisoncik, J. R., et al. "Into the Eye of the Cytokine Storm." *Microbiology and Molecular Biology Reviews*, vol. 76, no. 1, March 2012, pp. 16–32. doi:10.1128/MMBR.05015-11 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294426/pdf/zmr16.pdf

[49] https://science.sciencemag.org/content/369/6507/1041/tab-pdf and https://www.nejm.org/doi/pdf/10.1056/NEJMc2016359

[50] Gold, Larry. "SELEX: How It Happened and Where It Will Go." *Journal of Molecular Evolution*, vol. 81, no. 5–6, December 2015, pp. 140–143. doi:10.1007/s00239-015-9705-9 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4661202/pdf/239_2015_Article_9705.pdf

[51] De La Fuente, Adriana, et al. "Aptamers against Mouse and Human Tumor-Infiltrating Myeloid Cells as Reagents for Targeted Chemotherapy." *Science Translational Medicine*, vol. 12, no. 548, June 2020, p. eaav9760 doi:10.1126/scitranslmed.aav9760

[52] Hopfield, J. J. "Kinetic Proofreading: A New Mechanism for Reducing Errors in Biosynthetic Processes Requiring High Specificity." *Proc National Academy of Sciences*, vol. 71, no. 10, Oct. 1974, pp. 4135-4139. doi:10.1073/pnas.71.10.4135 ▪ https://www.pnas.org/content/pnas/71/10/4135.full.pdf

[53] Oran DP, Topol EJ. *Prevalence of Asymptomatic SARS-CoV-2 Infection : A Narrative Review.* Ann Intern Med. 2020 September 1;173(5):362-367. doi: 10.7326/M20-3012. Epub 2020 June 3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7281624/pdf/aim-olf-M203012.pdf

[54] Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, Raizada MK, Grant MB, Oudit GY. *Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2*. Circulation Research. 2020 May 8; 126(10):1456-1474. doi: 10.1161/CIRCRESAHA.120.317015. Epub 2020 April 8. www.ncbi.nlm.nih.gov/pmc/articles/PMC7188049/pdf/res-126-10.1161.circresaha.120.317015.pdf

[55] López-Otín, Carlos, and Judith S. Bond. "Proteases: Multifunctional Enzymes in Life and Disease." *Journal of Biological Chemistry*, vol. 283, no. 45, November 2008, pp. 30433–30437 doi:10.1074/jbc.R800035200 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2576539/pdf/30433.pdf

[56] Hoagland, M. B., Stephenson, M. L., Scott, J. F., Hecht, L. I., and Zamecnik, P. C. (1958) *A Soluble Ribonucleic Acid Intermediate in Protein Synthesis.* J. Biol. Chem. **231** 241–257. https://pdfs.semanticscholar.org/aad2/985a4bcb40430260e3570683cb2b3b79f7e7.pdf?_ga=2.242690306.1804402263.1599417152-1424810635.1595859001 ■ https://www.jbc.org/content/280/40/e37

[57] Brenner, S., Jacob, F. & Meselson, M. (1961). *An unstable intermediate carrying information from genes to ribosomes for protein synthesis.* Nature **190** 576–581

[58] Gros, F., Hiatt, H., Gilbert, W., Kurland, C. G.,Risebrough, R. W. & Watson, J. D. (1961). *Unstable ribonucleic acid revealed by pulse labelling of Escherichia coli.* Nature **190** 581–585

[59] Jacob, F. and Monod, J. (1961). *Genetic regulatory mechanisms in the synthesis of proteins.* Journal of Molecular Biology **3** 318–356

[60] Monod, J., Changeux, J. P. and Jacob, F. (1963). *Allosteric proteins and cellular control systems*. Journal of Molecular Biology **6** 306–329

[61] Alberts, Bruce and Frey, Linda (1970) *T4 Bacteriophage Gene 32: A Structural Protein in the Replication and Recombination of DNA.* Nature **227** 1313–1318 https://brucealberts.ucsf.edu/wp-content/uploads/2016/07/Alberts-and-Frey-1970-YO.pdf

[62] Tuerk, Craig and Gold, Larry (1990) *Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase.* Science **249** 505–510

[63] Ellington, Andy D. and Szostak, Jack W. (1990) *In vitro selection of RNA molecules that bind specific ligands.* Nature **346** 818–822

[64] Gold, Larry (2015) "SELEX: How It Happened and Where It Will Go." Journal of Molecular Evolution, vol. 81, no. 5–6, December 2015, pp. 140–143. doi:10.1007/s00239-015-9705-9 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4661202/pdf/239_2015_Article_9705.pdf

[65] Lakhin AV, Tarantul VZ, Gening LV. (2013) *Aptamers: problems, solutions and prospects.* Acta Naturae. 2013 October, 5(4):34-43. www.ncbi.nlm.nih.gov/pmc/articles/PMC3890987/pdf/AN20758251-19-034.pdf

[66] Ku TH, Zhang T, Luo H, Yen TM, Chen PW, Han Y, Lo YH. (2015) *Nucleic Acid Aptamers: An Emerging Tool for Biotechnology and Biomedical Sensing.* Sensors (Basel). 2015 July 6; 15(7): 16281-16313 doi: 10.3390/s150716281 www.ncbi.nlm.nih.gov/pmc/articles/PMC4541879/pdf/sensors-15-16281.pdf

[67] Kato, Teru, et al (2000) "In Vitro Selection of DNA Aptamers Which Bind to Cholic Acid." *Biochimica et Biophysica Acta (BBA) - Gene Structure and Expression*, vol. 1493, no. 1–2, September 2000, pp. 12–18. doi:10.1016/S0167-4781(00)00080-4

[68] Kalra, Priya, et al. "Simple Methods and Rational Design for Enhancing Aptamer Sensitivity and Specificity." *Frontiers in Molecular Biosciences*, vol. 5, May 2018, p. 41. doi:10.3389/fmolb.2018.00041 https://www.frontiersin.org/articles/10.3389/fmolb.2018.00041/pdf

[69] Strauss S, Nickels PC, Strauss MT, Jimenez Sabinina V, Ellenberg J, Carter JD, Gupta S, Janjic N, Jungmann R. (2018) *Modified aptamers enable quantitative sub-10-nm cellular DNA-PAINT imaging.* Nature Methods. 2018 Sep;15(9):685-688. doi: 10.1038/s41592-018-0105-0 Epub 2018 August 20. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6345375/pdf/emss-78630.pdf

[70] Kato Teru, Yano K, Ikebukuro K, Karube I. (2000) *Interaction of three-way DNA junctions with steroids.* Nucleic Acids Res. 2000 May 1; 28(9):1963-1968. doi: 10.1093/nar/28.9.1963 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC103303/pdf/gkd319.pdf

[71] Sun, B.B., Maranville, J.C., Peters, J.E. *et al.* (2018) *Genomic atlas of the human plasma proteome.* Nature **558** 73–79 (2018). https://doi.org/10.1038/s41586-018-0175-2

[72] Emilsson, Valur, et al (2018) *Co-Regulatory Networks of Human Serum Proteins Link Genetics to Disease.* Science, vol. 361, no. 6404, Aug. 2018, pp. 769–773. doi:10.1126/science.aaq1327

[73] Joshi A and Mayr M. (2018) *In Aptamers They Trust: The Caveats of the SOMAscan Biomarker Discovery Platform from SomaLogic.* Circulation. 2018 November 27; 138(22):2482-2485. doi: 10.1161/CIRCULATIONAHA.118.036823. Epub 2018 November 26. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6277005/pdf/emss-80116.pdf

[74] Zhang Y, Lai BS, Juhas M. *Recent Advances in Aptamer Discovery and Applications.* Molecules. 2019 Mar 7; 24(5):941. doi: 10.3390/molecules24050941 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429292/pdf/molecules-24-00941.pdf

[75] Song, Kyung-Mi; Lee, Seonghwan; Ban, Changill. 2012. "Aptamers and Their Biological Applications." *Sensors* 12, no. 1: 612-631. https://www.mdpi.com/1424-8220/12/1/612/pdf

[76] Wu, Yao, et al. "Perspective on the Future Role of Aptamers in Analytical Chemistry." *Analytical Chemistry*, vol. 91, no. 24, December 2019, pp. 15335–15344. doi:10.1021/acs.analchem.9b03853

[77] De La Fuente, Adriana, et al. "Aptamers against Mouse and Human Tumor-Infiltrating Myeloid Cells as Reagents for Targeted Chemotherapy." *Science Translational Medicine*, vol. 12, no. 548, June 2020, p. eaav9760. doi:10.1126/scitranslmed.aav9760.

[78] Schmitz, F.R.W., Valério, A., de Oliveira, D. *et al.* An overview and future prospects on aptamers for food safety. *Appl Microbiol Biotechnol* **104,** 6929–6939 (2020) https://doi.org/10.1007/s00253-020-10747-0 https://link.springer.com/content/pdf/10.1007/s00253-020-10747-0.pdf

[79] Sumedha D Jayasena, Aptamers: An Emerging Class of Molecules That Rival Antibodies in Diagnostics, *Clinical Chemistry*, Volume 45, Issue 9, 1 September 1999, Pages 1628-1650. https://doi.org/10.1093/clinchem/45.9.1628

[80] Hicke BJ, Stephens AW, Gould T, et al. (2006) Tumor targeting by an aptamer. *J Nucl Med*. 2006;47(4):668-678. http://jnm.snmjournals.org/content/47/4/668.full.pdf+html

[81] Trausch, Jeremiah J., et al. "Replacing Antibodies with Modified DNA Aptamers in Vaccine Potency Assays." *Vaccine*, vol. 35, no. 41, October 2017, pp. 5495–502. doi:10.1016/j.vaccine.2017.04.003

[82] Javier DJ, Nitin N, Levy M, Ellington A, Richards-Kortum R. *Aptamer-targeted gold nanoparticles as molecular-specific contrast agents for reflectance imaging*. Bioconjug Chem. 2008 June; 19(6):1309-12. doi: 10.1021/bc8001248. Epub 2008 May 31. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2651625/pdf/bc8001248.pdf

[83] Hianik T, Porfireva A, Grman I, Evtugyn G. EQCM biosensors based on DNA aptamers and antibodies for rapid detection of prions. *Protein Pept Lett*. 2009;16(4):363-367. doi:10.2174/092986609787848090

[84] Lee, J., So, H., Jeon, E. *et al.* Aptamers as molecular recognition elements for electrical nanobiosensors. *Anal Bioanal Chem* **390,** 1023–1032 (2008). https://doi.org/10.1007/s00216-007-1643-y https://link.springer.com/content/pdf/10.1007/s00216-007-1643-y.pdf

[85] Arshavsky-Graham, Sofia, et al. "Aptamers *vs.* Antibodies as Capture Probes in Optical Porous Silicon Biosensors." *The Analyst*, vol. 145, no. 14, 2020, pp. 4991–5003. doi:10.1039/D0AN00178C

[86] Zou X, Wu J, Gu J, Shen L, Mao L. Application of Aptamers in Virus Detection and Antiviral Therapy. Front Microbiol. 2019 July 3;10:1462. doi: 10.3389/fmicb.2019.01462. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6618307/pdf/fmicb-10-01462.pdf

[87] Ahn DG, Jeon IJ, Kim JD, et al. RNA aptamer-based sensitive detection of SARS coronavirus nucleocapsid protein. *Analyst*. 2009;134(9):1896-1901. doi:10.1039/b906788d https://pubs.rsc.org/en/content/articlepdf/2009/an/b906788d

[88] Wyllie, Anne L., et al. Saliva or Nasopharyngeal Swab Specimens for Detection of SARS-CoV-2. *New England J of Medicine*, Aug 2020, p. NEJMc2016359 doi:10.1056/NEJMc2016359 https://www.nejm.org/doi/pdf/10.1056/NEJMc2016359 https://science.sciencemag.org/content/369/6507/1041/tab-pdf

[89] Shubham, Shambhavi, "Selection of functional RNA aptamers against Ebola glycoproteins" (2017). Graduate Theses and Dissertations. Iowa State University. https://lib.dr.iastate.edu/etd/16528

[90] Eichel, H. J., et al. "Acid and Alkaline Ribonucleases of Human Parotid, Submaxillary, and Whole Saliva." *Archives of Biochemistry and Biophysics*, vol. 107, no. 2, August. 1964, pp. 197–208 doi:10.1016/0003-9861(64)90322-4

[91] Cho SJ, Woo HM, Kim KS, Oh JW, Jeong YJ. *Novel system for detecting SARS coronavirus nucleocapsid protein using an ssDNA aptamer.* J Biosci Bioeng. 2011 Dec; 112(6):535-40. doi: 10.1016/j.jbiosc.2011.08.014. www.ncbi.nlm.nih.gov/pmc/articles/PMC7106535/pdf/main.pdf

[92] Chen Z, Wu Q, Chen J, Ni X, Dai J. *DNA Aptamer Based Method for Detection of SARS-CoV-2 Nucleocapsid Protein*. Virol Sin. 2020 June; 35(3):351-354. doi: 10.1007/s12250-020-00236-z. Epub 2020 May 25. www.ncbi.nlm.nih.gov/pmc/articles/PMC7246297/pdf/12250_2020_Article_236.pdf

[93] *Nucleocapsid Phosphoprotein: Severe Acute Respiratory Syndrome Coronav - Protein - NCBI.* https://www.ncbi.nlm.nih.gov/protein/YP_009724397.2

[94] *Nucleocapsid Protein: Severe Acute Respiratory Syndrome-Related Corona - Protein - NCBI.* https://www.ncbi.nlm.nih.gov/protein/NP_828858.1

[95] Zhang, Liyun, et al. "Discovery of Sandwich Type COVID-19 Nucleocapsid Protein DNA Aptamers." *Chemical Communications*, vol. 56, no. 70, 2020, pp. 10235–10238. doi:10.1039/D0CC03993D. https://pubs-rsc-org.libproxy.mit.edu/en/content/articlepdf/2020/cc/d0cc03993d

[96] Li, Hui-Yan, et al. Advances in Detection of Infectious Agents by Aptamer-Based Technologies. *Emerging Microbes & Infections*, vol. 9, no. 1, January 2020, pp. 1671–1681. doi:10.1080/22221751.2020.1792352. https://www.tandfonline.com/doi/pdf/10.1080/22221751.2020.1792352?needAccess=true

[97] Lucia Wang and Maureen McKeague (2020) Aptamers in the pursuit of COVID-19 management. Aptamers (2020), Vol 4, in press. http://japtamers.co.uk/wp-content/uploads/2020/07/Wang.pdf

[98] https://www.aptamergroup.co.uk/aptamers-in-the-battle-against-covid19/

[99] Cleri, Fabrizio, Lensink, Marc F., Blossey, Ralf (2020): *DNA Aptamers Block the Receptor Binding Domain at the Spike Protein of SARS-CoV-2.* ChemRxiv. Preprint. https://doi.org/10.26434/chemrxiv.12696173.v1 https://chemrxiv.org/ndownloader/files/24042815

[100] NSF Award Abstract #2028531(RAPID) Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)-Prevention: Multiple-Site Binding with Fusing Aptamers to mitigate Coronavirus Disease 2019. https://www.nsf.gov/awardsearch/showAward?AWD_ID=2028531&HistoricalAwards=false

[101] Song, Yanling, et al. "Discovery of Aptamers Targeting the Receptor-Binding Domain of the SARS-CoV-2 Spike Glycoprotein." *Analytical Chemistry*, vol. 92, no. 14, July 2020, pp. 9895–900. doi:10.1021/acs.analchem.0c01394. https://pubs.acs.org/doi/pdf/10.1021/acs.analchem.0c01394

[102] Bojkova, D., Klann, K., Koch, B. *et al.* Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. *Nature* **583,** 469–472 (2020). https://doi.org/10.1038/s41586-020-2332-7 https://www.nature.com/articles/s41586-020-2332-7.pdf

[103] Wu, Canrong, et al. "Analysis of Therapeutic Targets for SARS-CoV-2 and Discovery of Potential Drugs by Computational Methods." *Acta Pharmaceutica Sinica B*, vol. 10, no. 5, May 2020, pp. 766–788. doi:10.1016/j.apsb.2020.02.008. https://www.sciencedirect.com/science/article/pii/S2211383520302999

[104] Thoms, Matthias, et al. "Structural Basis for Translational Shutdown and Immune Evasion by the Nsp1 Protein of SARS-CoV-2." *Science*, vol. 369, no. 6508, September 2020, pp. 1249–55. doi:10.1126/science.abc8665. https://science.sciencemag.org/content/369/6508/1249.full.pdf

[105] Rong, Y., et al. "*Post Hoc* Support Vector Machine Learning for Impedimetric Biosensors Based on Weak Protein–Ligand Interactions." *The Analyst*, vol. 143, no. 9, 2018, pp. 2066–2075. doi:10.1039/C8AN00065D https://pubs.rsc.org/ko/content/getauthorversionpdf/C8AN00065D

[106] Choi, Jong Hyun, et al. "Aptamer-Capped Nanocrystal Quantum Dots: A New Method for Label-Free Protein Detection." *Journal of the American Chemical Society*, vol. 128, no. 49, Dec. 2006, pp. 15584–85. doi:10.1021/ja066506k.

[107] Smith, Andrew M., et al. "Quantum Dot Nanocrystals for In Vivo Molecular and Cellular Imaging¶." *Photochemistry and Photobiology*, vol. 80, no. 3, 2004, p. 377. doi:10.1562/2004-06-21-IR-209.1

[108] Bagalkot, Vaishali, et al. "Quantum Dot–Aptamer Conjugates for Synchronous Cancer Imaging, Therapy, and Sensing of Drug Delivery Based on Bi-Fluorescence Resonance Energy Transfer." Nano Letters, vol. 7, no. 10, October 2007, pp. 3065–3070. doi:10.1021/nl071546n.

[109] Li, Zhiming, et al. "Aptamer-Conjugated Dendrimer-Modified Quantum Dots for Glioblastoma Cells Imaging." *J of Physics: Conference Series*, vol. 188, Sep 2009, p. 012032. doi:10.1088/1742-6596/188/1/012032.

[110] Roberts, Kenneth and Bumm Lloyd, A. (2010) *Quantum Dot Nano-crystals Coupled to DNA Aptamers: Sensors For Biological Weapons Detection.* https://apps.dtic.mil/dtic/tr/fulltext/u2/a567156.pdf

[111] Zhou, DJ (2012) *Quantum dot-nucleic acid/aptamer bioconjugate based fluorimetric biosensors.* Biochemical Society Transactions **40** 635 – 639 ISSN 0300-5127 https://doi.org/10.1042/BST20120059

[112] https://www.microsoft.com/en-us/hololens/hardware

[113] https://www.denso-wave.com/en/technology/vol1.html

[114] https://en.wikipedia.org/wiki/Kinect

[115] Carlo Tomasi and Takeo Kanade (1992) *Shape and Motion from Image Streams under Orthography: Factorization Method.* International Journal of Computer Vision 9:2, 137-154 https://people.eecs.berkeley.edu/~yang/courses/cs294-6/papers/TomasiC_Shape%20and%20motion%20from%20image%20streams%20under%20orthography.pdf

[116] https://www.microsoft.com/en-us/research/blog/in-search-for-future-of-cloud-storage-researchers-look-to-holographic-storage-solutions/

[117] https://emclamor.wixsite.com/mclamorelab

[118] Philip Levis, Sam Madden, David Gay, Joseph Polastre, Robert Szewczyk, Alec Woo, Eric Brewer and David Culler (2003) *The Emergence of Networking Abstractions and Techniques in TinyOS* www.usenix.org/legacy/events/nsdi04/tech/full_papers/levisEmerge/levisEmerge_html/tinyos-nsdi03.html

[119] McLamore, E.S., S.P.A. Datta, V. Morgan, N. Cavallaro, G. Kiker, D.M. Jenkins, Y. Rong, C. Gomes, J. Claussen, D. Vanegas, E.C. Alocilja (2019*) SNAPS: Sensor Analytics Point Solutions for Detection and Decision Support.* Sensors, vol. 19, no. 22, November 2019, p. 4935 www.mdpi.com/1424-8220/19/22/4935/pdf and https://dspace.mit.edu/handle/1721.1/123983

[120] Walker, Bruce (2020) MIT Biology course number 7.00 (COVID-19, SARS-CoV-2 and the Pandemic) https://biology.mit.edu/wp-content/uploads/2020/09/7.00_Syllabus_9.8.20.pdf and https://biology.mit.edu/undergraduate/current-students/subject-offerings/covid-19-sars-cov-2-and-the-pandemic/

[121] Jack-in-the-Box https://en.wikipedia.org/wiki/Jack-in-the-box

[122] Walls, Alexandra C., et al. "Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein." *Cell*, vol. 181, no. 2, April 2020, pp. 281-292.e6. doi:10.1016/j.cell.2020.02.058 https://www.cell.com/cell/pdf/S0092-8674(20)30262-2.pdf

[123] Ellen Shrock, Eric Fujimura, Tomasz Kula, Richard T. Timms, I-Hsiu Lee, Yumei Leng, Matthew L. Robinson, Brandon M. Sie, Mamie Z. Li, Yuezhou Chen, Jennifer Logue, Adam Zuiani, Denise Mcculloch, Felipe J. N. Lelis, Stephanie Henson, Daniel E. Monaco, Meghan Travers, Shaghayegh Habibi, William A. Clarke, Patrizio Caturegli, Oliver Laeyendecker, Alicja Piechocka-Trocha, Jon Li, Ashok Khatri, Helen Y. Chu, MGH COVID-19 Collection & Processing Team, Alexandra-Chloé Villani, Kyle Kays, Marcia B. Goldberg, Nir Hacohen, Michael R. Filbin, Xu G. Yu, Bruce D. Walker, Duane R. Wesemann, H. Benjamin Larman, James A. Lederer, and Stephen J. Elledge (2020) *Viral epitope profiling of covid-19 patients reveals cross-reactivity and correlates of severity.* Published online 29 sep 2020. Science doi: 10.1126/science.abd4250 https://science.sciencemag.org/content/early/2020/09/28/science.abd4250/tab-pdf

[124] McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. *Candidate drugs against SARS-CoV-2 and COVID-19.* Pharmacol Res. 2020 Jul;157:104859. doi: 10.1016/j.phrs.2020.104859. Epub 2020 Apr 29. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7189851/pdf/main.pdf

[125] Mark Fischetti, Veronica Falconieri Hays, Britt Glaunsinger and Jen Christiansen (2020) *Inside the Coronavirus.* Scientific American 323, 1, 32-37 (July 1, 2020) doi:10.1038/scientificamerican0720-32
A Visual Guide to the SARS-CoV-2 Coronavirus: What scientists know about the inner workings of the pathogen that has infected the world. July 1, 2020. Scientific American.
https://www.scientificamerican.com/article/a-visual-guide-to-the-sars-cov-2-coronavirus/
https://www.scientificamerican.com/interactive/inside-the-coronavirus/

[126] Glaunsinger, Britt (2020) MIT Biology course number 7.00 (COVID-19, SARS-CoV-2 and the Pandemic) https://biology.mit.edu/undergraduate/current-students/subject-offerings/covid-19-sars-cov-2-and-the-pandemic/ and https://biology.mit.edu/wp-content/uploads/2020/09/7.00_Syllabus_9.8.20.pdf

[127] Jia HP, Look DC, Shi L, Hickey M, Pewe L, Netland J, Farzan M, Wohlford-Lenane C, Perlman S, McCray PB Jr. *ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia.* J Virol. 2005 December; 79(23):14614-14621. doi: 10.1128/JVI.79.23.14614-14621.2005 www.ncbi.nlm.nih.gov/pmc/articles/PMC1287568/pdf/1240-05.pdf

[128] Saheb Sharif-Askari, Narjes, et al. "Airways Expression of SARS-CoV-2 Receptor, ACE2, and TMPRSS2 Is Lower in Children Than Adults and Increases with Smoking and COPD." *Molecular Therapy - Methods & Clin Development*, vol. 18, Sept. 2020, pp. 1–6. doi:10.1016/j.omtm.2020.05.013
https://www.cell.com/molecular-therapy-family/methods/pdf/S2329-0501(20)30100-5.pdf

[129] Hilgenfeld R. From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. *FEBS J.* 2014; 281(18):4085-4096. doi:10.1111/febs.12936
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7163996/pdf/FEBS-281-4085.pdf

[130] Goodsell, D. S. "Coronavirus Proteases." *RCSB Protein Data Bank*, February 2020. doi:10.2210/rcsb_pdb/mom_2020_2 https://pdb101.rcsb.org/motm/242

[131] Barretto, Naina, et al. "The Papain-Like Protease of Severe Acute Respiratory Syndrome Coronavirus Has Deubiquitinating Activity." *Journal of Virology*, vol. 79, no. 24, December 2005, pp. 15189–15198. doi:10.1128/JVI.79.24.15189-15198.2005 https://jvi.asm.org/content/jvi/79/24/15189.full.pdf

[132] Boras, Britton, et al. *Discovery of a Novel Inhibitor of Coronavirus 3CL Protease as a Clinical Candidate for the Potential Treatment of COVID-19*. preprint, Pharmacology and Toxicology, 13 September 2020. doi:10.1101/2020.09.12.293498 https://www.biorxiv.org/content/10.1101/2020.09.12.293498v2.full.pdf

[133] Xue, Xiaoyu, et al. "Structures of Two Coronavirus Main Proteases: Implications for Substrate Binding and Antiviral Drug Design." *Journal of Virology*, vol. 82, no. 5, March 2008, pp. 2515–2527. doi:10.1128/JVI.02114-07 https://jvi.asm.org/content/jvi/82/5/2515.full.pdf

[134] Tahir ul Qamar, Muhammad, et al. "Structural Basis of SARS-CoV-2 3CLpro and Anti-COVID-19 Drug Discovery from Medicinal Plants." *Journal of Pharmaceutical Analysis*, vol. 10, no. 4, Aug. 2020, pp. 313–319. doi:10.1016/j.jpha.2020.03.009 https://www.sciencedirect.com/science/article/pii/S2095177920301271

[135] Rathnayake, Athri D., et al. "3C-like Protease Inhibitors Block Coronavirus Replication in Vitro and Improve Survival in MERS-CoV–Infected Mice." *Sci Trans Med*, vol. 12, no. 557, Aug. 2020, p. eabc5332. doi:10.1126/scitranslmed.abc5332 https://stm.sciencemag.org/content/12/557/eabc5332/tab-pdf

[136] Zhang, Linlin, et al. "Crystal Structure of SARS-CoV-2 Main Protease Provides a Basis for Design of Improved α-Ketoamide Inhibitors." *Science*, March 2020, p. eabb3405. doi:10.1126/science.abb3405 https://science.sciencemag.org/content/368/6489/409/tab-pdf

[137] Báez-Santos YM, Barraza SJ, Wilson MW, Agius MP, Mielech AM, Davis NM, Baker SC, Larsen SD, Mesecar AD. (2014*) X-ray structural and biological evaluation of a series of potent and highly selective inhibitors of human coronavirus papain-like proteases.* J Med Chem. 2014 March 27; 57(6):2393-412. doi: 10.1021/jm401712t. Epub 2014 March 14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3983375/pdf/jm401712t.pdf

[138] Rut, Wioletta, et al. *Activity Profiling and Structures of Inhibitor-Bound SARS-CoV-2-PLpro Protease Provides a Framework for Anti-COVID-19 Drug Design*. preprint, Biochemistry, 29 April 2020. doi:10.1101/2020.04.29.068890 https://www.biorxiv.org/content/biorxiv/early/2020/04/29/2020.04.29.068890.full.pdf

[139] Shin, D., Mukherjee, R., Grewe, D. *et al.* Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity. *Nature* (2020). https://doi.org/10.1038/s41586-020-2601-5 https://www.nature.com/articles/s41586-020-2601-5_reference.pdf

[140] Thoms, Matthias, et al. "Structural Basis for Translational Shutdown and Immune Evasion by the Nsp1 Protein of SARS-CoV-2." *Science*, vol. 369, no. 6508, September 2020, pp. 1249–55. doi:10.1126/science.abc8665 https://science.sciencemag.org/content/369/6508/1249.full.pdf

[141] Kamitani W, Huang C, Narayanan K, Lokugamage KG, Makino S. (2009) *A two-pronged strategy to suppress host protein synthesis by SARS coronavirus Nsp1 protein.* Nat Struct Mol Biol. 2009 November; 16(11):1134-40. doi: 10.1038/nsmb.1680. Epub 2009 October 18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2784181/pdf/41594_2009_Article_BFnsmb1680.pdf

[142] Lapointe, Christopher P., et al. *Dynamic Competition between SARS-CoV-2 NSP1 and MRNA on the Human Ribosome Inhibits Translation Initiation*. preprint, Biophysics, 21 August 2020. doi:10.1101/2020.08.20.259770 https://www.biorxiv.org/content/10.1101/2020.08.20.259770v1.full.pdf

[143] Schubert, K., Karousis, E.D., Jomaa, A. *et al.* SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. *Nat Struct Mol Biol* (2020). https://doi.org/10.1038/s41594-020-0511-8 https://www.nature.com/articles/s41594-020-0511-8.pdf

[144] Lee, J.S., Shin, E. The type I interferon response in COVID-19: implications for treatment. *Nat Rev Immunol* **20,** 585–586 (2020). https://doi.org/10.1038/s41577-020-00429-3 https://www.nature.com/articles/s41577-020-00429-3.pdf

[145] Zhang, Qian, et al. "Inborn Errors of Type I IFN Immunity in Patients with Life-Threatening COVID-19." *Science*, September 24, 2020, p. eabd4570. doi:10.1126/science.abd4570 https://science.sciencemag.org/content/early/2020/09/23/science.abd4570/tab-pdf

[146] Hadjadj, Jérôme, et al. "Impaired Type I Interferon Activity and Inflammatory Responses in Severe COVID-19 Patients." *Science*, vol. 369, no. 6504, August 7, 2020, pp. 718–724. doi:10.1126/science.abc6027 https://science.sciencemag.org/content/369/6504/718/tab-pdf

[147] Xia, H., Cao, Z., Xie, X., Zhang, X., Yun-Chung Chen, J., Wang, H., Menachery, V.D., Rajsbaum, R., Shi, P.-Y. (2020) Evasion of type-I interferon by SARS-CoV-2, Cell Reports (2020). https://doi.org/10.1016/j.celrep.2020.108234 https://www.cell.com/action/showPdf?pii=S2211-1247%2820%2931223-7

[148] Ella Hartenian, Divya Nandakumar, Azra Lari, Michael Ly, Jessica M Tucker and Britt A Glaunsinger. "The Molecular Virology of Coronaviruses." *J of Biol Chem*, vol. 295, no. 37, Sept 2020, pp. 12910–12934. https://www.jbc.org/cgi/doi/10.1074/jbc.REV120.013930 https://www.jbc.org/content/early/2020/07/13/jbc.REV120.013930.full.pdf

[149] Eckerle LD, Becker MM, Halpin RA, Li K, Venter E, Lu X, Scherbakova S, Graham RL, Baric RS, Stockwell TB, Spiro DJ, Denison MR. (2010) *Infidelity of SARS-CoV Nsp14-exonuclease mutant virus replication is revealed by complete genome sequencing.* PLoS Pathog. 2010 May 6; 6(5):e1000896. doi: 10.1371/journal.ppat.1000896 www.ncbi.nlm.nih.gov/pmc/articles/PMC2865531/pdf/ppat.1000896.pdf

[150] Streisinger G, Okada Y, Emrich J, et al. (1966) Frameshift mutations and the genetic code. This paper is dedicated to Professor Theodosius Dobzhansky on the occasion of his 66th birthday. *Cold Spring Harb Symp Quant Biol.* 1966; 31:77-84. doi:10.1101/sqb.1966.031.01.014 http://symposium.cshlp.org/content/31/77.long

[151] Reddy, E. P., *et al.* A point mutation is responsible for the acquisition of transforming properties by the *T24* human bladder carcinoma oncogene. *Nature* **300**, 149–152 (1982)

[152] Ou X, Zheng W, Shan Y, Mu Z, Dominguez SR, Holmes KV, Qian Z. (2016) *Identification of the Fusion Peptide-Containing Region in Betacoronavirus Spike Glycoproteins.* J Virol. 2016 May 27; 90(12):5586-5600. doi: 10.1128/JVI.00015-16 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4886789/pdf/zjv5586.pdf

[153] Xu, Yanhui, et al. "Crystal Structure of Severe Acute Respiratory Syndrome Coronavirus Spike Protein Fusion Core." *Journal of Biological Chemistry*, vol. 279, no. 47, November 2004, pp. 49414–49419. doi:10.1074/jbc.M408782200 https://www.jbc.org/content/279/47/49414.full.pdf

[154] Madu IG, Roth SL, Belouzard S, Whittaker GR. (2009) *Characterization of a highly conserved domain within the severe acute respiratory syndrome coronavirus spike protein S2 domain with characteristics of a viral fusion peptide.* J Virol. 2009 Aug; 83(15):7411-21. doi: 10.1128/JVI.00079-09. Epub 2009 May 13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2708636/pdf/0079-09.pdf

[155] Tang T, Bidon M, Jaimes JA, Whittaker GR, Daniel S. (2020) *Coronavirus membrane fusion mechanism offers a potential target for antiviral development.* Antiviral Res. 2020 Jun; 178:104792. doi: 10.1016/j.antiviral.2020.104792. Epub 2020 Apr 6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7194977/pdf/main.pdf

[156] Pattnaik GP, Chakraborty H. *Entry Inhibitors: Efficient Means to Block Viral Infection*. J Membrane Biol. 2020 Aug 30:1–20. doi: 10.1007/s00232-020-00136-z https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456447/pdf/232_2020_Article_136.pdf

[157] Bosch BJ, Martina BE, Van Der Zee R, Lepault J, Haijema BJ, Versluis C, Heck AJ, De Groot R, Osterhaus AD, Rottier PJ. (2004) *Severe acute respiratory syndrome coronavirus (SARS-CoV) infection inhibition using spike protein heptad repeat-derived peptides.* Proc Natl Acad Sci U S A. 2004 June 1; 101(22):8455-60. doi: 10.1073/pnas.0400576101. Epub 2004 May 18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC420415/pdf/1018455.pdf

[158] Leila Kashefi-Kheyrabadi, Junmoo Kim, Sudesna Chakravarty, Sunyoung Park, Hogyeong Gwak, Seung-Il Kim, Mohsen Mohammadniaei, Min-Ho Lee, Kyung-A Hyun and Hyo-Il Jung (2020) Detachable microfluidic device implemented with electrochemical aptasensor (DeMEA) for sequential analysis of cancerous exosomes. *Biosensors & Bioelectronics* (IF 10.257) Published September 17, 2020. DOI: 10.1016/j.bios.2020.112622

[159] Contreras-Naranjo JC, Wu HJ, Ugaz VM. (2017) *Microfluidics for exosome isolation and analysis: enabling liquid biopsy for personalized medicine.* Lab Chip. 2017 October 25; 17(21):3558-3577. doi: 10.1039/c7lc00592j www.ncbi.nlm.nih.gov/pmc/articles/PMC5656537/pdf/nihms903616.pdf

[160] Economics of Technology (Collected Papers) http://bit.ly/Economics-of-Technology

[161] Brat, Gabriel A., et al. "International Electronic Health Record-Derived COVID-19 Clinical Course Profiles: The 4CE Consortium." *Npj Digital Medicine*, vol. 3, no. 1, December. 2020, p. 109. doi:10.1038/s41746-020-00308-0 https://www.nature.com/articles/s41746-020-00308-0.pdf

[162] Tromberg BJ, Schwetz TA, Pérez-Stable EJ, et al. Rapid Scaling Up of Covid-19 Diagnostic Testing in the United States - The NIH RADx Initiative. *N Engl J Med*. September 10, 2020; 383(11):1071-1077. doi:10.1056/NEJMsr2022263 www.nejm.org/doi/pdf/10.1056/NEJMsr2022263?articleTools=true

[163] Yan, Li-Meng, et al. *Unusual Features of the SARS-CoV-2 Genome Suggesting Sophisticated Laboratory Modification Rather Than Natural Evolution and Delineation of Its Probable Synthetic Route.* Sept. 2020. doi:10.5281/ZENODO.4028830 https://zenodo.org/record/4028830/files/The_Yan_Report.pdf?download=1

[164] Matus García, Mariana Guadalupe (2018) *Analysis of fecal biomarkers to impact clinical care and public health.* Thesis: Ph. D., Massachusetts Institute of Technology, Computational and Systems Biology Program, 2018. MIT Library https://dspace.mit.edu/handle/1721.1/119603

[165] Polo, David, et al. "Making Waves: Wastewater-Based Epidemiology for COVID-19 – Approaches and Challenges for Surveillance and Prediction." *Water Research*, vol. 186, November 2020, p. 116404. doi:10.1016/j.watres.2020.116404 www.ncbi.nlm.nih.gov/pmc/articles/PMC7480445/pdf/main.pdf

[166] Duvallet C, Hayes BD, Erickson TB, Chai PR, Matus M. (2020) *Mapping Community Opioid Exposure Through Wastewater-Based Epidemiology as a Means to Engage Pharmacies in Harm Reduction Efforts.* Prevention of Chronic Diseases 2020; 17:200053. DOI: http://dx.doi.org/10.5888/pcd17.200053

[167] Leonard, Maureen, et al. (2020) "Multi-Omics Analysis Reveals the Influence of Genetic and Environmental Risk Factors on Developing Gut Microbiota in Infants at Risk of Celiac Disease." *Microbiome*, vol. 8, no. 1, December 2020, p. 130. doi:10.1186/s40168-020-00906-w

[168] Lee, J., Hyeon, D.Y. and Hwang, D. (2020) Single-cell multiomics: technologies and data analysis methods. *Exp Mol Med* (2020). https://doi.org/10.1038/s12276-020-0420-2 https://www.nature.com/articles/s12276-020-0420-2.pdf

[169] Foy BH, Carlson JCT, Reinertsen E, et al. Association of Red Blood Cell Distribution Width (RDW) With Mortality Risk in Hospitalized Adults With SARS-CoV-2 Infection. *JAMA Network Open* 2020; 3(9):e2022058. doi:10.1001/jamanetworkopen.2020.22058 https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2770945

[170] Mackuľak, Tomáš, et al. "Music Festivals and Drugs: Wastewater Analysis." *Science of The Total Environment*, vol. 659, April 2019, pp. 326–334. doi:10.1016/j.scitotenv.2018.12.275

[171] Castiglioni, S. and Vandam, L. (2016) *A global overview of wastewater-based epidemiology*. pp. 45–54 in "Assessing illicit drugs in wastewater: advances in wastewater-based drug epidemiology" EMCDDA Insights 22 (EU). https://www.emcdda.europa.eu/system/files/publications/2273/TDXD16022ENC_4.pdf

[172] EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) (2020) PERSPECTIVES ON DRUGS: Wastewater analysis and drugs: results from a European multi-city study. Publications Office of the EU. www.emcdda.europa.eu/system/files/publications/2757/POD_Wastewater%20analysis_update2020.pdf

[173] Gina Pocock, Leanne Coetzee, Janet Mans, Maureen Taylor and Bettina Genthe (2020) *PROOF OF CONCEPT STUDY: Application of wastewater-based surveillance to monitor SARS-CoV-2 prevalence in South African communities.* Report to the Water Research Commission WRC Report no. TT 832/20 ISBN 978-0-6392-0187-0 (September 2020) Water Research Commission, South Africa www.wrc.org.za http://wrcwebsite.azurewebsites.net/wp-content/uploads/mdocs/TT%20832-20%20final%20web.pdf

[174] Delaney SK, Hultner ML, Jacob HJ, Ledbetter DH, McCarthy JJ, Ball M, Beckman KB, Belmont JW, Bloss CS, Christman MF, Cosgrove A, Damiani SA, Danis T, Delledonne M, Dougherty MJ, Dudley JT, Faucett WA, Friedman JR, Haase DH, Hays TS, Heilsberg S, Huber J, Kaminsky L, Ledbetter N, Lee WH, Levin E, Libiger O, Linderman M, Love RL, Magnus DC, Martland A, McClure SL, Megill SE, Messier H, Nussbaum RL, Palaniappan L, Patay BA, Popovich BW, Quackenbush J, Savant MJ, Su MM, Terry SF, Tucker S, Wong WT, Green RC. (2016) *Toward clinical genomics in everyday medicine: perspectives and recommendations.* Expert Rev Mol Diagn. 2016; 16(5):521-532. doi: 10.1586/14737159.2016.1146593. Epub 2016 February 24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4841021/pdf/iero-16-521.pdf

[175] http://www.opengroup.org/iot/odf/

[176] Perron, Paul. "Relire Le Fou d'Elsa de Louis Aragon." *Études Littéraires*, vol. 28, no. 1, April 2005, pp. 69–82. doi:10.7202/501111ar.

[177] Stephens DS, McElrath MJ. COVID-19 and the Path to Immunity. *JAMA*. Published online September 11, 2020. doi:10.1001/jama.2020.16656

[178] Korber, B., et al. Spike Mutation Pipeline Reveals the Emergence of a More Transmissible Form of SARS-CoV-2. preprint, Evolutionary Biology, 30 April 2020. doi:10.1101/2020.04.29.069054 https://www.biorxiv.org/content/10.1101/2020.04.29.069054v2.full.pdf

[179] Jerald Sadoff, Mathieu Le Gars, Georgi Shukarev, Dirk Heerwegh, Carla Truyers, Anne Marit de Groot, Jeroen Stoop, Sarah Tete, Wim Van Damme, Isabel Leroux-Roels, Pieter-Jan Berghmans, Murray Kimmel, Pierre Van Damme, Jan de Hoon, Williams Smith, Kathryn E. Stephenson, Dan H. Barouch, Stephen C. De Rosa, Kristen W. Cohen, M. Juliana McElrath, Emmanuel Cormier, Gert Scheper, Jenny Hendriks, Frank Struyf, Macaya Douoguih, Johan Van Hoof, and Hanneke Schuitemaker (2020) *Safety and Immunogenicity of the Ad26.COV2.S COVID-19 Vaccine Candidate: Interim Results of a Phase 1/2a, Double-Blind, Randomized, Placebo-Controlled Trial.* preprint, Infectious Diseases (except HIV/AIDS), 25 September 2020. doi:10.1101/2020.09.23.20199604 https://www.medrxiv.org/content/10.1101/2020.09.23.20199604v1.full.pdf

[180] Denis Y Logunov, Inna V Dolzhikova, Olga V Zubkova, Amir Tukhvatullin, Dmitry V Shcheblyakov, Alina S Dzharullaeva, Daria M Grousova, Alina S Erokhova, Anna V Kovyrshina, Andrei G Botikov, Fatima M Izhaeva, Olga Popova, Tatiana A Ozharovskaya, Ilias B Esmagambetov, Irina A Favorskaya, Denis I Zrelkin, Daria V Voronina, Dmitry N Shcherbinin, Alexander S Semikhin, Yana V Simakova, Elizaveta A Tokarskaya, Nadezhda L Lubenets, Daria A Egorova, Maksim Shmarov, Natalia Nikitenko, Lola F Morozova, Elena A Smolyarchuk, Evgeny V Kryukov, Vladimir F Babira, Sergei V Borisevich, Boris S Naroditsky, Alexander L Gintsburg (2020) *Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia.* Lancet 2020; 396: 887–897. Published Online September 4, 2020. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931866-3

[181] Chadi M. Saad-Roy, Caroline E. Wagner, Rachel E. Baker, Sinead E. Morris, Jeremy Farrar, Andrea l. Graham, Simon A. Levin, Michael J. Mina, C. Jessica E. Metcalf, and Bryan T. Grenfell (2020) Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next 5 years. Published 21 Sep 2020 doi:10.1126/science.abd7343 https://science.sciencemag.org/content/early/2020/09/18/science.abd7343 https://science.sciencemag.org/content/early/2020/09/18/science.abd7343/tab-pdf

[182] Anne M Neilan, Elena Losina, Audrey C Bangs, Clare Flanagan, Christopher Panella, G Ege Eskibozkurt, Amir Mohareb, Emily P Hyle, Justine A Scott, Milton C Weinstein, Mark J Siedner, Krishna P Reddy, Guy Harling, Kenneth A Freedberg, Fatma M Shebl, Pooyan Kazemian, and Andrea L Ciaranello (2020) Clinical Impact, Costs, and Cost-Effectiveness of Expanded SARS-CoV-2 Testing in Massachusetts. *Clinical Infectious Diseases* https://doi.org/10.1093/cid/ciaa1418

[183] The Global HIV/AIDS Epidemic https://www.kff.org/global-health-policy/fact-sheet/the-global-hivaids-epidemic/#footnote-475993-1

[184] Corey L, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine R&D. *Science.* 2020 May 29; 368(6494):948-950. doi: 10.1126/science.abc5312. Epub 2020 May 11. https://science.sciencemag.org/content/368/6494/948/tab-pdf

[185] E.J. Anderson, N.G. Rouphael, A.T. Widge, L.A. Jackson, P.C. Roberts, M. Makhene, J.D. Chappell, M.R. Denison, L.J. Stevens, A.J. Pruijssers, A.B. McDermott, B. Flach, B.C. Lin, N.A. Doria-Rose, S. O'Dell, S.D. Schmidt, K.S. Corbett, P.A. Swanson II, M. Padilla, K.M. Neuzil, H. Bennett, B. Leav, M. Makowski, J. Albert, K. Cross, V.V. Edara, K. Floyd, M.S. Suthar, D.R. Martinez, R. Baric, W. Buchanan, C.J. Luke, V.K. Phadke, C.A. Rostad, J.E. Ledgerwood, B.S. Graham, and J.H. Beigel, for the mRNA-1273 Study Group*(2020) Safety and immunogenicity of SARS-CoV-2 mRNA1273 vaccine in older adults. Published 29 September 2020. New England Journal of Medicine DOI: 10.1056/NEJMoa2028436 https://www.nejm.org/doi/pdf/10.1056/NEJMoa2028436?articleTools=true

[186] Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA1273 vaccine in older adults. N Engl J Med. DOI: 10.1056/NEJMoa2028436 https://www.nejm.org/doi/suppl/10.1056/NEJMoa2028436/suppl_file/nejmoa2028436_protocol.pdf

[187] Our World in Data https://ourworldindata.org/grapher/daily-covid-cases-7-day?time=2020-03-31..latest

[188] Endalew AD, Faburay B, Wilson WC, Richt JA. *Schmallenberg Disease-A Newly Emerged Culicoides-borne Viral Disease of Ruminants.* Viruses. 2019 November 15; 11(11):1065. doi: 10.3390/v11111065 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6893508/pdf/viruses-11-01065.pdf

[189] Collins ÁB, Doherty ML, Barrett DJ, Mee JF. *Schmallenberg virus: a systematic international literature review (2011-2019) from an Irish perspective.* Irish Vet J. 2019 Oct 9; 72:9. doi: 10.1186/s13620-019-0147-3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6785879/pdf/13620_2019_Article_147.pdf

[190] Lechevalier H. Dmitri Iosifovich Ivanovski (1864-1920). *Bacteriol Rev.* 1972 June; 36(2):135-45. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC408320/pdf/bactrev00200-0002.pdf

[191] Lustig, Alice and Levine, Arnold J. (1992) One hundred years of virology. J Virol. 1992 August; 66(8):4629-4631. doi: 10.1128/JVI.66.8.4629-4631.1992. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC241285/pdf/jvirol00040-0015.pdf

[192] Fauci, Anthony (2020) MIT Biology course number 7.00 (COVID-19, SARS-CoV-2 and the Pandemic) https://biology.mit.edu/undergraduate/current-students/subject-offerings/covid-19-sars-cov-2-and-the-pandemic/ and https://biology.mit.edu/wp-content/uploads/2020/09/7.00_Syllabus_9.8.20.pdf

[193] Baltimore, David (2020) MIT Biology course number 7.00 (COVID-19, SARS-CoV-2 and the Pandemic) https://biology.mit.edu/undergraduate/current-students/subject-offerings/covid-19-sars-cov-2-and-the-pandemic/ and https://biology.mit.edu/wp-content/uploads/2020/09/7.00_Syllabus_9.8.20.pdf

[194] Baltimore, David. https://www.nobelprize.org/prizes/medicine/1975/baltimore/facts/

[195] Tufekci, Zeynep. "This Overlooked Variable Is the Key to the Pandemic." *The Atlantic*, 30 Sept. 2020. https://www.theatlantic.com/health/archive/2020/09/k-overlooked-variable-driving-pandemic/616548/

[196] Kai Kupferschmidt (2020) Why do some COVID-19 patients infect many others, whereas most don't spread the virus at all? *Science.* May 19, 2020. doi:10.1126/science.abc8931

[197] Thurner, Stefan, et al. *Why Are Most COVID-19 Infection Curves Linear?* preprint, Epidemiology, 24 May 2020. doi:10.1101/2020.05.22.20110403. https://www.medrxiv.org/content/10.1101/2020.05.22.20110403v1.full.pdf

[198] Vilfredo Pareto, Cours d'conomie Politique Profess a l'Universit de Lausanne, Vol. I, 1896; Vol. II, 1897. https://pdfs.semanticscholar.org/ef82/dfe7b0ef7a88727636f5ad680a464e33e345.pdf

[199] Noah G. Schwartz, Anne C. Moorman, Anna Makaretz, Karen T. Chang, Victoria T. Chu, Christine M. Szablewski, Anna R. Yousaf, Marie M. Brown, Ailis Clyne, Amanda DellaGrotta, Jan Drobeniuc, Jacqueline Korpics, Adam Muir, Cherie Drenzek, Utpala Bandy, Hannah L. Kirking, Jacqueline E. Tate, Aron J. Hall, Tatiana M. Lanzieri and Rebekah J. Stewart (2020) *Adolescent with COVID-19 as the Source of an Outbreak at a 3-Week Family Gathering — Four States, June–July 2020.* CDC MMWR vol. 69, October 5, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6940e2-H.pdf

[200] Peccia, J., Zulli, A., Brackney, D.E. *et al.* Measurement of SARS-CoV-2 RNA in wastewater tracks community infection dynamics. *Nat Biotechnol* **38,** 1164–1167 (2020). https://doi.org/10.1038/s41587-020-0684-z and https://www.nature.com/articles/s41587-020-0684-z.pdf

[201] *MIT begins testing wastewater to help detect Covid-19 on campus.* https://news.mit.edu/2020/testing-wastewater-covid-19-1002

[202] Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, Watkins PC, Ottina K, Wallace MR, Sakaguchi AY, et al. (1983) A polymorphic DNA marker genetically linked to Huntington's disease. *Nature.* 1983 Nov 17-23; 306(5940): 234-8. doi: 10.1038/306234a0 https://www.nature.com/articles/306234a0

[203] Mazini PS, Alves HV, Reis PG, Lopes AP, Sell AM, Santos-Rosa M, Visentainer JE, Rodrigues-Santos P. (2016) Gene Association with Leprosy: A Review of Published Data. Front Immunol. 2016 January 12; 6:658. doi: 10.3389/fimmu.2015.00658 www.ncbi.nlm.nih.gov/pmc/articles/PMC4709443/pdf/fimmu-06-00658.pdf

[204] Dallmann-Sauer M, Fava VM, Gzara C, Orlova M, Van Thuc N, Thai VH, et al. (2020) The complex pattern of genetic associations of leprosy with HLA class I and class II alleles can be reduced to four amino acid positions. PLoS Pathog 16(8): e1008818. https://doi.org/10.1371/journal. ppat.1008818 https://journals.plos.org/plospathogens/article/file?id=10.1371/journal.ppat.1008818&type=printable

[205] Zeberg, H. and Pääbo, S. (2020) The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. *Nature* (30 September 2020). https://doi.org/10.1038/s41586-020-2818-3 https://www.nature.com/articles/s41586-020-2818-3_reference.pdf

[206] Kenney AD, Dowdle JA, Bozzacco L, McMichael TM, St Gelais C, Panfil AR, Sun Y, Schlesinger LS, Anderson MZ, Green PL, López CB, Rosenberg BR, Wu L, Yount JS. *Human Genetic Determinants of Viral Diseases.* Annu Rev Genet. 2017 Nov 27; 51:241-263. doi: 10.1146/annurev-genet-120116-023425 Epub 2017 Aug 30. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6038703/pdf/nihms-978947.pdf

[207] Rubin R. *Investigating Whether Blood Type Is Linked to COVID-19 Risk.* JAMA. 2020 September 16. doi: 10.1001/jama.2020.16516. https://jamanetwork.com/journals/jama/fullarticle/2770889

[208] Kaiser, Jocelyn. "How Sick Will the Coronavirus Make You? The Answer May Be in Your Genes." *Science*, March 27, 2020. doi:10.1126/science.abb9192

[209] Liu, Y.-M., Xie, J., Chen, M.-M., Zhang, X., Cheng, X., Li, H., Zhou, F., Qin, J.- J., Lei, F., Chen, Z., Lin, L., Yang, C., Mao, W., Chen, G., Lu, H., Xia, X., Wang, D., Liao, X., Yang, J., Huang, X., Zhang, B.-H., Yuan, Y., Cai, J., Zhang, X.-J., Wang, Y., Zhang, X., She, Z.-G., Li, H., *Kidney function indicators predict adverse outcomes of COVID-19*. Med (2020). https://www.cell.com/med/pdf/S2666-6340(20)30017-9.pdf

[210] Janardhan, Vallabh, et al. "COVID-19 as a Blood Clotting Disorder Masquerading as a Respiratory Illness: A Cerebrovascular Perspective and Therapeutic Implications for Stroke Thrombectomy." *J of Neuroimaging*, vol. 30, no. 5, September 2020, pp. 555–561. https://onlinelibrary.wiley.com/doi/epdf/10.1111/jon.12770

[211] Wilson, M (2020). 5-Cent Sensor Could Detect the Coronavirus in 10 Minutes at Home. *Fast Company*. www.fastcompany.com/90559744/a-5-cent-sensor-could-detect-the-coronavirus-in-10-minutes-at-home

[212] Sanjay E. Sarma, Stephen A. Weis, Daniel W. Engels (2002) *RFID Systems, Security and Privacy Implications.* White Paper. MIT Auto ID Center. Published November 1, 2002. https://cocoa.ethz.ch/downloads/2014/06/None_MIT-AUTOID-WH-014.pdf

[213] Mark Roberti (2004) *The 5-cent Challenge.* RFID Journal. Published August 30, 2004. https://www.rfidjournal.com/the-5-cent-challenge

[214] Parinaz Fozouni, Sungmin Son, María Díaz de León Derby, Gavin J. Knott, Carley N. Gray, Michael V. D'Ambrosio, Chunyu Zhao, Neil A. Switz, G. Renuka Kumar, Stephanie I. Stephens, Daniela Boehm, Chia-Lin Tsou, Jeffrey Shu, Abdul Bhuiya, Max Armstrong, Andrew Harris, Jeannette M. Osterloh, Anke Meyer-Franke, Charles Langelier, Katherine S. Pollard, Emily D. Crawford, Andreas S. Puschnik, Maira Phelps, Amy Kistler, Joseph L. DeRisi, Jennifer A. Doudna, Daniel A. Fletcher and Melanie Ott (2020) *Direct detection of SARS-CoV-2 using CRISPR-Cas13a and a mobile phone.* Published 30 Sep 2020 https://doi.org/10.1101/2020.09.28.20201947 https://www.medrxiv.org/content/10.1101/2020.09.28.20201947v1.full.pdf

[215] Rockefeller Foundation. *National Covid-19 testing and tracing action plan.* July 16, 2020. https://www-rockefellerfoundation-org.libproxy.mit.edu/wp-content/uploads/2020/07/TheRockefellerFoundation_ExecutiveSummary_7_20.pdf

[216] "The Nobel Prize in Chemistry 2020." https://www.nobelprize.org/uploads/2020/10/press-chemistryprize2020.pdf & https://www.nobelprize.org/prizes/chemistry/2020/press-release/ (10-7-2020)

[217] Service, R. New Test Detects Coronavirus in 5 Minutes. *Science*, 10-8-20. doi:10.1126/science.abf1752 https://www.sciencemag.org/news/2020/10/new-test-detects-coronavirus-just-5-minutes

[218] Service, Robert. In 'Milestone,' FDA OKs Simple, Accurate Coronavirus Test That Could Cost $5. *Science*, August 27-28, 2020. doi:10.1126/science.abe5319

[219] The Nobel Prize in Physiology or Medicine 2020. October 5, 2020. https://www.nobelprize.org/prizes/medicine/2020/press-release/

[220] Schweitzer, Albert (1922) *The Decay and the Restoration of Civilization* (Translated by C. T. Campion. Published by A. C. Black, London, 1923) https://ia800904.us.archive.org/9/items/p1decayrestorati00schwuoft/p1decayrestorati00schwuoft.pdf

[221] David M Cutler and Larry H Summers. *COVID-19 Pandemic and the $16 Trillion Virus. JAMA.* Published October 12, 2020. doi:10.1001/jama.2020.19759 https://jamanetwork.com/journals/jama/fullarticle/2771764

[222] "The World's $80 Trillion Economy - in One Chart." *World Economic Forum*, https://www.weforum.org/agenda/2018/10/the-80-trillion-world-economy-in-one-chart/

[223] https://www.worldometers.info/gdp/gdp-by-country

[224] Lulla, Valeria, et al. *Antisense Oligonucleotides Target a Nearly Invariant Structural Element from the SARS-CoV-2 Genome and Drive RNA Degradation*. preprint, Molecular Biology, 19 September 2020. doi:10.1101/2020.09.18.304139 https://www.biorxiv.org/content/10.1101/2020.09.18.304139v1.full.pdf

[225] David Chiriboga, Juan Garay, Paulo Buss, Rocío Sáenz Madrigal, Laetitia Charmaine Rispel (2020) "Health Inequity during the COVID-19 Pandemic: A Cry for Ethical Global Leadership." *The Lancet*, vol. 395, no. 10238, May 2020, pp. 1690–1691. doi:10.1016/S0140-6736(20)31145-4 https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931145-4

[226] Lorenzo Casalino, Zied Gaieb, Jory A. Goldsmith, Christy K. Hjorth, Abigail C. Dommer, Aoife M. Harbison, Carl A. Fogarty, Emilia P. Barros, Bryn C. Taylor, Jason S. McLellan, Elisa Fadda, and Rommie E. Amaro (2020) "Beyond Shielding: The Roles of Glycans in the SARS-CoV-2 Spike Protein." *ACS Central Science*, September 2020, p. acscentsci.0c01056. doi:10.1021/acscentsci.0c01056. https://pubs.acs.org/doi/pdf/10.1021/acscentsci.0c01056

[227] Shaman, J. and Galanti, Marta (2020) Will SARS-CoV-2 become endemic? *Science* 14 Oct 2020. DOI: 10.1126/science.abe5960 https://science.sciencemag.org/content/early/2020/10/13/science.abe5960/tab-pdf

[228] Datta, Shoumen. APPENDIX Figure 1: Description of Major Software Components https://github.com/shoumendatta/ADD-DIGITAL and James Lamb https://github.com/jameslamb

[229] Message Queueing using an open lightweight broker, such as, Message Queueing Telemetry Transport, MQTT (https://mqtt.org/) or RabbitMQ (https://www.rabbitmq.com/) or heavy-duty Apache Kafka (https://kafka.apache.org/). Self-managed or run behind a managed IoT service from cloud providers: AWS IoT Core (https://aws.amazon.com/iot-core/) or Azure IoT Hub (https://azure.microsoft.com/en-us/services/iot-hub/) or related services provided by other vendors (https://www.zdnet.com/article/the-top-cloud-providers-of-2020-aws-microsoft-azure-google-cloud-hybrid-saas/).

[230] Operational Data Store choices include InfluxDB (https://www.influxdata.com/), Apache Cassandra (https://cassandra.apache.org/) or Prometheus (https://prometheus.io/). Managed cloud database from Amazon https://docs.aws.amazon.com/amazondynamodb/latest/developerguide/Introduction.html.

[231] Amazon S3 Glacier https://aws.amazon.com/glacier/

[232] Enterprise Resource Planning (ERP) – Master Data Management: Architecture and Technology https://www.element61.be/en/resource/master-data-management-mdm-architecture-technology

[233] Vesna Vučković (2008) *Image and its Matrix, Matrix and its Image.* Преглед НЦД 12 (2008) 17–31 http://elib.mi.sanu.ac.rs/files/journals/ncd/12/ncd12017.pdf

[234] H3: Uber's Hexagonal Hierarchical Spatial Index https://eng.uber.com/h3/

[235] Liu J, Ranka S, Kahveci T. *Classification and feature selection algorithms for multi-class CGH data.* Bioinformatics. 2008 July 1; 24(13):i86-95. doi: 10.1093/bioinformatics/btn145 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2718623/pdf/btn145.pdf

[236] Bommert, Andrea, et al. "Benchmark for Filter Methods for Feature Selection in High-Dimensional Classification Data." *Computational Statistics & Data Analysis*, vol. 143, Mar. 2020, p. 106839. *DOI.org (Crossref)*, doi:10.1016/j.csda.2019.106839.

[237] Chen, R., Dewi, C., Huang, S. *et al.* Selecting critical features for data classification based on machine learning methods. *Journal of Big Data* **7,** 52 (2020). https://doi.org/10.1186/s40537-020-00327-4 https://journalofbigdata.springeropen.com/track/pdf/10.1186/s40537-020-00327-4

[238] Object stores: Amazon https://aws.amazon.com/s3/; Google Cloud https://cloud.google.com/storage; Microsoft Azure Blob https://azure.microsoft.com/en-us/services/storage/blobs/); Apache Cassandra https://medium.com/walmartglobaltech/building-object-store-storing-images-in-cassandra-walmart-scale-a6b9c02af593

[239]Query-Over-Files Engines: Presto (https://prestodb.io/), Apache Drill (https://drill.apache.org/) or Apache Spark SparkSQL (https://spark.apache.org/sql/). If using application-specific custom code that directly reads files, orchestrated with batch-scheduling engine: Apache Airflow (https://airflow.apache.org/) or Prefect (https://www.prefect.io/)

[240] Lechner, M., Hasani, R., Amini, A. *et al.* Neural circuit policies enabling auditable autonomy. *Nature Machine Intelligence* **2,** 642–652 (13 October 2020). https://doi.org/10.1038/s42256-020-00237-3

[241] Analytical Data Store: Traditional relational database PostgreSQL (https://www.postgresql.org/) or hosted relational database products provided by cloud providers (https://aws.amazon.com/rds/). If intelligent caching of repeated queries is needed, data warehouse technologies (managed cloud service) include: Snowflake (https://www.snowflake.com/), Amazon Redshift (https://aws.amazon.com/redshift) or Google BigQuery (https://cloud.google.com/bigquery). If cloud is inaccessible, for on-premises option: Teradata (https://www.teradata.com/).

[242] Machine Learning (ML) model training tools: Apache Spark (https://spark.apache.org/), Dask (https://dask.org/) or Ray (https://rise.cs.berkeley.edu/projects/ray/). If application specificity does not require high degree of customization - use "autoML" tools - DataRobot (https://www.datarobot.com/), h2o (https://docs.h2o.ai/h2o/latest-stable/h2o-docs/automl.html), Amazon SageMaker Autopilot (https://aws.amazon.com/blogs/aws/amazon-sagemaker-autopilot-fully-managed-automatic-machine-learning/) or Google Cloud AutoML (https://cloud.google.com/automl).

[243] Tauro, C.J., Ganesan, N., Mishra, S.R., & Bhagwat, A. (2012). Object Serialization: A Study of Techniques of Implementing Binary Serialization in C++, Java and .NET. *International Journal of Computer Applications, 45*, 25-29. https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.685.1077&rep=rep1&type=pdf

[244] Common Object Request Broker Architecture (CORBA) https://www.corba.org/

[245] Container: Docker https://www.docker.com/resources/what-container

[246] Developer's language of choice may include (but the "menu" is certainly not limited to): Java jar (https://en.wikipedia.org/wiki/JAR_(file_format)), Python pickle file (https://docs.python.org/3/library/pickle.html), R rds file (https://stat.ethz.ch/R-manual/R-devel/library/base/html/readRDS.html) or a precompiled executable which can read in input data from "stdin" (standard input is a stream from which a program reads its input data) or from a file, created with C/C++ or language-agnostic description of a model: Predictive Model Markup Language (https://en.wikipedia.org/wiki/Predictive_Model_Markup_Language) or Portable Format for Analytics (http://dmg.org/pfa/)

ACKNOWLEDGEMENTS

The author is thankful to Brittany Newell (section 2), Larry Gold (section 5), Andrew Fire and Greg Winter (for section 6) as well as Britt Glaunsinger and Sanjay Sarma (for general review).