Aptamers for Detection and Diagnostics (ADD) is a proposed mobile app acquiring optical data from conjugated quantum nanodots to identify molecules indicating presence of SARS-CoV-2 virus: Why public health and healthcare need smartphone sensors as a platform for early detection and prevention

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DRAFT

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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 dissemination¹ to benefit public health² by integrating the principle³ of internet of things⁴ (IoT⁵ as a design metaphor).

	Emergence	Cases	Fatality Rate	Transmissibility
SARS	2003	8,098	11%	+
MERS	2011	2,519	34%	+
SARS-CoV-2	2019	> 50 million	0.5-1% Est	+++
SARS-CoV-3?	??	??	??	??
SARS-CoV-4?	??	??	??	??

Table 1: Is the eight⁶ year interval between SARS, MERS and COVID-19 just an unrelated coincidence?

2. Aptamers for Detection and Diagnostics (ADD)

Single stranded (ss) DNA aptamers (ssRNA⁷ are equally useful⁸ but susceptible to degradation by ribonuclease) bind with **specificity** to SARS-CoV-2⁹ 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 (ENGases¹⁰) 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 (Kalman¹¹ 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 privacy¹².

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 (PAPPU¹³) 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 science¹⁴ 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 illustrated¹⁵ 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 idea¹⁶ of an "anti-sense" approach¹⁷) 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 “digital¹⁸ by design” metaphor. Cartoon shows the potential path of raw data from the hypothetical binding between a sensor and a target¹⁹ 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 tests²⁰ (separate from false positives / false negatives in machine learning²¹ 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 latency²² 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 internet²³.

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-type²⁴ 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 training²⁵ 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 PCR²⁶ 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 prone²⁷. 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 model²⁸ training. It is absolutely central that model scoring requires **“features”** (characteristics germane to model/analysis). Creating features²⁹ 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 automated³⁰ feature³¹ selection/extraction³² 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 (DDS³³) tools to aggregate or explore cumulative analytics, integrated with other systems, for example, geographic information systems³⁴ 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 wellness³⁵. GSPs may try not to dwell on genomics³⁶ (DNA) and expression³⁷ (RNA³⁸) in imprecision³⁹ medicine but include proteomics because gene expression is insufficient unless the **functions** are **implemented** by proteins. Aptamers⁴⁰ in proteomic profiling (GWAS⁴¹, metabolomics) and other applications⁴² including ADD may benefit from synergistic integration to help predict status of health (collected papers⁴³ 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 bind⁴⁴ in a myriad of ways⁴⁵ 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 spec⁴⁶ tools only capture *snapshots*. Can proteomics make sense⁴⁷ of a cytokine storm as markers of counter-anti-inflammatory response⁴⁸ even before the infectious agent is detected? Perhaps it is utopian to expect proteomic profiling as a daily practice in healthcare and home-health.

<https://dspace.mit.edu/handle/1721.1/56251>

Weigh-scale, BMI, FOBT, urine analysis, sugar, ketone body analysis, blood pressure monitor, pulse oximeter, networked to phone via WiFi and/or Bluetooth with biometrics and face recognition for secure communication with physician and hospital or clinic, globally.

5. Prevention follows Detection and Diagnostics

If viewed⁵⁰ as non-classical antibodies⁵¹ 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 kinetics⁵²) 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. Asymptomatic⁵³, pauci-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-2⁵⁴ 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 essential⁵⁵ 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 tRNA⁵⁶ 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 Brenner⁵⁷ and Gros⁵⁸ as well as the *lac operon* model of feedback inhibition by Jacob and Monod⁵⁹, all three published in 1961. The role of proteins in regulation⁶⁰ emerged as central to physiology and metabolism. In transcription, translation and replication⁶¹ the binding between proteins and nucleic acids acted as a “switch” (mechanism of action). The notion⁶² of aptamers⁶³ germinated⁶⁴ in 1990 but it drew on knowledge from binding between oligonucleotides and proteins. Aptamers may be 20-60⁶⁵ oligonucleotides or more. Binding specificity⁶⁶ of an enriched pool may be orders of magnitude different (K_d) between a nearest neighbor or an analog. Sequential steps⁶⁷ 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 evolved⁶⁸ in complexity⁶⁹ and unique structures may be involved⁷⁰ in conferring specificity. In many applications⁷¹ of aptamers⁷² the debate also involves issues pertaining to trust and doubts⁷³ due to the constant demand for increasing accuracy and precision with respect to sensitivity, selectivity and specificity, in detection and diagnostics.

Current and future⁷⁴ application⁷⁵ of aptamers include chemistry⁷⁶, chemotherapy⁷⁷, food⁷⁸ safety, diagnostics⁷⁹, antibodies⁸⁰, alt-vaccines⁸¹, imaging⁸² and different⁸³ types⁸⁴ of biosensors⁸⁵. 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 tools⁸⁶ 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 RNA⁸⁷ aptamer in a nanoarray. Tests using saliva⁸⁸ may be unsuitable for RNA⁸⁹ aptamers due to presence of ribonuclease⁹⁰ (RNase). DNA aptamers previously shown to bind to the N protein of SARS-CoV (K_d 4.93±0.3nM⁹¹) also⁹² binds to the N protein of SARS-CoV-2. The N protein⁹³ of SARS-CoV-2 shares 91% sequence homology with the N protein⁹⁴ of SARS-CoV but is less similar (16% - 38%) with N protein from the other 5 known human coronaviruses. Thus, detection⁹⁵ of N protein in saliva using an aptamer-based ADD aptasensor is *possible*. Aptamer-based technologies⁹⁶ directed toward SARS-CoV-2 Spike protein are gaining⁹⁷ momentum⁹⁸. Blocking⁹⁹ the S protein from attaching to hACE-2 may perturb viral entry and prevent¹⁰⁰ the spread of infection. Aptamers created against the S1 RBD¹⁰¹ may block binding to hACE-2 (internally) or serve as a detection tool (external ADD aptasensor) to test saliva/sputum for SARS-CoV-2. Other¹⁰² SARS-CoV-2 targets¹⁰³ including Nsp1¹⁰⁴ 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 spectroscopy¹⁰⁵) signals, optical signals are preferred because data acquisition using cameras and apps in smartphones are feasible in locations where resources may be limiting. Protein¹⁰⁶ detection¹⁰⁷ by conjugating aptamers with quantum dots¹⁰⁸ is a tried¹⁰⁹ and true¹¹⁰ process¹¹¹ 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 HoloLens¹¹² app in smartphones may scan the saliva sample (think barcode or QR¹¹³ code scan). Cameras (sensors) associated with the holo-lens (Kinect¹¹⁴) can scan the “field” and collects data to create a digital geometry¹¹⁵ (digital model, 3D image). For ADD, HoloLens tools required for holographic functions¹¹⁶ 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: **Multiplexed¹¹⁷ 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/adsorbed 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 (tinyDB¹¹⁸) 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 SNAPS¹¹⁹ 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 protein¹²⁰) 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” toy¹²¹. These segments of the Spike protein are *better conserved* and occupy a distinctly different part of the Spike protein (Figure 5).

Figure 5: Sequence conservation¹²² 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 epitopes¹²³ 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.

Interfering¹²⁴ 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 American¹²⁵).

Figure 6: Cascade of events¹²⁶ 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 surface¹²⁷ 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 brushings¹²⁸.

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-viral¹²⁹ strategies. Virus-encoded proteases¹³⁰ are distinct¹³¹ from cellular proteases and may serve as good¹³² targets. The viral protease¹³³ 3-chymotrypsin-like protease¹³⁴ or 3CLpro¹³⁵ aka M^{Pro} is encoded by Nsp5 and appears¹³⁶ 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 protease¹³⁷ PLpro (ORF 1a, Nsp3¹³⁸), cleaves¹³⁹ proteinaceous post-translational (ref 131) modifications on host proteins to evade host anti-viral immune responses. Nsp1¹⁴⁰ suppresses host translation by cleaving cell mRNAs¹⁴¹ and competes¹⁴² with mRNAs for binding to human 40S ribosomal mRNA channel¹⁴³ (as well as 43S, 80S subunits). Type 1¹⁴⁴ interferon¹⁴⁵ (IFN-1) response¹⁴⁶ 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 molecules¹⁴⁷ involved in catalyzing the IFN-1 response.

Figure 7: (Top) SARS-CoV-2 genome¹⁴⁸ 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 -fold¹⁴⁹ 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 errors¹⁵⁰ 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 humans¹⁵¹ 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 (LVPRGSGGSGGSGGLEVLFFQGP). 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, prevent¹⁵⁵ membrane fusion and block viral entry¹⁵⁶ with the same aptamer or another type of molecule based¹⁵⁷ 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 DeMEA¹⁵⁸ (but it uses high cost microfluidics¹⁵⁹).

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 technology¹⁶⁰ to facilitate diffusion and adoption. Bringing data and information together to make sense and extract foresight (uncertain of the value of hindsight¹⁶¹) will be a challenge which new initiatives¹⁶² 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 crisis¹⁶³ at hand, we must also utilize this disaster as an opportunity to deploy profiling as a healthcare staple. Other tools, for example, wastewater¹⁶⁴ analysis¹⁶⁵ may offer transparency¹⁶⁶ 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 microbiomes¹⁶⁷. Isolated snapshots of data may be rate-limiting for communities under economic constraints. But, convergence of data from ADD along with multiple levels of profiling¹⁶⁸ (DNA, RNA, protein, RDW¹⁶⁹) as well as environmental¹⁷⁰ and wastewater¹⁷¹ data¹⁷², if included¹⁷³, may augment the value of information, which could be catalytic for medicine¹⁷⁴, in general, if aggregated and shared between open¹⁷⁵ 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 future¹⁷⁶.

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 (top¹⁷⁷). Low variation (Fig 10) in SARS-CoV-2 Spike protein is good news but mutations, D614G (middle panel and bottom) may still complicate¹⁷⁸ the immune response and expected anamnestic response to reinfection or use of classical¹⁷⁹ approaches¹⁸⁰ to vaccination.

If immunity from traditional vaccines are uncertain¹⁸¹, can we supplement with *alt-vaccines* (which are non-immunogenic, for example, aptamers), to better prepare for low-cost and rapid¹⁸² response to public health during future epidemics / pandemics?

9. Complexity of the biomedical scenario, socio-economic catastrophe and the public health crisis

Since 1980's the HIV epidemic has infected ~76 million people¹⁸³ (~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 collaboration¹⁸⁴ 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 Development¹⁸⁴ (mRNA-1273 vaccine¹⁸⁵) 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 (stabilized¹⁸⁶ with two Proline¹⁸⁷ substitutions at the top of the central helix in S2 subunit). mRNA is encapsulated in lipid nanoparticles (0.5 mg per mL) and diluted with normal saline to achieve the final target vaccine concentrations¹⁸⁸.

Figure 14: 7-day rolling average of new COVID-19 cases¹⁸⁹ 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 diseases¹⁹⁰ due to relatively unknown viruses¹⁹¹, 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 1890-1892¹⁹² but after more than 100 years¹⁹³ 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)¹⁹⁴

Figure 16: Coronavirus pandemic wasn't really expected¹⁹⁵ according to at least one global expert¹⁹⁶. The coronavirus has the largest RNA genome. Is it just a coincidence or is there any bio-medical correlation?

While we still remain clueless about what constitutes virulence, the genome size does not offer any solace or solution. New evidence about Neuropilin-1 as a host factor¹⁹⁷ which facilitates cell entry¹⁹⁸ further thickens the plot. The deep quagmire¹⁹⁹ about R_0 and k ²⁰⁰ for COVID-19 defies epidemiological models²⁰¹ but prefers apocryphal Pareto²⁰² principles which suggests that 80% of new infections may be caused by only 20% (or less - 10% - see Figure 17 and reference 216) of the infected individuals. Are these individuals a high risk group due to inborn errors of immunity caused by mutations of genes involved in regulation of type I and type III interferons²⁰³ (IFN)? How many more genetic factors may underlie the differentiation between super-spreaders²⁰⁴ vs sub-spreaders for SARS-CoV-2? If the latter is true then how valuable is *generalizing* infection dynamics²⁰⁵ from communities as a prediction tool for *overall* public health, advance planning and use as early warning²⁰⁶ for cautionary preparation?

In future, genomic analysis may enlighten us if there are polymorphisms²⁰⁷ 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*. Genes²⁰⁸ 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-DR β 1 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-DR β 1 and HLA-A] and one being protective²⁰⁹.

The demographics of infection by SARS-CoV-2 may be due to genetic²¹⁰ determinants²¹¹ and individual outcomes²¹² may be determined by our genes²¹³ as well as epigenetic factors which may be mapped to biomarkers²¹⁴. 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 disorder²¹⁵? Cardiovascular disease? Autoimmune disease? Opportunistic “killer” for (~10%) patients with severe COVID-19 pneumonia and high titers of autoantibodies²¹⁶ against different types (type I IFN- α 2 and IFN- ω) of interferons?

Figure 18: Hypothetical²¹⁷ 5²¹⁸ cent²¹⁹ *déjà vu* graphene sensor (RIGHT) detects SARS-CoV-2 antigens. Can smartphone detection²²⁰ adapt²²¹ to other²²² sensors²²³ (LEFT) to detect²²⁴ SARS-CoV-2 in exhaled²²⁵ breath²²⁶ by mouth? Smartphone²²⁷ *breathalyzer* for malaria²²⁸ and marijuana (tetrahydrocannabinol)²²⁹ is close at hand. Can it serve²³⁰ as a global surveillance tool to bridge the chasm of inequity?

Figure 19: Detection of one copy RNA per μL (microL) from SARS-CoV-2²³¹ 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 billion²³².

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. CRISPR²³³-based tests may be promising²³⁴ in the future (see Figure 19). BinaxNOW \$5 test²³⁵ is at hand but may not be feasible for daily use in communities under economic constraints. The case of Hepatitis-C²³⁶ 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 civilization²³⁷ 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 trillion²³⁸. The US economy is about a quarter of the global economy²³⁹, hence, extrapolation suggests that losses due to this pandemic may be an estimated \$64 trillion, globally (about 80% of the global GDP²⁴⁰).

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 oligonucleotides²⁴¹) to partially bridge the chasm of inequity²⁴² 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 a few years. The quintessential ingredients for public health and global rejuvenation are scientific credibility, color-blind magnanimity and ethical leadership.

Figure 20: Similar to HIV, SARS-CoV-2 Spike protein uses a N-glycan shield²⁴³ to thwart the host immune response (coating of N-glycans in cobalt blue, right). Mutations²⁴⁴, inborn errors of the immune system and other factors may make SARS-CoV-2 endemic²⁴⁵. Thus, it behooves us to explore other risk mitigation strategies. Anti-sense oligonucleotides, mini protein inhibitors²⁴⁶ and aptamers (this proposal) are alternatives.

10. Post-Pandemic Public Health and Healthcare: Broad Spectrum use of Sensors with Smartphones

Transaction cost²⁴⁷ of *humans-in-the-loop* detection or surveillance²⁴⁸ is often astronomical²⁴⁹ and the burden of cost²⁵⁰ for public health and healthcare systems is prohibitive even for affluent nations. For resource constrained communities, the mortality and morbidity due to lack of access to primary care must be reduced. Can we effectively combine the ecosystem of sensors, smartphones and data informed decision analytics to deliver usable information at the point of care or point of need, in near real-time?

In general, part of the solution may be found in remote sensing and imaging tools (oil and gas pipelines²⁵¹, leaves²⁵², tree²⁵³ canopy^{254,255}, radiation²⁵⁶). SEE or “sense everything everywhere” (paint-based computation²⁵⁷, sensors in fabrics²⁵⁸) was a ‘touchy-feely’ mantra at the turn of the millenium buoyed by the principle of ubiquitous²⁵⁹ computing²⁶⁰ but stumbled in practice due to the cost²⁶¹ of computation²⁶². Vinton Cerf’s “I P on Everything”²⁶³ (I *pee* on everything) was the witty clarion call for embedding the IPv6²⁶⁴ standard²⁶⁵ in all things²⁶⁶ to enable “bit dribbling” between “digital” objects. These ideas were preceded by “tangible bits”²⁶⁷ from Hiroshi Ishi²⁶⁸ and the “atoms to bits” paradigm²⁶⁹ of “*Internet 0*” from Raffi Krikorian²⁷⁰ and Neil Gershenfeld²⁷¹ followed by the origins²⁷² of internet of things²⁷³ by Sanjay Sarma^{274, 275} and others²⁷⁶. The borborygmi of radio frequency identification (RFID) and standardization of the electronic product code (EPC²⁷⁷) shifted the thinking from stationary goods and products with static bar codes to dynamic digital objects which can be uniquely identified in any process or supply chain and tracked and traced digitally between any number of transactions, globally.

Project Oxygen²⁷⁸ offered extraordinary insight into the art of the possible²⁷⁹ and represented a consilience and confluence²⁸⁰ of ideas but it was cost-prohibitive for real world applications, circa 2000. With decreasing cost of computation²⁸¹, memory²⁸², data storage²⁸³ and transmission²⁸⁴, these streams, which were occasionally bubbling since Isaac Asimov’s²⁸⁵ *Sally*²⁸⁶ in 1953, turned into a raging river bursting its banks. The convergence of these tools with initial thoughts about the networked physical world²⁸⁷ were far more than the sum of the parts. It exploded to become the inescapable tsunami of IoT²⁸⁸ which has infected every domain. The anastomosis²⁸⁹ of IoT with cyberphysical systems²⁹⁰ (CPS²⁹¹) has penetrated almost every field from asteroids to zeolites and engulfed them within the new²⁹² laissez-faire world of DIKW²⁹³ hierarchy. The mobile smartphone represents the grand conduit for the aggregated dissemination of distributed facets emanating from the DIKW pyramid. The mobile platform appears to be the global choice to access and implement all and any service which is possible, via the smartphone, in some form or the other, where the ubiquitous device serves as the platform for information²⁹⁴ arbitrage.

ADD is a recognition element and a tiny part of this landscape. ADD enables the sensor, data is captured, analyzed, communicated and visualized on a smartphone. It may detect infectious molecules relevant to SARS-CoV-2 in saliva and nasal swabs for early detection to prevent the spread of the virus. This principle is applicable to *any* infectious agent as well as any physiological molecule of interest (see Figure 21). The potential of developing a “breathalyzer” (identifying molecules in breath, see Figure 18) may make it easier to detect any molecule or molecules which are either volatile or lighter than air.

Based on the idea of swappable, modular, flash drives, sensors-on-a-chip in the form factor of flashdrives are not hypothetical but frontrunners as potential tools for dealing with infectious²⁹⁵ diseases. Cameras, accelerometers (speed, movement), gyroscopes (tilt, orientation), magnetometers (compass), lidars (range, depth sensing from reflected laser signal), GPS and other “sensing” tools are increasingly “standard” with smartphones. These “detectors” makes it possible to use multiple mediums and phases for detection of signals from molecules, changes in dipole moments (electro-magnetic field) and perhaps even perturbation *ambient* electromagnetic waves (transmission and capture of reflected radio waves).

Figure 21: Billions of users in underserved geographies may access limited health services by using²⁹⁶ ubiquitous tools that does not require installation of new infrastructure and re-uses “mobile lifestyle” devices to partially bridge the scarcity of resources. Smartphones may be catalytic for delivery of service, remote monitoring²⁹⁷ and health surveillance, not restricted to infectious diseases but as physiological probes for health and homeostasis or detecting onset of disequilibrium (BNP, Brain Natriuretic Peptide).

Using information arbitrage to better contain the pandemic is the thrust of ADD. Expanding this principle as a routine for public health and healthcare, in general, is not a leap of imagination but natural progression. It bears reiteration that data informed decision analytics (DIDAS) must embrace sensor data plus smartphone (SDS) applications not as “pilot” projects but science in the service of society to catalyze the **SENSIBLE** system (**SENS**ors and **I**nformation arbitrage via **moBiLE** system). The marriage of DIDAS with SDS in the affluent world is a matter of social acceptance of SENSIBLE but the penchant for profit-first and lack of leadership are holding us back. In the rest of the world the barrier to diffusion of life-saving tools are, albeit with exceptions, greed, pursuit of unethical profitability, cost or paucity of infrastructure (engineering, energy, telecommunications) and rampant inequity in social cohesion.

One milestone for smartphone-based health surveillance may be the non-invasive²⁹⁸ glucose²⁹⁹ monitoring³⁰⁰ system which the healthcare system failed to aggressively adopt³⁰¹ despite significant³⁰² advances³⁰³. The chest-thumping about diabetes pandemic³⁰⁴ continues in parallel with avoidance of available³⁰⁵ solutions³⁰⁶. Cholesterol³⁰⁷ monitoring³⁰⁸ using smartphones³⁰⁹ may be a preventative measure for adults at increased risk for a slew cardiovascular diseases, a few of which may not show symptoms.

Decades after the discovery of atrial natriuretic peptide³¹⁰ (ANP, 1981), brain or B-type natriuretic peptide³¹¹ (BNP, 1987) and C-type natriuretic peptide³¹² (CNP, 1990), we *still* do not have SENSIBLE monitoring for BNP even though BNP sensors³¹³ including an aptamer-based³¹⁴ sensor for BNP-32 and cardiac Troponin I are available. These and other³¹⁵ biomarkers (CRP5/CRP6, TNF α) are indicators of cardiovascular dysfunction including congestive heart failure (CHF) and state of the patient after myocardial infarction, in addition to other conditions. BNP and other markers are key to risk stratification, diagnosis, prognosis, disease monitoring, titration of therapy, and identification of therapeutic targets for cardiovascular disease. Brain Natriuretic Peptide concentrations >400 pg/mL and N-terminal (NT) pro-BNP >400-900 pg/mL (age related) are prognosticators of congestive heart failure. Analysis of 48,629 patients³¹⁶ of acute decompensated heart failure found linear correlation between BNP levels and in-hospital mortality. Failure of BNP to decline during hospitalization predicts death or rapid re-hospitalization. However, BNP levels of 250 picograms per mL (pg/mL) or less during discharge predicts potential for survival. Accelerating availability of sensors³¹⁷ and transforming innovations³¹⁸ to SENSIBLE systems for prevention of cardiovascular disease should neither suffer from paralysis due to analysis nor asphyxiated by the rancour over margin of profitability.

Figure 22: Tip of the Ischemic Iceberg³¹⁹ hides >63% of the individuals who lack symptoms but are increasingly at risk for CVD, ischemia, myocardial infarction, congestive heart failure. BNP and other bio-markers may reduce the risk using the SENSIBLE system. We know these facts³²⁰ for ~40 years. Yet, the proponents of prevention *policies* wear that perpetual unctuous grin assimilating both the promises of a television evangelist and the sympathies of a funeral home director of marketing.

Figure 23: Smartphone cameras, LEDs, LiDARs and a FEAST³²¹ of signal transduction tools (optical, Raman spectroscopy, electrochemical impedance spectroscopy, surface plasmon resonance) are now available as data carriers. Cartoon (top) shows smartphone-based blood pressure³²² and non-invasive blood glucose³²³ monitoring³²⁴. The SENSIBLE system may be used to estimate blood cholesterol level, hemoglobin^{325, 326, 327} and uric³²⁸ acid³²⁹ as indicators of health, albeit imperfect. Data from smartphone based optic disc³³⁰ exam, photoplethysmography³³¹, electrocardiograph for arrhythmias³³² (see bottom panels), general ECG³³³, heart³³⁴ rate, respiratory³³⁵ rate (*reflection* of radio waves), pulse oximetry³³⁶ and other vitals, collectively, may create precision physiology portfolios (open data source interoperability).

It is likely that *hundreds* of papers are published *weekly* on sensors, many of which may be adapted/adopted as a part of the SENSIBLE family. Biosensing using mobile devices at the point of use is a staple, for example, in the food industry (spoilage, contamination, security), soil, water, agriculture, manufacturing, chemical industry, transportation, energy, etc. But, lack of open data and restrictions on data interoperability makes the transformation of data to information quite difficult. Scientists are eager to drill deeper to develop yet another sophisticated³³⁷ sensor but real-world user are in quest of *answers* at the point of use, and does not have the luxury to deal with numbers, compilers and programmers.

This discussion about the cacophony of available sensors is an embarrassment of riches from decades of research and development scattered as parts, in silos or locked by patents. The form and functional orchestration and integration necessary for sensors to contribute to precision physiology requires cross-pollination of ideas. Multi-disciplinary teams are necessary to create end-to-end working SENSIBLE systems which can be synchronized, if authorized, as a part of the public health information system. If that data is shared in real time, it may reduce mortality, morbidity, cost to society, decrease the burden on emergency medical professionals, and actually aid in preventing dysfunction. If this data is anonymized to serve molecular epidemiology, it may help precision public health and channel benefits to the community by revealing the environmental conditions or instances which need additional attention.

A plethora of brilliant experts with deep knowledge can fill any university hall but few have the breadth of ideas which, if synthesized, synergized and integrated, may helps to address or even solve a real problem in the public domain where non-experts are the end users. Solutions based approach must combine depth with breadth to deliver the fruits of science to society as global public goods. The latter may be missing in the academic context where chronic search for scholastic erudition is the norm. The concept of essential products and services as global public goods may not be appetizing in the corporate context due to their perpetual penchant to promote profit and profiteering, first. The cleavage between purpose and profit needs a new bridge and a new breed of thinkers and leaders with altruistic traits.

The laser-focus of biomedical professionals on saving the lives of those affected by COVID-19 and the public health community on preventing the spread of infection by SARS-CoV-2 is the only path, at present, to lift us out of the quagmire of the raging pandemic. Yet it may be crucial to use this disaster as a global opportunity to strengthen public private partnerships (academic-industry-government) for the ubiquitous deployment of global tools for early detection and prevention, not only for pandemics, but for public health and healthcare, in general. It is an enormous task and requires global leadership.

Ubiquity of smartphones is the available SENSIBLE platform to create at least one bridge over the chasm separating the *haves* from *have nots*. Inextricably linked economies of the under-developed, developing and developed nations makes it imperative that the leadership for global public health must be agnostic of prejudice. Trans-disciplinary cooperation and collaboration between corporations must rise above conventional economics³³⁸, narcissism, egocentricity and personal wealth creation. We need an overwhelming force for good, for a greater purpose, for the greatest number³³⁹ (of people).

11. Concluding Comments

The complexity of the physiological dysfunctions associated with the SARS-CoV-2 pandemic calls for multiple routes for detection, prevention and therapy. ADD is a tool for detection and perhaps an alternative approach to treatment that does not depend on the immune system due to reported heterogeneity of response, partially based on individual genetic constitution or inborn genetic errors.

The global diffusion of smartphones as ubiquitous devices is an opportunity for digital³⁴⁰ public health to accelerate the use of smartphones for detection of any infectious agent. ADD is one tiny sub-component of the proposed SENSIBLE system. Realization of the SENSIBLE system is a difficult task. The deployment of the SENSIBLE system, with ADD and other sensor components, is an essential task, unless the veneer of health equity³⁴¹ is only that, that is talk, or in other words *lippenbekenntnis*³⁴².

The caveat in this line of thinking is the over-emphasis on the sensor and the SENSIBLE system as if the value proposition is undeniable. The latter is true for the affluent economies of the world but detection without follow-up is an exercise in futility. The latter is common in communities under economic constraints where tools to detect (SENSIBLE system) are impotent because there are very few resources to attend to the public health or healthcare need identified by the SENSIBLE system. Just because the user can detect the presence of mercury in drinking water does not mean that the user has another alternative source of drinking water in under-served or dystopian communities. Is it more or less psychologically debilitating to drink water or consume food if the user is cognizant that the water is contaminated with mercury³⁴³ or the food is laced with bacteria³⁴⁴ beyond the level of food safety?

Incongruity between the *pursuit* of science, *implementation* of the fruits of science and science as a *measurable service* to society is a conundrum beyond the horizon of tools and technology, for example, the SENSIBLE system. Entrepreneurial innovation can create SENSIBLE but implementing SENSIBLE requires leadership imbued with a sense of the future, especially for low-income countries with ultra-low per capita *disposable* income. In the absence of charity, SENSIBLE for public health and healthcare must carry with it a pay-per-use price tag which may be a micro-payment or even a nano-payment but still it *must* be a non-zero payment for the system to be sustainable and survive long enough to deliver value.

Ephemeral gimmicks demonstrating SENSIBLE in geographies with GDP which may be less than an average household income in Europe is a deliberate act to deceive, dressed up in a marketing³⁴⁵ garb by the glib, the smug and the smarmy. Enabling a SENSIBLE future and making it sustainable for most segments of the community, in greatest numbers, is a mission for a visionary leader who radiates the aura that kindness is a strength, not a weakness, humility is a virtue, not a lack of knowledge, that agreeing to disagree is a mark of civility³⁴⁶ and dignity, not a character flaw, that fear is not a tool for maiming diversity, speech or peace, that progress of civilization is development of the freedom³⁴⁷ to act on remediable injustices³⁴⁸ and lift many boats, not a few yachts. The best man for *that* job is a *woman*.

APPENDIX

APPENDIX I - Brief Description of the Components³⁴⁹ for SARS-CoV-2 ADD Decision System (Fig 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 (MQ³⁵⁰) 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 Store³⁵¹), 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 blob 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 record³⁵² which includes raw data uploaded from the application, similar to “master data” in ERP³⁵³). Feature Extractor may convert the uploaded image into a numeric matrix³⁵⁴ or create hash table or representation of a region³⁵⁵ and correct for differences in resolution (for example, variation due to pixel density of cameras on different smartphones). Feature³⁵⁶ vectors³⁵⁷ may be maintained in the long-term system of record. It may be written to the operational data store to enable extraction/selection³⁵⁸ 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 store³⁵⁹. 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 engines³⁶⁰. 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-specific³⁶¹ machine learning (ML) models to assign risk scores to samples. Analytical data store (ADS database³⁶²) may be populated with data from the long-term system of record using scheduled batch data uploads.

Model Training

In model training³⁶³, a statistical model is built from historical data. Models should be serializable³⁶⁴ 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 CORBA³⁶⁵ 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 container³⁶⁶ (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 language³⁶⁷ of choice. Model scoring requires features created previously by the feature extractor (feature selection is critical).

APPENDIX II – CREATING THE PROPOSED “SENSIBLE” SYSTEM: PROMISE AND PERILS

There is ABSOLUTELY nothing new in proposing that we apply a 30 year old idea (aptamers) to a nascent problem (SARS-CoV-2). The expectation is that a credible scientific investigation may reveal if aptamers may indeed serve as an alternate to conventional wisdom (immune response). The scientific strength of this idea is based on a rigorous tenet of molecular biology which has repeatedly demonstrated that proteins bind to nucleic acids, as a fundamental mechanism of action in biological regulation. If this approach succeeds, it may help and save lives in the less affluent nations (80% of the global population). The R&D pillars in the process are as follows (same numbers imply parallel lines of research):

[1] Selection of DNA aptamers that bind with SARS-CoV-2 proteins (which proteins?) with an affinity which is (*at least*) one order of magnitude higher than the nearest neighbor (similar protein competitor based on shape and similar by amino acid sequence). This is the bedrock of whatever may follow and calls for “hard” science (nauseatingly quantitative, repeatedly reproducible, criticism from real experts).

[2] Test DNA aptamer binding to sensor material (laser inscribed graphene, Au/Pt nano-materials, etc). Establish metrics for stability of binding, using linkers to attach aptamers (covalent), using lectins and/or chemical tails, eg, poly(N-isopropylacrylamide).

[3] Test stability of conjugation of nano-dots with aptamers (cadmium, carbon, other). Is the optical signal (with/without protein) vs noise sufficiently reliable and reproducible under different conditions?

[4] Repeat [3] with aptamers linked/adsorbed on sensor material surface (choose the best outcome from each type of sensor material tested in [2]. Is the optical signal vs noise quantitative or qualitative? Prefer quantitative because qualitative offers “yes/no” (with reservations) and depends on limit of detection.

[5] Repeat best outcome from [4] using selected aptamers from [2]. If signal over noise is statistically significant ($P < 0.001$) after data acquisition by a mobile platform, then we may have the basic science and engineering tools for applications related to tools for detection/diagnostics/screening/surveillance. The latter involves entrepreneurial product innovation and engineering to design form factors, product development (breathalyzer) and product imagination to transform the idea of USB connected modular, mobile, adaptable, *sensor-on-a-chip* to link to smartphones (any USB port) to create the **molecularphone**.

EXPECTATION OF A QUANTUM LEAP: APTAMERS MAY BE USED AS THERAPEUTIC DRUGS?

Are aptamers alternate vaccines? Antibody-like “inhibition” by aptamers (*in vivo*) may offer a therapeutic path³⁶⁸ for low-cost pharmaceuticals. Aptamers identified in step [1] may *also* act as inhibitors *in vivo* (unless bioavailability or cyto-toxicity poses insurmountable problems). Testing aptamers in cell culture is the quick and dirty first choice. However, extrapolating from *in vitro* tissue culture and *in vivo* animal models (next mandatory step) to humans is neither prudent nor a *bona fide* scientific process. But prior success helps to justify the path forward. Compassionate use followed by standard human clinical trials for aptamer drugs are necessary to transform this vision into reality.

APPENDIX III – THE MOLECULAR BASIS OF DISEASE

Variability in Immune Response to SARS-CoV-2 Infection: Conundrum, Conjecture, Common Themes

The spectrum of immunological diversity³⁶⁹ presented by CoVID-19 reinforces the value of thinking broadly³⁷⁰ and thinking differently. It may not be unwise to forward hypothesis or conjectures which may or may not provide clues to understand or unravel the biological basis of this conundrum. On the other hand, based on common themes in molecular biology and genetics, perhaps what we are observing is not a conundrum at all. This discussion brings together what we think we may know.

Let us commence with the observation that bacteria belonging to even one strain, for example, *Escherichia coli* (O104:H4, O157:H7, O121) if sequenced (DNA genome), will reveal that their genomes, in terms of DNA sequence are not exactly identical. One explanation based on the molecular biology of CRISPR (clustered regularly interspaced short palindromic repeats) indicates acquisition of new spacer sequences³⁷¹ from foreign DNA necessary to adapt CRISPR-Cas³⁷² system to confer adaptive immunity. The human genome³⁷³ revealed our genomes³⁷⁴ are similar but not identical (even between twins), due to unequally distributed single nucleotide polymorphisms (SNPs) in coding and non-coding sequences.

Figure 24: Acquired spacer sequences in bacteria is one reason why genomic sequences differ even within the same strain. What is the impact of the integration and the heterogeneity of the type and number of spacers on bacterial gene expression, protein expression, physiology and metabolism?

The conundrum about the variation in human immune response to CoVID-19 may be *natural* if we consider that each human is genetically unique. We have known for 2 decades that approx. 3 million nucleotides (including about 2 million SNPs) are different between our genomes (why we are genetically unique) which contain ~6.4 billion base pairs³⁷⁵ (6.4 billion nucleotides - A, T, G, C – in diploid human genome or 3.2 billion base pairs, monoploid). These differences are significant when evaluating drugs. Hence, genetic³⁷⁶ stratification of humans in clinical trials are now almost routine.

The biological explanation as to why the efficacy and effectiveness of the same drug may be quite different between two human subjects, may be applied, partially, to explain the observed variations³⁷⁷ in immune³⁷⁸ responses³⁷⁹ to CoVID-19. SARS-CoV-2 infection induces a multi-factorial³⁸⁰ physiological³⁸¹ cascade of events³⁸² involving systems³⁸³ and network of factors³⁸⁴ each of which may be linked to genetic predispositions and may influence the phenotypic expression, to different degrees, directly or indirectly, in each human. It is not only genomics but **regulation** of gene³⁸⁵ expression³⁸⁶ (transcriptomics), protein interactions (proteomics) and metabolism (rates of anabolism and catabolism, metabolomics). Omics may be affected by epigenetic factors (food, air, water, environment³⁸⁷) and modulated by microbiomes (viromes). These internal changes will affect detectable symptoms and clinical outcomes.

In humans, multiple processes and DNA sequences flanking the immunoglobulin genes (V, D, J) influences the genetic rearrangement of the gene segments followed by somatic hypermutation³⁸⁸ which contributes to the great diversity of our immunoglobulin repertoire. It is one of the key tools available to the immune system to design antibodies and respond appropriately upon presentation of an antigen. Somatic mutations vastly differentiate and enhances the scope of response which may be otherwise restricted if the system were to depend only on the inherited genetic components (germ line theory³⁸⁹).

The machinery available to antibody-producing cells for executing somatic changes in genes and gene expression is an evolutionary process. Creative application of this machinery may generate quite a variation in phenotypic response in CoVID-19. Somatic reshuffling in combination with differences between SNPs may result in an inordinate number of different permutations and combinations. Hence, the spectrum of CoVID-19 symptoms. SARS-CoV-2 proteins³⁹⁰ may induce somatic hypermutation in cells and tissues to result in perturbation of homeostasis. Epigenetic modifications triggered by sequence cassettes³⁹¹ may affect basic processes (transcription, translation, post-translational modifications, etc.).

Figure 25: Discovery³⁹² of transposons in maize³⁹³ revealed that segments of genes “jump” from one genome to another (see left, kernel colors³⁹⁴). Variations of this “dynamic” concept are found in influenza³⁹⁵, Trypanosomes³⁹⁶, Plasmodium³⁹⁷ and other organisms. SARS-CoV-2 may hijack this mechanism, create *ad hoc* changes and alter therapeutic targets.

BACK TO BASIC SCIENCES

Molecular dissection of the SARS-CoV-2 genome³⁹⁸ to delineate the functional role of each viral protein is fundamental. Testing infectivity of single gene knockouts (and multi-gene combinations) may be one essential step. Physiological exploration of the >332 human proteins (Gordon *et al*, 2020) which may interact with SARS-CoV-2 proteins is crucial. A global collaboration may be necessary to analyze the *value of each nucleotide* in the ~30KB single stranded RNA genome³⁹⁹ of SARS-CoV-2. The analytical rigor of this approach may mimic the incisive minutiae of mutagenesis⁴⁰⁰ as applied to beta lactamase. Thoughtful design and detailed execution of this megaproject may provide clues to what constitutes virulence⁴⁰¹. Metrics of virulence is pivotal to deconstructing its cryptic complexity and reconstructing the role of molecular medicine in healthcare for humans and animals infected with virulent agents.

In the interim, undergraduates in molecular biology may undertake the theoretical analysis of SARS-CoV-2 proteins. For each known viral protein, it may be useful to list expected modifications in primary amino acid sequence (if any) due to changes in the 3rd position of the RNA codon (Fig 26, L). For example, if AGU mutates to AGC, the amino acid Serine is still the same (silent mutation) due to the degeneracy of the triplet⁴⁰² genetic code. If AGU/AGC mutates to AGA/AGG then Serine is replaced by Arginine. Using the Ramachandra Plot (Fig 26, R) students may explore which values of the ψ and ϕ angles are possible for *that* amino acid residue which *changed* in the viral protein. Can the change in the codon create an amino acid substitution which can influence the conformation of the viral protein? Structure and function are inextricably integrated in biological activity. This exercise may uncover targets for experimental analysis and predict which changes in the codon and primary sequence, may be of consequence with respect to interaction between viral proteins and their putative human targets.

Figure 26: RNA Codon⁴⁰³ table⁴⁰⁴ (L). Ramachandran Plot⁴⁰⁵ of allowed values of the ψ and ϕ angles (R).

The diversity and acuity of symptoms suggests SARS-CoV-2 proteins may have accessed the genetic circuitry⁴⁰⁶ of developmental⁴⁰⁷ clocks⁴⁰⁸ and may be “playing” with master⁴⁰⁹ switches⁴¹⁰ or re-wiring⁴¹¹ circuits or “time⁴¹² spoofing” the expression in some form⁴¹³ to modulate⁴¹⁴ differentiation. It is possible that developmentally re-programmed genetic circuits or regressively differentiated cells may express proteins and synthesize *other molecules* which are not in our ‘*data dictionary*’ because it is not a part of our *differentiated* physiology. Therefore, known therapeutic targets and approved drugs⁴¹⁵ may not be effective⁴¹⁶ because the virus is deploying different set of molecules to wreak havoc. The virus is *changing our targets* to escape host defense (immune system) and offense (drugs).

To improve our public health preparation for future epidemics and pandemics we need robust metrics to understand virulence of infecting agents in terms of molecular structure and function. These are tasks for dedicated bench scientists who may toil for long hours to contribute even an infinitesimal iota of data to inform our understanding. Science in the service of society is a purveyor for the progress of civilization. Credible advances in science may not be achieved by flaky⁴¹⁷, fluffy⁴¹⁸ and fuzzy⁴¹⁹ flash of publicity, chicanery and malarkey⁴²⁰.

Figure 27: With >50 million infected by SARS-CoV-2 (actual number may be >250 million) the clinical deluge to deal with CoVID-19 patients may leave little time to pursue molecular stratification. At best, cluster treatment (top, right) is the optimum expectation. We must go beyond the simplistic hierarchical model (bottom, right) to understand the molecular basis of the disease. Investing in basic science to probe the molecular basis of disease and virulence may offer a better compass for our tryst with destiny.

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, Jacob A. 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 – An Incomplete Review of Ideas and Facts about SARS-CoV-2* <https://dspace.mit.edu/handle/1721.1/128017> and <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://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 papers and books 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*, 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: recognizing the importance of place in primary care research & 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. 1316-17 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 Spit Shines <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*. *Annals of Internal Medicine*. 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): 16281-313 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 September; 15(9):685-688. doi: 10.1038/s41592-018-0105-0 Epub 2018 Aug 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.aag1327
- 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 March 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 Micro Biotech* 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.” *Arch 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.” *Chem 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., Blosssey, 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." *J of the American Chemical Society*, vol. 128, no. 49, December 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 & 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, September 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/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
- 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](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 July; 157:104859. doi: 10.1016/j.phrs.2020.104859. Epub 2020 April 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](https://doi.org/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 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](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. *Nature Review of Immunology* 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, September 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. 49414-419. 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 August; 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 June; 178:104792. doi: 10.1016/j.antiviral.2020.104792. Epub 2020 April 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 Biology. 2020 August 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-Kheyraadi, Junmoo Kim, Sudesna Chakravarty, Sunyoung Park, Hogleong 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 Mariana Guadalupe Matus García (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 Duvall 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: <https://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> & 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 Mackul'ak, 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). 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*. EU Publications Office 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 Logunov, D. Y. et al (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 I. 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 Neilan, A. M. et al (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-hiv-aids-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 Anderson E. J. et al and the mRNA-1273 Study Group* (2020) *Safety and immunogenicity of SARS-CoV-2 mRNA1273 vaccine in older adults*. Published 29 Sep 2020 NEJM DOI: 10.1056/NEJMoa2028436
<https://www.nejm.org/doi/pdf/10.1056/NEJMoa2028436?articleTools=true>
- ¹⁸⁶ McLellan JS, Chen M, Joyce MG, Sastry M, Stewart-Jones GB, Yang Y, Zhang B, Chen L, Srivatsan S, Zheng A, Zhou T, Graepel KW, Kumar A, Moin S, Boyington JC, Chuang GY, Soto C, Baxa U, Bakker AQ, Spits H, Beaumont T, Zheng Z, Xia N, Ko SY, Todd JP, Rao S, Graham BS, Kwong PD. *Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus*. *Science*. 2013 November 1; 342(6158):592-8. doi: 10.1126/science.1243283. Erratum in: *Science*. 2013 November 22;342(6161):931
- ¹⁸⁷ Hsieh CL, Goldsmith JA, Schaub JM, DiVenere AM, Kuo HC, Javanmardi K, Le KC, Wrapp D, Lee AG, Liu Y, Chou CW, Byrne PO, Hjorth CK, Johnson NV, Ludes-Meyers J, Nguyen AW, Park J, Wang N, Amengor D, Maynard JA, Finkelstein IJ, McLellan JS. *Structure-based Design of Prefusion-stabilized SARS-CoV-2 Spikes*. bioRxiv. 2020 May 30:2020.05.30.125484. doi: 10.1101/2020.05.30.125484. Update: *Science*. 2020 July 23.

- ¹⁸⁸ Anderson EJ, Roupahel 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
- ¹⁸⁹ Our World in Data
<https://ourworldindata.org/grapher/daily-covid-cases-7-day?time=2020-03-31..latest>
- ¹⁹⁰ 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>
- ¹⁹¹ Collins ÁB, Doherty ML, Barrett DJ, Mee JF. *Schmallenberg virus: a systematic international literature review (2011-19) 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
- ¹⁹² 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>
- ¹⁹³ 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>
- ¹⁹⁴ Fauci, Anthony (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/>
- ¹⁹⁵ 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
- ¹⁹⁶ Baltimore, David. <https://www.nobelprize.org/prizes/medicine/1975/baltimore/facts/>
- ¹⁹⁷ Daly, James L., et al. “Neuropilin-1 Is a Host Factor for SARS-CoV-2 Infection.” *Science*, Oct 20, 2020. p. eabd3072. doi:10.1126/science.abd3072.
- ¹⁹⁸ Cantuti-Castelvetri, Ludovico, et al. “Neuropilin-1 Facilitates SARS-CoV-2 Cell Entry and Infectivity.” *Science*, October 20, 2020, p. eabd2985. doi:10.1126/science.abd2985.
- ¹⁹⁹ 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/>
- ²⁰⁰ 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
- ²⁰¹ 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>
- ²⁰² Vilfredo Pareto, *Cours d'économie Politique* Professa à l'Université de Lausanne, Vol. I, 1896; Vol. II, 1897. <https://pdfs.semanticscholar.org/ef82/dfef7b0ef7a88727636f5ad680a464e33e345.pdf>

- ²⁰³ Zhang, Qian, *et al.* Inborn Errors of Type I IFN Immunity in Patients with Life-Threatening COVID-19. *Science*, vol. 370, no. 6515, October 23, 2020, p. eabd4570. doi:10.1126/science.abd4570.
- ²⁰⁴ 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>
- ²⁰⁵ Peccia, J., Zulli, A., Brackney, D.E. *et al.* Measurement of SARS-CoV-2 RNA in wastewater tracks community infection dynamics. *Nature Biotechnology* 38, 1164–1167 (2020). <https://doi.org/10.1038/s41587-020-0684-z> and <https://www.nature.com/articles/s41587-020-0684-z.pdf>
- ²⁰⁶ MIT begins testing wastewater to help detect Covid-19 on campus. <https://news.mit.edu/2020/testing-wastewater-covid-19-1002>
- ²⁰⁷ 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 November 17-23; 306(5940): 234-8. doi: 10.1038/306234a0 <https://www.nature.com/articles/306234a0>
- ²⁰⁸ 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*. *Frontiers in Immunology*. 2016 January 12; 6:658. doi: 10.3389/fimmu.2015.00658 www.ncbi.nlm.nih.gov/pmc/articles/PMC4709443/pdf/fimmu-06-00658.pdf
- ²⁰⁹ 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>
- ²¹⁰ 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
- ²¹¹ 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 August 30. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6038703/pdf/nihms-978947.pdf>
- ²¹² 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>
- ²¹³ 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

- ²¹⁴ 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](https://www.cell.com/med/pdf/S2666-6340(20)30017-9.pdf)
- ²¹⁵ 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>
- ²¹⁶ Bastard, Paul, et al. Autoantibodies against Type I IFNs in Patients with Life-Threatening COVID-19. *Science*, vol. 370, no. 6515, October 23, 2020, p. eabd4585. doi:10.1126/science.abd4585.
- ²¹⁷ Torrente-Rodriguez, Rebeca et al., *SARS-CoV-2 RapidPlex: A Graphene-Based Multiplexed Telemedicine Platform for Rapid and Low-Cost COVID-19 Diagnosis and Monitoring*. Matter (Oct 1, 20)
<https://doi.org/10.1016/j.matt.2020.09.027> ; [www.cell.com/matter/pdfExtended/S2590-2385\(20\)30553-1](https://www.cell.com/matter/pdfExtended/S2590-2385(20)30553-1)
- ²¹⁸ 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
- ²¹⁹ Mark Roberti (2004) *The 5-cent Challenge*. RFID Journal. Published August 30, 2004.
<https://www.rfidjournal.com/the-5-cent-challenge>
- ²²⁰ Zhou, Lian, et al. *Detection of SARS-CoV-2 in Exhaled Breath from COVID-19 Patients Ready for Hospital Discharge*. preprint, Public and Global Health, 2 June 2020. doi:10.1101/2020.05.31.20115196.
<https://www.medrxiv.org/content/10.1101/2020.05.31.20115196v1.full.pdf>
- ²²¹ Ma, Jianxin, et al. *Exhaled Breath Is a Significant Source of SARS-CoV-2 Emission*. preprint, Public and Global Health, 2 June 2020. doi:10.1101/2020.05.31.20115154.
<https://www.medrxiv.org/content/10.1101/2020.05.31.20115154v1.full.pdf>
- ²²² Emam, Shadi, et al. *Verification of Gas Sensors to Detect Alzheimer's Disease Biomarkers with Diabetic Rats*. ALZ, 2020. *alz.confex.com*, <https://alz.confex.com/alz/20amsterdam/meetingapp.cgi/Paper/43611>
<https://www.wired.com/story/could-breathalyzers-make-covid-testing-quicker-and-easier>
- ²²³ Kybert, Nicholas, et al. "Exploring Ovarian Cancer Screening Using a Combined Sensor Approach: A Pilot Study." *AIP Advances*, vol. 10, no. 3, March 2020, p. 035213. doi:10.1063/1.5144532
<https://aip.scitation.org/doi/pdf/10.1063/1.5144532>
- ²²⁴ Shan, Benjie, et al. "Multiplexed Nanomaterial-Based Sensor Array for Detection of COVID-19 in Exhaled Breath." *ACS Nano*, vol. 14, no. 9, Sept. 2020, pp. 12125–32. *ACS Publications*, doi:10.1021/acsnano.0c05657. <https://pubs.acs.org/doi/pdf/10.1021/acsnano.0c05657>
- ²²⁵ Kahn N, Lavie O, Paz M, Segev Y, Haick H. (2015) *Dynamic Nanoparticle-Based Flexible Sensors: Diagnosis of Ovarian Carcinoma from Exhaled Breath*. *Nano Lett.* 2015 October 14;15(10):7023-8. doi: 10.1021/acs.nanolett.5b03052. Epub 2015 Sep 11.
<https://pubs.acs.org/doi/pdf/10.1021/acs.nanolett.5b03052>

- ²²⁶ Chandrapalan, S. *et al* (2020) *Breath diagnostics in the era of SARS-CoV-2 - clinical and research arena*. Journal of Breath Research 14 042002
<https://iopscience.iop.org/article/10.1088/1752-7163/ab924a/pdf>
- ²²⁷ Oliveira AD, Prats C, Espasa M, Zarzuela Serrat F, Montañola Sales C, Silgado A, Codina DL, Arruda ME, I Prat JG, Albuquerque J. (2017) *The Malaria System MicroApp: A New, Mobile Device-Based Tool for Malaria Diagnosis*. JMIR Research Protocols. 2017 April 25; 6(4):e70. doi: 10.2196/resprot.6758.
- ²²⁸ Pirnstill CW, Coté GL. *Malaria Diagnosis Using a Mobile Phone Polarized Microscope*. Nature Science Reports 2015 Aug 25; 5:13368. doi: 10.1038/srep13368.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4548194/pdf/srep13368.pdf>
- ²²⁹ Hwang SI, Franconi NG, Rothfuss MA, Bocan KN, Bian L, White DL, Burkert SC, Euler RW, Sopher BJ, Vinay ML, Sejdic E, Star A. (2019) *Tetrahydrocannabinol Detection Using Semiconductor-Enriched Single-Walled Carbon Nanotube Chemiresistors*. ACS Sensors 2019 August 23; 4(8): pp. 2084-2093. doi: 10.1021/acssensors.9b00762. Epub 2019 August 1.
- ²³⁰ SARS-CoV-2 (COVID-19) Detection Using the Breath Analyzer TeraSystem
<https://clinicaltrials.gov/ct2/show/NCT04497610>
- ²³¹ 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>
- ²³² 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
- ²³³ “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)
- ²³⁴ 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>
- ²³⁵ Service, Robert. In ‘Milestone,’ FDA OKs Simple, Accurate Coronavirus Test That Could Cost \$5. *Science*, August 27-28, 2020. doi:10.1126/science.abe5319
- ²³⁶ The Nobel Prize in Physiology or Medicine 2020. October 5, 2020.
<https://www.nobelprize.org/prizes/medicine/2020/press-release/>
- ²³⁷ Schweitzer, Albert (1922) *The Decay and the Restoration of Civilization* (Translated by C. T. Champion. Published by A. C. Black, London, 1923)
<https://ia800904.us.archive.org/9/items/p1decayrestorati00schwuoft/p1decayrestorati00schwuoft.pdf>
- ²³⁸ David M Cutler and Larry H Summers. *COVID-19 Pandemic and the \$16 Trillion Virus*. JAMA. Pub Oct 12, 2020. doi:10.1001/jama.2020.19759 <https://jamanetwork.com/journals/jama/fullarticle/2771764>

- ²³⁹ “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/>
- ²⁴⁰ <https://www.worldometers.info/gdp/gdp-by-country>
- ²⁴¹ 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>
- ²⁴² 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>
- ²⁴³ 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>
- ²⁴⁴ Hodcroft, Emma B., et al. *Emergence and Spread of a SARS-CoV-2 Variant through Europe in the Summer of 2020*. preprint, Epidemiology, 28 October 2020. doi:10.1101/2020.10.25.20219063.
- ²⁴⁵ 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>
- ²⁴⁶ Cao L, Goreshnik I, Coventry B, Case JB, Miller L, Kozodoy L, Chen RE, Carter L, Walls L, Park YJ, Stewart L, Diamond M, Veelsler D, Baker D. *De novo design of picomolar SARS-CoV-2 miniprotein inhibitors*. bioRxiv [Preprint]. 2020 Aug 3. DOI: 10.1101/2020.08.03.234914. *Science* 23 October 2020: Vol. 370, Issue 6515, pp. 426–431 DOI: 10.1126/science.abd9909.
<https://www.biorxiv.org/content/10.1101/2020.08.03.234914v1.full.pdf>
- ²⁴⁷ Coase, R. H. (1937) “The Nature of the Firm.” *Economica*, vol. 4, no. 16, Nov. 1937, pp. 386–405.
doi:10.1111/j.1468-0335.1937.tb00002.x
<https://www.law.uchicago.edu/files/file/coase-nature.pdf> <http://bit.ly/COASE5PAPERS>
- ²⁴⁸ Stephanie K. Pell and Christopher Soghoian (2014) Your Secret Stingray’s No Secret Anymore: The Vanishing Government Monopoly Over Cell Phone Surveillance and Its Impact On National Security and Consumer Privacy. *Harvard Journal of Law and Technology* Volume 28, Number 1 Fall 2014
- ²⁴⁹ Kevin S. Bankston and Ashkan Soltani (2014) Tiny Constables and the Cost of Surveillance: Making Cents Out of United States v. Jones, 123 Yale Law Journal ONLINE 335 (2014)
<http://yalelawjournal.org/forum/tiny-constables-and-the-cost-of-surveillance-making-cents-out-of-united-states-v-jones>
- ²⁵⁰ Roosa Tikkanen and Melinda K. Abrams (2020) U.S. Health Care from a Global Perspective, 2019: Higher Spending, Worse Outcomes? January 30, 2020
<https://www.commonwealthfund.org/publications/issue-briefs/2020/jan/us-health-care-global-perspective-2019>

- ²⁵¹ Landgrebe, D. (1998) *Information Extraction Principals and Methods for Multispectral and Hyperspectral Image Data, Information processing for Remote Sensing*. World Scientific Publishing Co. <https://engineering.purdue.edu/~landgreb/whitepaper.pdf>
- ²⁵² Moghimi, Ali, et al. "A Novel Machine Learning Approach to Estimate Grapevine Leaf Nitrogen Concentration Using Aerial Multispectral Imagery." *Remote Sensing*, vol. 12, no. 21, October 2020, p. 3515. doi:10.3390/rs12213515. <https://www.mdpi.com/2072-4292/12/21/3515/pdf>
- ²⁵³ Huang, Y., Ren, Z., Li, D. et al. Phenotypic techniques and applications in fruit trees: a review. *Plant Methods* 16, 107 (2020). <https://doi.org/10.1186/s13007-020-00649-7>
- ²⁵⁴ Lorenzen, Bent & Arne, Jensen (1988) "Reflectance of Blue, Green, Red and near Infrared Radiation from Wetland Vegetation Used in a Model Discriminating Live and Dead above Ground Biomass." *New Phytologist*, vol. 108, no. 3, March 1988, pp. 345–55. doi:10.1111/j.1469-8137.1988.tb04173.x.
- ²⁵⁵ Soo Chung, Lane E. Breshears and Jeong-Yeol Yoon, "Smartphone Near Infrared Monitoring of Plant Stress," *Computers and Electronics in Ag*, 2018, 154: 93-98. <https://doi.org/10.1016/j.compag.2018.08.046>
- ²⁵⁶ Marturano F, Ciparisse JF, Chierici A, d'Errico F, Di Giovanni D, Fumian F, Rossi R, Martellucci L, Gaudio P, Malizia A. *Enhancing Radiation Detection by Drones through Numerical Fluid Dynamics Simulations*. *Sensors* (Basel). 2020 March 23; 20(6):1770. doi: 10.3390/s20061770. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7147154/pdf/sensors-20-01770.pdf>
- ²⁵⁷ William Joseph Butera (2002) *Programming a Paintable Computer*. Submitted to the Program in Media Arts & Sciences, School of Architecture and Planning, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Media Arts & Sciences, Massachusetts Institute of Technology February 2002 <http://cba.mit.edu/docs/theses/02.02.butera.pdf>
http://cba.mit.edu/events/01.11.retreat/Butera/Butera_files/v3_document.htm
- ²⁵⁸ Wicaksono, I., Tucker, C.I., Sun, T. et al. A tailored, electronic textile conformable suit for large-scale spatiotemporal physiological sensing in vivo. *npj Flex Electron* 4, 5 (2020). <https://doi.org/10.1038/s41528-020-0068-y>
- ²⁵⁹ Mark Weiser, Rich Gold and John Seeley Brown (1999) The origins of ubiquitous computing research at PARC in the late 1980s. *IBM Systems Journal*, vol 38, no. 4, pp. 693-696, 1999. <http://www.cs.cmu.edu/~jasonh/courses/ubicomp-sp2007/papers/03-weiser-origins.pdf>
- ²⁶⁰ Mark Weiser (1991) *The Computer for the 21st Century*. *Scientific American* 265, No. 3, pp. 94 –104 (September 1991). <https://www.lri.fr/~mbl/Stanford/CS477/papers/Weiser-SciAm.pdf>
- ²⁶¹ William D. Nordhaus (2001) *Progress of Computing*. Cowles Foundation Discussion Paper No. 1324. Cowles Foundation For Research in Economics, Yale University, New Haven, Connecticut, USA. <http://cowles.econ.yale.edu/> <https://cowles.yale.edu/sites/default/files/files/pub/d13/d1324.pdf> and <https://aiimpacts.org/trends-in-the-cost-of-computing/>
- ²⁶² David H Wolpert. (2019) The stochastic thermodynamics of computation, *Journal of Physics A: Mathematical and Theoretical* (2019). DOI: 10.1088/1751-8121/ab0850
- ²⁶³ Charles, J. (2012) <https://jcharles00.wordpress.com/2012/05/>
- ²⁶⁴ What is IPv6? <https://www.internetsociety.org/deploy360/ipv6/>

-
- ²⁶⁵ Hinden, Bob and Krishnan, Suresh (2018) IPv6 is an Internet Standard.
<https://www.ietf.org/blog/ipv6-internet-standard/>
- ²⁶⁶ Raffi C. Krikorian (2004) *Internet 0*. Submitted to the Program in Media Arts & Sciences, School of Architecture and Planning in partial fulfillment of the requirements for the degree of Master of Science in Media Arts & Sciences at the Massachusetts Institute Of Technology, August 2004
<https://dspace.mit.edu/bitstream/handle/1721.1/28866/60412683-MIT.pdf?sequence=2&isAllowed=y>
- ²⁶⁷ Ishii, H. and Ullmer, B. (1997) *Tangible Bits: Towards Seamless Interfaces between People, Bits, and Atoms*. Proceedings of CHI'97 (ACM, March 1997) <http://tangible.media.mit.edu/person/hiroshi-ishii/>
- ²⁶⁸ Hiroshi Ishi <https://tangible.media.mit.edu/person/hiroshi-ishii/>
- ²⁶⁹ Gershenfeld, Neil A. *When Things Start to Think*. 1st ed, Henry Holt, 1999.
- ²⁷⁰ Nelson Minar, Matthew Gray, Oliver Roup, Raffi Krikorian and Patti Maes “Hive: Distributed Agents for Networking Things.” *IEEE Concurrency*, vol. 8, no. 2, Apr. 2000, pp. 24-33. doi:10.1109/4434.846191
- ²⁷¹ Gershenfeld, Neil. <http://ng.cba.mit.edu/>
- ²⁷² Origins of IoT <https://autoid.mit.edu/>
- ²⁷³ Greengard, Samuel. *The Internet of Things*. MIT Press, 2015.
- ²⁷⁴ <https://autoid.mit.edu/people-2>
- ²⁷⁵ <https://openlearning.mit.edu/about/our-team/sanjay-sarma>
- ²⁷⁶ Simon, Herbert, A. The Steam Engine and the Computer: What Makes Technology Revolutionary. *EDUCOM Bulletin*, vol. 22, no.1, pp. 2-5 Spring 1987
<https://er.educause.edu/-/media/files/article-downloads/erm0132.pdf>
<http://digitalcollections.library.cmu.edu/awweb/awarchive?type=file&item=34057>
- ²⁷⁷ Sarma, S., Brock, D. and Engels, D. (2001) “Radio Frequency Identification and the Electronic Product Code,” *IEEE Micro*, vol. 21, no. 6, December 2001, pp. 50–54. doi:10.1109/40.977758.
- ²⁷⁸ MIT Project Oxygen (2001) Computer Science and Artificial Intelligence Laboratory, MIT.
<http://www.ai.mit.edu/projects/oxygen/oxygen-book2001/oxygenbook2001.pdf>
- ²⁷⁹ Katz, Randall (2002) Sketch - <http://oxygen.csail.mit.edu/videosketching.html> and Sketch Video Demonstration <http://oxygen.csail.mit.edu/videos/sketching.mpeg>
- ²⁸⁰ Project Oxygen. Massachusetts Institute of Technology <http://oxygen.csail.mit.edu/Overview.html>
- ²⁸¹ Jorgenson, Dale Weldeau, et al., editors. *Measuring and Sustaining the New Economy: Report of a Workshop*. National Academy Press, 2002. <https://www.nap.edu/download/10282>
- ²⁸² <https://www.pcgamesn.com/intel/memory-nand-ssd-price-drop-2019-oversupply>
- ²⁸³ <https://www.iotone.com/term/decreasing-cost-of-storage/t172>
- ²⁸⁴ Golubchik, Leana, Khuller, Samir, Mukherjee, Koyel and Yao, Yuan. (2013). *To send or not to send: Reducing the cost of data transmission*. IEEE Infocom. 2472-2478. Doi: 10.1109/INFCOM.2013.6567053
- ²⁸⁵ Asimov, Isaac (1953) [http://www.self.gutenberg.org/articles/Sally_\(short_story\)](http://www.self.gutenberg.org/articles/Sally_(short_story))
- ²⁸⁶ Asimov, Isaac. *The Complete Robot*. HarperCollins, 1995.
[https://en.wikipedia.org/wiki/Sally_\(short_story\)](https://en.wikipedia.org/wiki/Sally_(short_story))

- ²⁸⁷ Sanjay Sarma, David Brock and Kevin Ashton (1999) “*The Networked Physical World - Proposals for Engineering the Next Generation of Computing, Commerce, and Automatic-Identification*,” MIT Auto-ID Center White Paper. MIT-AUTOID-WH001, 1999. <https://autoid.mit.edu/publications-0>
<https://pdfs.semanticscholar.org/88b4/a255082d91b3c88261976c85a24f2f92c5c3.pdf>
- ²⁸⁸ Ghasempour, Alireza. *Internet of Things in Smart Grid: Architecture, Applications, Services, Key Technologies, and Challenges*. Inventions, vol. 4, no. 1, Mar 2019, p. 22. doi:10.3390/inventions4010022
- ²⁸⁹ Christopher Greer, Martin Burns, David Wollman and Edward Griffor (2019) *Cyber-Physical Systems and Internet of Things*. <https://doi.org/10.6028/NIST.SP.1900-202>
<https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.1900-202.pdf>
- ²⁹⁰ Edward A. Lee and Sanjit A. Seshia. *Introduction to Embedded Systems, A Cyber-Physical Systems Approach*, Second Edition, MIT Press, 2017. ISBN 978-0-262-53381-2
https://ptolemy.berkeley.edu/books/leeseshia/releases/LeeSeshia_DigitalV2_2.pdf
- ²⁹¹ Rajkumar R, Lee I, Sha L, Stankovic J (2010) *Cyber-Physical Systems: The Next Computing Revolution*. Proceedings of the 47th Design Automation Conference (IEE, Anaheim, CA), pp 731– 736.
<https://ieeexplore.ieee.org/document/5523280>
<https://www.cs.virginia.edu/~stankovic/psfiles/Rajkumar-DAC2010-Final.pdf>
- ²⁹² Robert E. Horn (2015) *Information Design: Emergence of a New Profession*
<https://steinhardtapps.es.its.nyu.edu/create/courses/2015/reading/Horn.pdf>
- ²⁹³ Jacobson, Robert E., editor. *Information Design*. MIT Press, 1999.
<https://epdf.pub/queue/information-design.html>
- ²⁹⁴ Jimmy Soni and Rob Goodman (2018) *A Mind at Play: How Claude Shannon Invented the Information Age*. Simon & Schuster (July 17, 2018) ISBN13: 9781476766690
<https://spectrum.ieee.org/geek-life/history/a-man-in-a-hurry-claude-shannons-new-york-years>
- ²⁹⁵ Pham NM, Karlen W, Beck HP, Delamarche E. *Malaria and the 'last' parasite: how can technology help?* Malaria Journal 2018 July 11; 17(1):260. doi: 10.1186/s12936-018-2408-0
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6042346/pdf/12936_2018_Article_2408.pdf
- ²⁹⁶ Pierce, David (2016) *Project Ara Lives: Google's Modular Phone Is Ready for You Now*.
<https://www.wired.com/2016/05/project-ara-lives-googles-modular-phone-is-ready/>
- ²⁹⁷ NK Labs, Cambridge, Massachusetts <https://www.nklabs.com/ara-knaian>
- ²⁹⁸ Bhardwaj, Vinay, and Vinod Gaur. “Raman Spectroscopy as a Blood Glucose Monitoring Tool.” *European Pharmaceutical Review*, vol. 22, no. 3, 2017, pp. 26–29.
- ²⁹⁹ Pandey R, Paidi SK, Valdez TA, Zhang C, Spegazzini N, Dasari RR, Barman I. *Noninvasive Monitoring of Blood Glucose with Raman Spectroscopy*. Acc Chem Res. 2017 February 21; 50(2):264-272. doi: 10.1021/acs.accounts.6b00472. Epub 2017 January 10.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5896772/pdf/nihms955832.pdf>
- ³⁰⁰ Kakkar, T., Richards, B., Jha, A., Saha, S., Ajjan, R., Grant, P. and Jose, G. (2015) Glucosense: Photonic Chip Based Non-Invasive Glucose Monitor. *Diabetes Technology Therapeutics*, vol. 17, pp. A82-A83
- ³⁰¹ Jose, Gin. GLUCOSENSE. University of Leeds, UK. www.leeds.ac.uk/site/custom_scripts/profile-single.php?profileTypeID=3&categoryID=2000&profileID=116

- ³⁰² Jung, D.G.; Jung, D.; Kong, S.H. (2017) A Lab-on-a-Chip-Based Non-Invasive Optical Sensor for Measuring Glucose in Saliva. *Sensors* **2017**, *17*, 2607. <https://www.mdpi.com/1424-8220/17/11/2607/pdf>
- ³⁰³ Zhang R, Liu S, Jin H, Luo Y, Zheng Z, Gao F, Zheng Y. (2019) *Noninvasive Electromagnetic Wave Sensing of Glucose*. *Sensors* (Basel). 2019 March 7; 19(5):1151. doi: 10.3390/s19051151 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6427587/pdf/sensors-19-01151.pdf>
- ³⁰⁴ Narayan KMV, Zhang P, Kanaya AM, et al. *Diabetes: The Pandemic and Potential Solutions*. In: Jamison DT, Breman JG, Measham AR, et al., editors. *Disease Control Priorities in Developing Countries*. 2nd ed. Washington (DC): International Bank for Reconstruction and Development, The World Bank. 2006. Chapter 30. Oxford University Press, NY. <https://www.ncbi.nlm.nih.gov/books/NBK11777/> https://www.ncbi.nlm.nih.gov/books/NBK11777/pdf/Bookshelf_NBK11777.pdf
- ³⁰⁵ Villena Gonzales W, Mobashsher AT, Abbosh A. *The Progress of Glucose Monitoring-A Review of Invasive to Minimally and Non-Invasive Techniques, Devices and Sensors*. *Sensors* (Basel). 2019 Feb 15; 19(4):800. doi: 10.3390/s19040800 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6412701/pdf/sensors-19-00800.pdf>
- ³⁰⁶ Kang, Jeon Woong, et al. (2020) "Direct Observation of Glucose Fingerprint Using in Vivo Raman Spectroscopy." *Science Advances*, vol. 6, no. 4, Jan. 2020, p. eaay5206. doi:10.1126/sciadv.aay5206
- ³⁰⁷ Zhu, Lian, et al. (2013) "Direct Electrochemistry of Cholesterol Oxidase Immobilized on Gold Nanoparticles-Decorated Multiwalled Carbon Nanotubes and Cholesterol Sensing." *Talanta*, vol. 106, March 2013, pp. 192–99. doi:10.1016/j.talanta.2012.12.036
- ³⁰⁸ N. Agrawal, B. Zhang, C. Saha, C. Kumar, X. Pu and S. Kumar. *Ultra-Sensitive Cholesterol Sensor Using Gold and Zinc-Oxide Nanoparticles Immobilized Core Mismatch MPM/SPS Probe*. *Journal of Lightwave Technology*, vol. 38, no. 8, pp. 2523-2529, 15 April 2020. doi: 10.1109/JLT.2020.2974818
- ³⁰⁹ Oncescu V, Mancuso M, Erickson D. *Cholesterol testing on a smartphone*. *Lab Chip*. 2014 Feb 21; 14(4):759-63. doi: 10.1039/c3lc51194d. Epub 2013 December 13.
- ³¹⁰ de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. (1981) *A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats*. *Life Sci* 1981; vol. 28: pp. 89–94
- ³¹¹ Sudoh, T., Kangawa, K., Minamino, N. et al. (1988) A new natriuretic peptide in porcine brain. *Nature* **332**, 78–81 (1988). <https://doi.org/10.1038/332078a0>
- ³¹² Sudoh T, Minamino N, Kangawa K, Matsuo H. *C-type natriuretic peptide (CNP): A new member of natriuretic peptide family identified in porcine brain*. *Biochem Biophys Res Commun* 1990; 168: 863–870
- ³¹³ Pollok, Nicole E., et al. *Electrochemical Detection of NT-ProBNP Using a Metalloimmunoassay on a Paper Electrode Platform*. *ACS Sensors*, vol. 5, n. 3, Mar 2020, p 853-60. doi: 10.1021/acssensors.0c00167
- ³¹⁴ Grabowska I, Sharma N, Vasilescu A, Iancu M, Badea G, Boukherroub R, Ogale S, Szunerits S. *Electrochemical Aptamer-Based Biosensors for the Detection of Cardiac Biomarkers*. *ACS Omega*. 2018 September 30; 3(9): pp. 12010-12018. doi: 10.1021/acsomega.8b01558. Epub 2018 September 26.
- ³¹⁵ Gaetano Ruocco, Marco Pellegrini, Carmelo De Gori, Beatrice Franci, Ranuccio Nuti, Alberto Palazzuoli. (2016) *The prognostic combined role of B-type natriuretic peptide, blood urea nitrogen and congestion signs persistence in patients with acute heart failure*. *Journal of Cardiovascular Medicine*, vol. 17, no. 11, pp. 818-827 (2016) doi: 10.2459/JCM.0000000000000350

- ³¹⁶ Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M; ADHERE Scientific Advisory Committee and Investigators. *Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure*. Journal of the American College of Cardiology. 2007 May 15; 49(19): pp. 1943-50. doi: 10.1016/j.jacc.2007.02.037. Epub 2007 April 30.
- ³¹⁷ Lin, Chung-Yin, et al. "Detection of Oxytocin, Atrial Natriuretic Peptide, and Brain Natriuretic Peptide Using Novel Imprinted Polymers Produced with Amphiphilic Monomers." *Journal of Peptide Science*, vol. 25, no. 3, March 2019. doi:10.1002/psc.3150
- ³¹⁸ Ven Manda, Tommy D. Bennett and Zhongping Yang (2003) *Implantable biosensor devices for monitoring cardiac marker molecules* <https://patents.google.com/patent/US7632234B2/en> <https://patentimages.storage.googleapis.com/20/27/7b/4ba70677881f9c/US7632234.pdf>
- ³¹⁹ Guterman, David (2013) *Silent Myocardial Ischemia* <https://www.escardio.org/static-file/Escardio/education/live-events/courses/education-resource/Fri-11-SMI-Guterman.pdf>
- ³²⁰ Deanfield JE, Maseri A, Selwyn AP, Ribeiro P, Chierchia S, Krikler S, Morgan M. (1983) *Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes*. Lancet. 1983 Oct 1; 2(8353): pp. 753-758. doi: 10.1016/s0140-6736(83)92295-x.
- ³²¹ Eric S. McLamore, Evanglyn Alocilja, Carmen Gomes, Sundaram Gunasekaran, Daniel Jenkins, Yanbin Li, Yu (Jessie) Mao, Sam R. Nugen, Jose Reyes De Corcuera, Paul Takhistov, Olga Tsyusko, Jarad P. Cochran, Tzuen-Rong (Jeremy) Tzeng, Jeong-Yeol Yoon, Chenxu Yu, and Anhong Zhou (2020). *A FEAST of Biosensors: Food, Environment, Agriculture, Science, Technology (FEAST) for Biosensing in North America* (in preparation)
- ³²² Schoettker P, Degott J, Hofmann G, Proença M, Bonnier G, Lemkaddem A, Lemay M, Schorer R, Christen U, Knebel JF, Wuerzner A, Burnier M, Wuerzner G. *Blood pressure measurements with the OptiBP smartphone app validated against reference auscultatory measurements*. Nature Science Reports 2020 October 20; 10(1):17827. doi: 10.1038/s41598-020-74955-4 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7576142/pdf/41598_2020_Article_74955.pdf
- ³²³ *Noninvasive Device Could End Daily Finger Pricking for People with Diabetes*. <https://medicalxpress.com/news/2015-07-noninvasive-device-daily-finger-people.html>
- ³²⁴ *Glucosense Monitoring*. University of Leeds, UK <https://www.youtube.com/watch?v=j--utQE9Pz8>
- ³²⁵ Sato H, Chiba H, Tashiro H, Ozaki Y.(2001) *Excitation wavelength-dependent changes in Raman spectra of whole blood and hemoglobin: comparison of the spectra with 514.5-, 720-, and 1064-nm excitation*. J Biomed Opt. 2001 July; 6(3): pp. 366-370. doi: 10.1117/1.1380668 <https://www.spiedigitallibrary.org/journalArticle/Download?fullDOI=10.1117%2F1.1380668>
- ³²⁶ Hasan MK, Haque MM, Adib R, Tumpa JF, Begum A, Love RR, Kim YL, Sheikh IA. (2018) *SmartHeLP: Smartphone-based Hemoglobin Level Prediction Using an Artificial Neural Network*. AMIA Annual Symposium Proceedings. 2018 December 5 : pp. 535-544. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6371334/pdf/2976625.pdf>
- ³²⁷ Mannino, R.G., Myers, D.R., Tyburski, E.A. et al. (2018) *Smartphone app for non-invasive detection of anemia using only patient-sourced photos*. Nature Communications 9, 4924 (2018). <https://doi.org/10.1038/s41467-018-07262-2>

- ³²⁸ Yan, Q., Zhi, N., Yang, L. *et al.* A highly sensitive uric acid electrochemical biosensor based on a nano-cube cuprous oxide/ferrocene/uricase modified glassy carbon electrode. *Sci Rep* 10, 10607 (2020). <https://doi.org/10.1038/s41598-020-67394-8>
- ³²⁹ Yang, Y., Song, Y., Bo, X. *et al.* A laser-engraved wearable sensor for sensitive detection of uric acid and tyrosine in sweat. *Nat Biotechnol* 38, 217–224 (2020). <https://doi.org/10.1038/s41587-019-0321-x>
- ³³⁰ Bastawrous A, Giardini ME, Bolster NM, Peto T, Shah N, Livingstone IA, Weiss HA, Hu S, Rono H, Kuper H, Burton M. (2016) *Clinical Validation of a Smartphone-Based Adapter for Optic Disc Imaging in Kenya*. *JAMA Ophthalmology* 2016 Feb; 134(2): pp.151-158. doi: 10.1001/jamaophthalmol.2015.4625 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5321504/pdf/emss-71475.pdf>
- ³³¹ Di Santo P, Harnett DT, Simard T, Ramirez FD, Pourdjabbar A, Yousef A, Moreland R, Bernick J, Wells G, Dick A, Le May M, Labinaz M, So D, Motazedian P, Jung RG, Chandrasekhar J, Mehran R, Chong AY, Hibbert B. *Photoplethysmography using a smartphone application for assessment of ulnar artery patency: a randomized clinical trial*. *CMAJ*. 2018 April 3; 190(13): E380-E388. doi: 10.1503/cmaj.170432 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5880645/pdf/190e380.pdf>
- ³³² Malamas, Peter (2011) *A 3-D Heart Model for Arrhythmia Simulation and Visualization* <https://sunfest.seas.upenn.edu/wp-content/uploads/2018/07/MALAMASPETER.pdf>
- ³³³ Saxon Leslie A. *Ubiquitous wireless ECG recording: a powerful tool physicians should embrace*. *J Cardiovasc Electrophysiol*. 2013 April; 24(4): pp. 480-483. doi: 10.1111/jce.12097. Epub 2013 Feb 19.
- ³³⁴ Fadel Adib, Hongzi Mao, Zachary Kabelac, Dina Katabi and Robert C. Miller. “Smart Homes That Monitor Breathing and Heart Rate.” *Proceedings of the 33rd Annual ACM Conference on Human Factors in Computing Systems*, Association for Computing Machinery, 2015, pp. 837–846. *ACM Digital Library*, doi:10.1145/2702123.2702200. <http://www.mit.edu/~fadel/papers/vitalradio-paper.pdf> <http://witrack.csail.mit.edu/vitalradio/>
- ³³⁵ Fadel Adib and Dina Katabi (2013) *See Through Walls with Wi-Fi*. SIGCOMM’13, August 12–16, 2013. Hong Kong, China. <https://people.csail.mit.edu/fadel/papers/wivi-paper.pdf>
- ³³⁶ Tomlinson S, Behrmann S, Cranford J, Louie M, Hashikawa A. (2018) *Accuracy of Smartphone-Based Pulse Oximetry Compared with Hospital-Grade Pulse Oximetry in Healthy Children*. *Telemed J E Health*. 2018 July; 24(7): pp. 527-535. doi: 10.1089/tmj.2017.0166. Epub 2017 December 7.
- ³³⁷ Hansen CH, Yang D, Koussa MA, Wong WP. *Nanoswitch-linked immunosorbent assay (NLISA) for fast, sensitive, and specific protein detection*. *Proc Natl Acad Sci*. 2017 Sep 26; 114(39):10367-10372. doi: 10.1073/pnas.1708148114 www.ncbi.nlm.nih.gov/pmc/articles/PMC5625919/pdf/pnas.201708148.pdf
- ³³⁸ Banerjee, Abhijit and Duflo, Esther (2019) *Good Economics for Hard Times*. PublicAffairs, a division of Perseus Books, a subsidiary of Hachette Book Groups (Nov 12, 2019) ISBN-13: 978-1610399500
- ³³⁹ Howes, Anton. *Arts and Minds: How the Royal Society of Arts Changed a Nation*. Princeton University Press, 2020. ISBN-13: 978-0691182643
- ³⁴⁰ Budd J, Miller BS, Manning EM, Lampos V, Zhuang M, Edelstein M, Rees G, Emery VC, Stevens MM, Keegan N, Short MJ, Pillay D, Manley E, Cox IJ, Heymann D, Johnson AM, McKendry RA. *Digital technologies in the public-health response to COVID-19*. *Nature Med* 2020 Aug 7; 26(8):1183-1192. doi: 10.1038/s41591-020-1011-4. Epub 2020 Aug 7. www.nature.com/articles/s41591-020-1011-4.pdf

- ³⁴¹ Butler SM. Four COVID-19 Lessons for Achieving Health Equity. *JAMA Health Forum*. Nov 5, 2020. doi:10.1001/jamahealthforum.2020 <https://jamanetwork.com/channels/health-forum/fullarticle/2772835>
- ³⁴² <https://www.dict.cc/german-english/Lippenbekenntnis.html>
- ³⁴³ Y. Rong, A.V. Padrona, K. J. Hagerty, N. Nelson, S. Chic, N. O. Keyhani, J. Katz, S.P.A. Datta, C. Gomes, and E.S. McLamore (2018) Post Hoc Support Vector Machine Learning for Impedimetric Biosensors Based on Weak Protein–Ligand Interactions. *The Analyst*, vol. 143, no. 9, pp. 2066–2075 doi:10.1039/C8AN00065D <https://pubs.rsc.org/en/content/getauthorversionpdf/C8AN00065D>
- ³⁴⁴ Cassie A. Giacobassi, Daniela A. Oliveira, Cicero C. Pola, Dong Xiang, Yifan Tang, Shoumen Palit Austin Datta, Eric S. McLamore and Carmen Gomes (2020) *Sense-Analyze-Respond-Actuate (SARA) systems span nanoscale and macroscale actuation for detection of Escherichia coli in water* (in press)
- ³⁴⁵ Nassauer, Sarah. “WSJ News Exclusive | Walmart Scraps Plan to Have Robots Scan Shelves.” *Wall St J*, 2 Nov 2020. www.wsj.com/articles/walmart-shelves-plan-to-have-robots-scan-shelves-11604345341
- ³⁴⁶ Bejan, Teresa (2017) *Mere Civility: Disagreement and the Limits of Toleration*. Harvard University Press, 2017. ISBN-13 : 978-0674545496
- ³⁴⁷ Sen, Amartya (1999) *Development as Freedom*. Alfred A. Knopf, New York, 1999. ISBN-13 : 978-0385720274
- ³⁴⁸ Sen, Amartya (2009) *The Idea of Justice*. Belknap Press of Harvard University Press; 1st edition (September 30, 2009) ISBN-13 : 978-0674036130
- ³⁴⁹ Datta, Shoumen. APPENDIX Figure 1: Description of Major Software Components <https://github.com/shoumendatta/ADD-DIGITAL> and James Lamb <https://github.com/jameslamb>
- ³⁵⁰ 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/>).
- ³⁵¹ 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>.
- ³⁵² Amazon S3 Glacier <https://aws.amazon.com/glacier/>
- ³⁵³ Enterprise Resource Planning (ERP) – Master Data Management: Architecture and Technology <https://www.element61.be/en/resource/master-data-management-mdm-architecture-technology>
- ³⁵⁴ Vesna Vučković (2008) *Image and its Matrix, Matrix and its Image*. Преглед НЦД (NCD Review) 12 (2008) 17–31 <http://elib.mi.sanu.ac.rs/files/journals/ncd/12/ncd12017.pdf>
- ³⁵⁵ H3: Uber’s Hexagonal Hierarchical Spatial Index <https://eng.uber.com/h3/>
- ³⁵⁶ 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>

³⁵⁷ Bommert, Andrea, et al. “Benchmark for Filter Methods for Feature Selection in High-Dimensional Classification Data.” *Computational Statistics & Data Analysis*, vol. 143, March 2020, p. 106839. doi:10.1016/j.csda.2019.106839.

³⁵⁸ 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>

³⁵⁹ 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>

³⁶⁰ 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/>)

³⁶¹ 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>

³⁶² 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>). For on-premises option: Teradata (<https://www.teradata.com/>).

³⁶³ Machine Learning (see the cartoon on page 75 of this article) 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>).

³⁶⁴ Tauro, C.J., Ganesan, N., Mishra, S.R., & Bhagwat, A. (2012). Object Serialization: A Study of Techniques of Implementing Binary Serialization in C++, Java & .NET. *Intl J of Computer Applications*, 45, 25-29. <https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.685.1077&rep=rep1&type=pdf>

³⁶⁵ Common Object Request Broker Architecture (CORBA) <https://www.corba.org/>

³⁶⁶ Container: Docker <https://www.docker.com/resources/what-container>

³⁶⁷ Developer’s language of choice may include (but the “menu” is not limited to):

Java jar ([https://en.wikipedia.org/wiki/JAR_\(file_format\)](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 ML (https://en.wikipedia.org/wiki/Predictive_Model_Markup_Language) or Portable Format for Analytics (<http://dmg.org/pfa/>)

³⁶⁸ Parashar A. *Aptamers in Therapeutics*. J of Clinical Diagnostic Research 2016 Jun; 10(6):BE01-6. doi: 10.7860/JCDR/2016/18712.7922. Epub 2016 June 1.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4963637/pdf/jcdr-10-BE01.pdf>

³⁶⁹ Immune Responses and Immunity to SARS-CoV-2. European Centre for Disease Prevention and Control (30 June 2020) <https://www.ecdc.europa.eu/en/covid-19/latest-evidence/immune-responses>

³⁷⁰ Eric J. Topol and Zeynep Tufekci (2020) The Remarkable Value of Thinking Broadly: A COVID-19 Trifecta.” *Medscape* (October 28, 2020) <http://www.medscape.com/viewarticle/938808>

³⁷¹ Barrangou R, Fremaux C, Deveau H, Richards M, Boyaval P, Moineau S, Romero DA, Horvath P. *CRISPR provides acquired resistance against viruses in prokaryotes*. *Science*. 2007 March 23; 315(5819): pp. 1709-1712. doi: 10.1126/science. <https://science.sciencemag.org/content/315/5819/1709.long>

³⁷² Doudna JA, Charpentier E. *Genome editing. The new frontier of genome engineering with CRISPR-Cas9*. *Science*. 2014 November 28; 346(6213):1258096. doi:10.1126/science.1258096 <https://science.sciencemag.org/content/346/6213/1258096.long>

³⁷³ Lander, Eric S. *et al* Initial sequencing and analysis of the human genome. *Nature*. 2001 February 15; 409(6822): pp. 860-921. doi: 10.1038/35057062. <https://www.nature.com/articles/35057062.pdf>

³⁷⁴ Venter, J. Craig *et al* The sequence of the human genome. *Science*. 2001 February 16; 291(5507): pp.1304-1351. doi: 10.1126/science. <https://science.sciencemag.org/content/sci/291/5507/1304.full.pdf>

³⁷⁵ Brown TA. *Genomes*. 2nd edition. Oxford: Wiley-Liss; 2002. Chapter 1, The Human Genome. <https://www.ncbi.nlm.nih.gov/books/NBK21134/>

³⁷⁶ National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Roundtable on Genomics and Precision Health; Forum on Drug Discovery, Development, and Translation. *Enabling Precision Medicine: The Role of Genetics in Clinical Drug Development*: Proceedings of a Workshop. Washington (DC): National Academies Press (US); 2017 July 10. 4, Integrating Genetics into the Drug Development Pathway for Complex Diseases. <https://www.ncbi.nlm.nih.gov/books/NBK458881/>

³⁷⁷ Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, Rawlings SA, Sutherland A, Premkumar L, Jadi RS, Marrama D, de Silva AM, Frazier A, Carlin AF, Greenbaum JA, Peters B, Krammer F, Smith DM, Crotty S, Sette A. *Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals*. *Cell*. 2020 June 25; 181(7):1489-1501.e15. doi: 10.1016/j.cell.2020.05.015. Epub 2020 May 20. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7237901/pdf/main.pdf>

³⁷⁸ García LF (2020) Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. *Front. Immunol.* 11:1441. doi: 10.3389/fimmu.2020.01441 <https://www.frontiersin.org/articles/10.3389/fimmu.2020.01441/pdf>

³⁷⁹ World Health Organization. What we know about the COVID-19 immune response (02 Aug 2020) www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update-34-immunity-2nd.pdf

- ³⁸⁰ NIAID Strategic Plan Details COVID-19 Research Priorities (April 22, 2020) *Immune Response to COVID-19: Comprehensive analyses of innate and adaptive immune responses during acute COVID-19 infection and convalescence*. <https://www.niaid.nih.gov/research/immune-response-covid-19>
- ³⁸¹ Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, et al. *Presence of SARS-CoV-2 reactive T cells in COVID-19 patients and healthy donors*. medRxiv. 2020:2020.04.17.20061440. <https://www.medrxiv.org/content/10.1101/2020.04.17.20061440v1.full.pdf>
- ³⁸² Karki, R., Sharma, B.R., Tuladhar, S., Williams, E.P., Zalduondo, L., Samir, P., Zheng, M., Sundaram, B., Banoth, B., Malireddi, R.K.S., Schreiner, P., Neale, G., Vogel, P., Webby, R., Jonsson, C.B., Kanneganti, T.-D. (2020) *Synergism of TNF- α and IFN- γ triggers inflammatory cell death, tissue damage, and mortality in SARS-CoV-2 infection and cytokine shock syndromes*. Cell (13 November 2020) <https://doi.org/10.1016/j.cell.2020.11.025>. [https://www.cell.com/cell/pdf/S0092-8674\(20\)31542-7.pdf](https://www.cell.com/cell/pdf/S0092-8674(20)31542-7.pdf) <https://www.biorxiv.org/content/10.1101/2020.10.29.361048v3.full.pdf>
- ³⁸³ Arunachalam PS, Wimmers F, Mok CKP, Perera RAPM, Scott M, Hagan T, Sigal N, Feng Y, Bristow L, Tak-Yin Tsang O, Wagh D, Collier J, Pellegrini KL, Kazmin D, Alaaeddine G, Leung WS, Chan JMC, Chik TSH, Choi CYC, Huerta C, Paine McCullough M, Lv H, Anderson E, Edupuganti S, Upadhyay AA, Bosinger SE, Maecker HT, Khatri P, Roupahel N, Peiris M, Pulendran B. *Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans*. Science. 2020 September 4; 369(6508): pp. 1210-1220. doi: 10.1126/science.abc6261. Epub 2020 August 11/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7665312/pdf/369_1210.pdf
- ³⁸⁴ Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, Péré H, Charbit B, Bondet V, Chenevier-Gobeaux C, Breillat P, Carlier N, Gauzit R, Morbieu C, Pène F, Marin N, Roche N, Szwedebel TA, Merkling SH, Treluyer JM, Veyer D, Mouthon L, Blanc C, Tharaux PL, Rozenberg F, Fischer A, Duffy D, Rieux-Laucat F, Kernéis S, Terrier B. *Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients*. Science. 2020 Aug 7; 369(6504): pp. 718-724. doi: 10.1126/science.abc6027. Epub 2020 July 13. <https://science.sciencemag.org/content/369/6504/718> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7402632/pdf/369_718.pdf
- ³⁸⁵ Struhl K. *Naturally occurring poly(dA-dT) sequences are upstream promoter elements for constitutive transcription in yeast*. Proc Natl Acad Sci. 1985 Dec; 82(24): pp. 8419-23. doi: 10.1073/pnas.82.24.8419 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC390927/pdf/pnas00364-0155.pdf>
- ³⁸⁶ Hasegawa Y, Struhl K. *Promoter-specific dynamics of TATA-binding protein association with the human genome*. Genome Res. 2019 Dec; 29(12): pp. 1939-1950. doi: 10.1101/gr.254466.119. Epub 2019 November 15. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6886507/pdf/1939.pdf>
- ³⁸⁷ Thompson C, Grayson N, Paton R, Lourenço J, Penman B, Lee LN, et al. *Neutralising antibodies to SARS coronavirus 2 in Scottish blood donors - a pilot study of the value of serology to determine population exposure*. medRxiv 2020. <https://www.medrxiv.org/content/10.1101/2020.04.13.20060467v2.full.pdf>
- ³⁸⁸ Tonegawa S, Steinberg C, Dube S, Bernardini A. *Evidence for somatic generation of antibody diversity*. Proc Natl Acad Sci U S A. 1974 Oct; 71(10): pp. 4027-4031. doi: 10.1073/pnas.71.10.4027. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC434321/pdf/pnas00073-0237.pdf> http://tonegawalab.mit.edu/wp-content/uploads/2014/06/087_BiosciRept_Tonegawa_1988.pdf

³⁸⁹ Janeway CA Jr, Travers P, Walport M, et al. *Immunobiology: The Immune System in Health and Disease*. 5th edition, 2001. The generation of diversity in immunoglobulins.

<https://www.ncbi.nlm.nih.gov/books/NBK27140/>

³⁹⁰ Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, O'Meara MJ, Rezelj VV, Guo JZ, Swaney DL, Tummino TA, Hüttenhain R, Kaake RM, Richards AL, Tutuncuoglu B, Foussard H, Batra J, Haas K, Modak M, Kim M, Haas P, Polacco BJ, Braberg H, Fabius JM, Eckhardt M, Soucheray M, Bennett MJ, Cakir M, McGregor MJ, Li Q, Meyer B, Roesch F, Vallet T, Mac Kain A, Miorin L, Moreno E, Naing ZZC, Zhou Y, Peng S, Shi Y, Zhang Z, Shen W, Kirby IT, Melnyk JE, Chorba JS, Lou K, Dai SA, Barrio-Hernandez I, Memon D, Hernandez-Armenta C, Lyu J, Mathy CJP, Perica T, Pilla KB, Ganesan SJ, Saltzberg DJ, Rakesh R, Liu X, Rosenthal SB, Calviello L, Venkataramanan S, Liboy-Lugo J, Lin Y, Huang XP, Liu Y, Wankowicz SA, Bohn M, Safari M, Ugur FS, Koh C, Savar NS, Tran QD, Shengjuler D, Fletcher SJ, O'Neal MC, Cai Y, Chang JCJ, Broadhurst DJ, Klippsten S, Sharp PP, Wenzell NA, Kuzuoglu-Ozturk D, Wang HY, Trenker R, Young JM, Caverio DA, Hiatt J, Roth TL, Rathore U, Subramanian A, Noack J, Hubert M, Stroud RM, Frankel AD, Rosenberg OS, Verba KA, Agard DA, Ott M, Emerman M, Jura N, von Zastrow M, Verdin E, Ashworth A, Schwartz O, d'Enfert C, Mukherjee S, Jacobson M, Malik HS, Fujimori DG, Ideker T, Craik CS, Floor SN, Fraser JS, Gross JD, Sali A, Roth BL, Ruggero D, Taunton J, Kortemme T, Beltrao P, Vignuzzi M, García-Sastre A, Shokat KM, Shoichet BK, Krogan NJ. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature*. 2020 July; 583(7816): pp. 459-468. doi: 10.1038/s41586-020-2286-9. Epub 2020 April 30.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7431030/pdf/nihms-1587111.pdf>

³⁹¹ Zhang JR, Hardham JM, Barbour AG, Norris SJ. *Antigenic variation in Lyme disease borreliae by promiscuous recombination of VMP-like sequence cassettes*. *Cell*. 1997 April 18; 89(2): 275-85.

doi: 10.1016/s0092-8674(00)80206-8. Erratum in: *Cell* 1999 February 5; 96(3): pp. 447

<https://www.cell.com/action/showPdf?pii=S0092-8674%2800%2980206-8>

³⁹² McClintock B (1950) The origin and behavior of mutable loci in maize. *Proc Natl Acad Sci USA* 36(6): 344–355. <https://www.pnas.org/content/pnas/36/6/344.full.pdf>

³⁹³ “The Nobel Prize in Physiology or Medicine 1983.” *NobelPrize.Org*

<https://www.nobelprize.org/prizes/medicine/1983/mcclintock/facts/>

³⁹⁴ “Happy Birthday, Barbara McClintock.” *Wired*.

<https://www.wired.com/2012/06/happy-birthday-barbara-mcclintock/>

³⁹⁵ Bean, W., Cox, N. and Kendal, A. *Recombination of human influenza A viruses in nature*.

Nature 284, 638–640 (1980) <https://doi.org/10.1038/284638a0>

³⁹⁶ Pays E, Van Assel S, Laurent M, Darville M, Vervoort T, Van Meirvenne N, Steinert M. *Gene conversion as a mechanism for antigenic variation in trypanosomes*. *Cell*. 1983 Sep; 34(2): pp.371-381

doi: 10.1016/0092-8674(83)90371-9. [https://www.cell.com/cell/pdf/0092-8674\(83\)90371-9.pdf](https://www.cell.com/cell/pdf/0092-8674(83)90371-9.pdf)

- ³⁹⁷ Scherf A, Hernandez-Rivas R, Buffet P, Bottius E, Benatar C, Pouvelle B, Gysin J, Lanzer M. *Antigenic variation in malaria: in situ switching, relaxed and mutually exclusive transcription of var genes during intra-erythrocytic development in Plasmodium falciparum*. EMBO J. 1998 Sep 15; 17(18): pp. 5418-5426. doi: 10.1093/emboj/17.18.5418
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1170867/pdf/005418.pdf>
- ³⁹⁸ Khailany RA, Safdar M, Ozaslan M. *Genomic characterization of a novel SARS-CoV-2*. Gene Rep. 2020 June; 19:100682. doi: 10.1016/j.genrep.2020.100682. Epub 2020 April 16.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7161481/pdf/main.pdf>
- ³⁹⁹ Bar-On YM, Flamholz A, Phillips R, Milo R. SARS-CoV-2 (COVID-19) by the numbers. Elife. April 2, 2020. 9:e57309. doi: 10.7554/eLife.57309
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7224694/pdf/elife-57309.pdf>
- ⁴⁰⁰ Oliphant, A. R. and Struhl, K. *An efficient method for generating proteins with altered enzymatic properties: application to beta-lactamase*. Proc Natl Acad Sci U S A. 1989 December; 86(23): pp. 9094-9098. doi: 10.1073/pnas.86.23.9094. Erratum in: Proc Natl Acad Sci 1992 May 15; 89(10): pp. 4779.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC298440/pdf/pnas00290-0052.pdf>
- ⁴⁰¹ B. N. Fields and Karen Byers (1983) "The Genetic Basis of Viral Virulence." *Philosophical Transactions of the Royal Society of London. B, Biological Sciences*, vol. 303, no. 1114, 15 September 1983, pp. 209–218. doi:10.1098/rstb.1983.0094
<https://royalsocietypublishing.org/doi/pdf/10.1098/rstb.1983.0094>
- ⁴⁰² Yanofsky, Charles. "Establishing the Triplet Nature of the Genetic Code." *Cell*, vol. 128, no. 5, March 2007, pp. 815-818. doi:10.1016/j.cell.2007.02.029.
<https://www.cell.com/action/showPdf?pii=S0092-8674%2807%2900253-X>
- ⁴⁰³ Matthaei JH, Jones OW, Martin RgG and Nirenberg MW. *Characteristics and composition of RNA coding units*. Proc Natl Acad Sci U S A. 1962 April 15; 48(4):666-77. doi: 10.1073/pnas.48.4.666.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC220831/pdf/pnas00227-0188.pdf>
- ⁴⁰⁴ <https://www.genome.gov/genetics-glossary/Genetic-Code>
- ⁴⁰⁵ Ramachandran GN, Ramakrishnan C and Sasisekharan V. *Stereochemistry of polypeptide chain configurations*. J Mol Biol. 1963 July; 7:95-99. doi: 10.1016/s0022-2836(63)80023-6.
- ⁴⁰⁶ Tapscott SJ. The circuitry of a master switch: MyoD and the regulation of skeletal muscle gene transcription. Development. 2005 June; 132(12):268526-95. doi: 10.1242/dev.01874.
<https://dev.biologists.org/content/develop/132/12/2685.full.pdf>
- ⁴⁰⁷ Kang, Hyuckjoon, et al. "Bivalent Complexes of PRC1 with Orthologs of BRD4 and MOZ/MORF Target Developmental Genes in *Drosophila*." *Genes & Dev*, vol. 31, no. 19, Oct. 2017, pp. 1988–2002 doi:10.1101/gad.305987.117
- ⁴⁰⁸ Andrew Wilber, Arthur W. Nienhuis, Derek A. Persons; Transcriptional regulation of fetal to adult hemoglobin switching: new therapeutic opportunities. *Blood* 2011; 117 (15): 3945–3953.
<https://doi.org/10.1182/blood-2010-11-316893>
<https://ashpublications.org/blood/article-pdf/117/15/3945/1461649/zh801511003945.pdf>

- ⁴⁰⁹ Cho, JH., Tsai, MJ. The role of *BETA2/NeuroD1* in the development of the nervous system. *Mol Neurobiol* **30**, 35–47 (2004). <https://doi.org/10.1385/MN:30:1:035>
- ⁴¹⁰ Chen YC, Ma NX, Pei ZF, Wu Z, Do-Monte FH, Keefe S, Yellin E, Chen MS, Yin JC, Lee G, Minier-Toribio A, Hu Y, Bai YT, Lee K, Quirk GJ, Chen G. A *NeuroD1* AAV-Based Gene Therapy for Functional Brain Repair after Ischemic Injury through In Vivo Astrocyte-to-Neuron Conversion. *Molecular Therapy* 2020 January 8; 28(1):217–234. doi: 10.1016/j.ymthe.2019.09.003. Epub 2019 September 6. [www.cell.com/molecular-therapy-family/molecular-therapy/pdfExtended/S1525-0016\(19\)30404-6](http://www.cell.com/molecular-therapy-family/molecular-therapy/pdfExtended/S1525-0016(19)30404-6)
- ⁴¹¹ Deshmukh R, Lakhe D, Kunte K. (2020) *Tissue-specific developmental regulation and isoform usage underlie the role of doublesex in sex differentiation and mimicry in Papilio swallowtails*. *Royal Society Open Science* **7**: 200792. <http://dx.doi.org/10.1098/rsos.200792> <https://royalsocietypublishing.org/doi/pdf/10.1098/rsos.200792>
- ⁴¹² Zhang Z, Zhan X. GNSS Spoofing Network Monitoring Based on Differential Pseudorange. *Sensors* (Basel). 2016 October 23; 16(10):1771. doi: 10.3390/s16101771. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5087555/pdf/sensors-16-01771.pdf>
- ⁴¹³ Kalsotra A, Cooper TA. *Functional consequences of developmentally regulated alternative splicing*. *Nature Reviews Genetics* 2011 September 16; 12(10):715–29. doi: 10.1038/nrg3052. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3321218/pdf/nihms-366480.pdf>
- ⁴¹⁴ Weyn-Vanhentenryck, S.M., Feng, H., Ustianenko, D. *et al.* Precise temporal regulation of alternative splicing during neural development. *Nature Communications* **9** 2189 (2018). <https://doi.org/10.1038/s41467-018-04559-0> <https://www.nature.com/articles/s41467-018-04559-0.pdf>
- ⁴¹⁵ <https://www.fda.gov/media/137564/download>
- ⁴¹⁶ Carey, Benedict. “W.H.O. Rejects Antiviral Drug Remdesivir as a Covid Treatment.” *The New York Times*, 20 November 2020. <https://www.nytimes.com/2020/11/19/health/remdesivir-covid-19.html>
- ⁴¹⁷ Lalmuanawma S, Hussain J, Chhakchhuak L. *Applications of machine learning and artificial intelligence for Covid-19 (SARS-CoV-2) pandemic: A review*. *Chaos Solitons Fractals*. 2020 Oct; 139:110059. doi: 10.1016/j.chaos.2020.110059. Epub 2020 June 25. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7315944/pdf/main.pdf>
- ⁴¹⁸ Whitelaw, Sera, et al. “Applications of Digital Technology in COVID-19 Pandemic Planning and Response.” *The Lancet Digital Health*, vol. 2, no. 8, August 2020, pp. e435–40. doi:10.1016/S2589-7500(20)30142-4 <https://www.thelancet.com/action/showPdf?pii=S2589-7500%2820%2930142-4>
- ⁴¹⁹ J. Laguarda, F. Hueto and B. Subirana, "COVID-19 Artificial Intelligence Diagnosis using only Cough Recordings," in *IEEE Open J of Engineering in Medicine and Biology*, doi: 10.1109/OJEMB.2020.3026928. <https://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=9208795>
- ⁴²⁰ Yglesias, Matthew. “‘No Malarkey,’ Joe Biden’s Unabashedly Lame New Slogan, Explained.” *Vox*, 3 December 2019. <https://www.vox.com/policy-and-politics/2019/12/3/20991841/joe-biden-no-malarkey>

Cartoon for Reference # 363: Machine Learning Algorithms – ML makes better sense without the misnomer of AI

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