KFAS COVID-19 WEEKLY BRIEF OF OCTOBER 2020
**Executive Summaries**

**Infection Control and Prevention:** Combating the COVID-19 pandemic will involve driving down both transmission rates and severity of disease. There is increasing evidence that suggests that universal facial mask-wearing might benefit both components of the response. Researchers are theorizing that masks not only protect the wearer from becoming infected, by blocking viral particles from entering the nose and mouth, but even if small amounts virus slips through it will decrease the viral load significantly. This will result in stimulating an immune response that can protect the individual from future attacks but not severe enough to make an individual sick. In other words masks may allow us to become immune and remain asymptomatic.

**Diagnosis and Testing:** At-home Covid-19 tests would allow patients to collect their own samples and save health professionals valuable personal protective equipment (PPE) and time needed for sample collection. However, these tests still require labs for processing and often struggle to deliver results quickly due to shortages in equipment and personnel at processing labs. Enter the new at-home test from computer vision company Gauss, and biotech company Cellex, the first test that can be “fully performed at home without involving a laboratory”. Although the test has not yet received an Emergency Use Authorization (EUA) from the US Food and Drug administration (FDA), its approval and release could reduce pressure on labs and offer schools, businesses, and community living centers the rapid testing needed to quickly identify and isolate positive Covid-19 cases. The Gauss-Cellex Rapid At-Home Test promises results in 15 minutes and can be performed by any individual with a smartphone, anywhere with a reported sensitivity of 90%.

**Treatment and Therapies:** The speed of COVID-19 vaccine development has led to questions about the safety of the vaccines. Are expected and required standards of scientific rigor being compromised in the race to effective vaccines? Will the vaccines be safe? Because vaccines are administered to healthy children and adults to keep them healthy, vaccine safety is of the utmost importance. The response to this legitimate concern should be strong and certain: there will be no compromises in the scientific assessment of vaccines in clinical trials, even though the development processes are on accelerated timelines, as is appropriate in this global emergency. Vaccine developers and manufacturers, engaged government agencies, and clinical trialists and laboratorians at academic institutions and clinical research organizations are achieving speed through intense effort; use of pre-existing and rapid vaccine platforms (e.g., RNA, nonreplicating viral vectors); and the performance of certain research steps and at-risk manufacturing in parallel rather than in series, in accordance with US Food and Drug Administration (FDA) guidance. All standard safety assessments are being completed; to do less would be unethical.

The RNA sequence of the SARS-CoV-2 genome was made public on January 10, 2020. Candidate vaccines emerged rapidly for human safety and immunogenicity studies. Interim reports of short-term follow-up after vaccination of tens or hundreds of study participants indicated that these candidate vaccines are safe and produce immune responses that might be protective. Longer-term vaccine safety and the duration of vaccine-induced immune responses continue to be studied. The critical questions of vaccine efficacy and safety in thousands of participants will largely be answered in phase 3 vaccine efficacy trials, a few of which have recently begun.

Protein immunogens are a different, and traditional, category of anticipated COVID-19 vaccines. Protein immunogens may be delivered as viral subunit proteins, virus-like particles, or as inactivated virus; are produced in a laboratory; and are often administered with an adjuvant to increase response magnitude and durability. Xia1 and colleagues' preliminary report indicates that the inactivated whole-virus vaccine candidate was tolerated, safe, and produced neutralizing antibodies at 14 days after booster vaccination.
Exit Strategies:
The COVID-19 pandemic has presented an opportunity to further the evolution of precision public health, in order to mitigate risk and to help the transition from response to recovery. To establish such an approach will require investment in technology and infrastructure to drive the evidence and data needed for decision making, and in developing tailored and targeted interventions to address a public health emergency at a given time. Developing this capability, will also allow for a better understanding on how to best integrate these data sources to inform public health as a means to address the continued challenges of the COVID-19 pandemic and for any future public health emergencies that may arise.
Scientists relieved as coronavirus vaccine trial restarts — but question lack of transparency Nature

Eli Lilly reports first, promising results for an antibody against COVID-19 Science

Coronavirus: Marseille’s Covid-19 hospital beds ‘close to saturation’ BBC

Study hints Covid-19 may have been in the US as early as December CNN

COVID-19: Antibody fragment could prevent infection Medical News Today

From leprosy to COVID-19, how stigma makes it harder to fight epidemics Science

Sweden spared European surge as coronavirus infections stay low The Guardian

COVID-19 may become a seasonal virus Live Science

Defining COVID-19 immunity: CDC, EU researchers tap Siemens Healthineers to help standardize antibody tests Fierce Biotech

New report says Covid-19 pandemic has caused historic setbacks in global health STAT

Blood Clotting Tied to Worse COVID-19 Outcomes WebMD

As Campuses Become COVID-19 Hot Spots, Colleges Strain Under Financial Pressures NPR

Stress, anxiety and depression levels soar under UK Covid-19 restrictions The Guardian

As evidence builds that COVID-19 can damage the heart, doctors are racing to understand it Science

UK to ration COVID-19 testing amid testing failures ABC News

CDC study: Covid-19 complications killed 121 Americans under age 21 through July STAT

In WHO global pulse survey, 90% of countries report disruptions to essential health services since COVID-19 pandemic WHO

How COVID-19 can damage the brain Nature

NIH awards contracts to develop innovative digital health technologies for COVID-19 NIH

Coronavirus: Commission starts testing interoperability gateway service for national contact tracing and warning apps EU

Does Wearing Glasses Protect You From Coronavirus? NY Times

Fast coronavirus tests: what they can and can’t do Nature

As Second Wave of Virus Builds, U.K. Enters New Testing Crisis NY Times

NIH ‘Very Concerned’ about Serious Side Effect in Coronavirus Vaccine Trial Scientific American

The lasting misery of coronavirus long-haulers Nature
As the COVID-19 pandemic continues to spread around the world and the world awaits for the arrival of a safe and effective vaccine, a new theory has made its way into the public eye: that masks might help to crudely immunize some people against the virus.

**What is Variolation?**

Variolation (or inoculation) was the deliberate inoculation of an uninfected person with the smallpox virus through pustular matter. The practice was widely practiced before the era of vaccination as prophylaxis against the severe form of smallpox. The risky procedure eventually fell out of favor but paved the way for the rise of modern vaccines.

A long-standing viral pathogenesis theory states that the disease's severity is proportionate to the viral inoculum (or viral load) received. With viral infections in which the host's immune reaction plays a predominant role in viral pathogenesis, such as SARS-CoV-2, high doses of viral inoculum can overwhelm and dysregulate the immune defenses and increasing the severity of the disease.

**How can masks be a form of variolation?**

Facial masks help by reducing the amount of viral count that enters into an individual's airway. In this manner, it may reduce that individual's chances of getting sick. Suppose a small number of pathogens still slip through the facial mask. In that case, these pathogens might then stimulate the body to produce immune cells that can remember the virus and fight it off again without overwhelming and dysregulating the immune system leaving the patient asymptomatic (or with very mild symptoms). In this manner, the individual may have the virus but remain asymptomatic. By universal mask-wearing, rates of asymptomatic infection with masks will increase and hence variolate the population.

**What is the supporting evidence?**

The theory that masks may be a form of variolation is still unproven. However, the authors of the commentary on this theory released by the New England Journal of medicine use the following evidence:
1. **Scientific hypothesis:**

If the viral inoculum matters in determining the severity of SARS-CoV-2 infection, an additional hypothesized reason for wearing facial masks would be to reduce the viral inoculum the wearer is exposed to and the subsequent clinical impact of the disease. Since masks can filter out some virus-containing droplets (with filtering capacity determined by mask type), masking might reduce the inoculum that an exposed person inhales. If this theory is correct, population-wide masking, with any mask that increases acceptability and adherence, might contribute to increasing the proportion of SARS-CoV-2 infections that are asymptomatic.

2. **Observational evidence:**

   a. The typical rate of asymptomatic infection with SARS-CoV-2 was estimated to be 40% by the CDC in mid-July, but asymptomatic infection rates are reported to be higher than 80% in settings with universal facial masking.

   b. Countries that have adopted population-wide masking have fared better in terms of rates of severe COVID-19-related illnesses and death, which, in environments with limited testing, suggests a shift from symptomatic to asymptomatic infections.

   c. In an outbreak on a closed cruise ship, where passengers were provided with surgical masks and staff with N95 masks, the rate of asymptomatic infection was 81%. This is in stark comparison with 20% in earlier cruise ship outbreaks without universal masking.

   d. In two recent outbreaks in U.S. food-processing plants, where all workers were issued masks each day and were required to wear them, the proportion of asymptomatic infections among the more than 500 people who became infected was 95%, with only 5% in each outbreak experiencing mild-to-moderate symptoms.

   e. Case-fatality rates in countries with mandatory masking have remained low, even with numbers increased after lockdowns were lifted.

   f. Data linking dose to symptoms have been gathered for other pathogens that attack the human airway, including influenza viruses and tuberculosis.

3. **Animal studies:**

An experiment done on hamsters showed that when they the hamsters wore simulated surgical masking, they were less likely to get infected, and if they did get infected, they either were asymptomatic or had milder symptoms than unmasked hamsters.
The variolation theory has gained traction; however, it remains mostly unproven. Below are the main issues with acquiring evidence for the theory:

a. The theory cannot be proven without clinical trials that compare the outcomes of people who are masked in the presence of the SARS-CoV-2 virus with those who are unmasked. A trail that will be difficult to accomplish ethically.

b. The variolation theory for SAR-CoV-2 is based on two main assumptions that are difficult to prove. Lower doses of the virus lead to less severe disease, and mild or asymptomatic infections can lead to long-term immunity. Although studies on pathogens offer some precedent for both concepts, the evidence for the SARS-CoV-2 remains sparse.

c. The exact mechanics of airborne transmission remains mostly unknown. It is difficult to identify the infectious dose required to make an individual "sick." Disease severity also will vary from person to person. Factors such as genetics, immune status, nasopharyngeal anatomy, and existing comorbidities can influence how much the virus can colonize the respiratory tract.

Bottom line

1. Universal facial masking remains a central pillar in controlling the COVID-19 pandemic.

2. Universal facial masking might help reduce the severity of disease and ensure that a greater proportion of new infections are asymptomatic.

3. Public health measures like universal facial masking could increase population-wide immunity without severe illnesses and deaths.

4. Masked exposures are no substitute for a safe and effective vaccine.

5. Universal facial masking should be part of a broader prevention strategy: avoiding crowds, physical distancing, and hand hygiene. All these behaviors overlap in their effects but do not replace one another.

6. To test the variolation hypothesis, more studies are needed to compare the strength and durability of SARS-CoV-2-specific T-cell immunity between people with asymptomatic infection and those with symptomatic infection.

7. Studies demonstrating the natural slowing of SARS-CoV-2 spread in areas with a high proportion of asymptomatic infections are also needed.


NYT: A New Theory Asks: Could a Mask Be a Crude Vaccine? By Katherine J. Wu https://nyti.ms/3FgoW4C
At-home rapid Covid-19 tests have been hailed as game changers, allowing patients to collect their own samples and saving health professionals valuable personal protective equipment (PPE) needed for sample collection. However, these tests still require labs for processing and often struggle to deliver results quickly due to shortages in equipment and personnel at processing labs. Enter the new at-home test from computer vision company Gauss, and biotech company Cellex, the first test that can be “fully performed at home without involving a laboratory.”^{1} Although the test has not yet received an Emergency Use Authorization (EUA) from the US Food and Drug administration (FDA), it could reduce pressure on labs and offer schools, businesses, and community living centers the rapid testing needed to quickly identify and isolate positive Covid-19 cases.

SalivaDirect test offers similar sensitivity to standard RT-PCR techniques

The Gauss-Cellex Rapid At-Home test is an antigen test, meaning it tests for and identifies specific viral proteins found on the surface of the virus. Antigen tests identify individuals that are currently infected by the virus, unlike antibody tests which identify those previously infected, but are less sensitive than the golden standard PCR tests which test for viral genetic material. PCR tests are able to identify a single molecule of viral RNA when performed correctly, while antigen-based tests need thousands of viral particles for detection to occur and perform best within one week of symptom onset.

Antigen tests, though less sensitive, are faster, cheaper and easier to perform. Some antigen tests that have already received FDA Emergency Use Approval include tests from pharmaceutical companies Abbott, Quidel, and Becton Dickinson (BD) and have been reviewed in previous publications.^{2} Quidel reported a test sensitivity of 96.7% for their antigen-based rapid test, while BD reported a sensitivity of around 84%. While lab-based analysis of antigen tests have a higher sensitivity than at-home tests, home tests offer faster results and the opportunity for repeat tests to confirm results.\(^{3}\) Most antigen tests are currently being administered by trained professionals but others, like the Gauss-Cellex assay or a test currently in development from Sona Nanotech, hope to make the assays as available and easy to use as at-home pregnancy tests.\(^{4}\)

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The at-home test by Gauss-Cellex is simple enough to be performed by any individual with a smartphone, anywhere and promises results in 15 minutes. If validated, this test would allow for easy identification of even asymptomatic individuals through widespread routine use, and enable those with negative results to return to day-to-day activities stress-free. Test users would download an application on their smartphones and follow step-by-step video instructions in the app to correctly collect a nasal swab sample from both nostrils and place the swab in a small vial with a buffer liquid solution. Next four drops from the liquid solution are placed in a rapid test cassette (similar to a pregnancy test cassette) and the user is instructed to wait for lines to appear. Once the lines appear about 15 minutes later, the user is instructed to upload an image of the results and the application uses artificial intelligence (AI) based neural network software to read and analyze the lines, producing a positive or negative result within seconds. The application is encrypted and HIPAA-compliant for patient privacy and security.5,6

This test would be the first test that can be completed to results at home, and according to Cellex CEO James Li, has shown a sensitivity of nearly 90% and a specificity of about 100%. The CEO also emphasizes this test is significant in that it allows for self-monitoring and self-isolation which is essential for the future of managing the Covid-19 pandemic. FDA Emergency use approval would be the final step in ensuring this test is made widely available in the near future and should be tracked.7

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The so-called genetic immunization candidate vaccines, including messenger RNA, DNA, and nonreplicating viral vectors such as recombinant adenovirus, were the first vaccine candidates to report interim results of early-phase clinical trials because these platforms are pre-existing, flexible, rapid, and scalable. Therefore, genetic immunization approaches are particularly suited to a rapid pandemic response. While no genetic immunization vaccine has ever been licensed by the FDA for human use, these platforms hold great promise. Genetic immunization candidates can be seen as mimics of natural infection or of traditional live-attenuated vaccines, like the measles-mumps-rubella vaccine. These vaccines deliver instructions, encoded in nucleic acid sequences, that direct the body's cells to manufacture the vaccine protein in vivo. The safety of these vaccines will be of interest to scientists, regulators, and the public.

Protein immunogens are a different, and traditional, category of anticipated COVID-19 vaccines. Protein immunogens may be delivered as viral subunit proteins; virus-like particles, or as inactivated virus; are produced in a laboratory; and are often administered with an adjuvant to increase response magnitude and durability. The hepatitis A vaccine and the Salk inactivated polio vaccine are examples of licensed inactivated whole-virus vaccines.

Xia and colleagues¹ report results from an interim analysis of data for a SARS-CoV-2–inactivated virus vaccine plus adjuvant, the first protein immunogen COVID-19 vaccine candidate to be reported. The authors report preliminary findings from phase 1 and 2 randomized, active-controlled (aluminum hydroxide [alum]), double-blind, clinical trials of a β-propiolactone–inactivated SARS-CoV-2 vaccine adjuvanted in 0.5 mg of aluminum hydroxide. Healthy participants aged 18 to 59 years were enrolled and the trials were conducted in Henan Province, China. In phase 1, which included 96 healthy adults, 3 immunogen (inactivated virus) dose levels were studied (2.5, 5, and 10 µg, and an alum adjuvant–only dose; 24 participants in each group) and 3 vaccinations were administered on days 0, 28, and 56. For phase 2, which included 224 healthy adults, the middle dose (5 µg) was selected and administered twice at intervals shorter than in phase 1, either days 0 and 14 or days 0 and 21 (n=84 in each group; plus 28 alum-only participants for each schedule).
Tolerability was assessed with a diary card, which participants completed for 7 days after each vaccination and recorded the presence, severity, and duration of solicited local reactions (e.g., injection site pain, redness, swelling) and solicited systemic reactions (e.g., fever, headache, fatigue). Safety was assessed by analysis of blood chemistry and hematology at 4 days after each injection and by collection of unsolicited adverse events and serious adverse events occurring during the 28-day period after vaccinations. The primary immunogenicity end point was SARS-CoV-2 neutralization measured as a 50% plaque reduction neutralization test (PRNT50) of serum samples collected 14 days after final vaccination. This preliminary report indicates that the inactivated whole-virus vaccine candidate was tolerated, safe, and produced neutralizing antibodies at 14 days after booster vaccination. The primary safety outcome, 7-day post injection adverse reactions, occurred in the phase 1 trial in 3 (12.5%), 5 (20.8%), 4 (16.7%), and 6 (25.0%) patients in the alum-only, low-dose, medium-dose, and high-dose groups, respectively, and in the phase 2 trial occurred in 5 (6.0%), 4 (14.3%), 16 (19.0%), and 5 (17.9%) patients in the days 0 and 14 vaccine, days 0 and 14 alum-only, days 0 and 21 vaccine, and days 0 and 21 alum-only groups, respectively. The most common adverse events were injection site pain, followed by fever, both of which were self-limited and mild. For the primary immunogenicity outcome, neutralizing antibody response at 14 days after the final booster vaccination, the geometric mean titers of neutralizing antibodies in the phase 1 trial in the low-, medium-, and high-dose groups were 316 (95% CI, 218-457), 206 (95% CI, 123-343), and 297 (95% CI, 208-424), respectively, and in the phase 2 trial were 121 (95% CI, 95-154) and 247 (95% CI, 176-345), respectively, in the days 0 and 14 and days 0 and 21 vaccine groups.

Acknowledged and acceptable limitations of the interim report of the ongoing phase 1/2 studies included the absence of data for persistence of antibody response, the absence of longer-term safety information, and the inability to assess vaccine protection against COVID-19. Additional follow-up in the ongoing phase 1/2 studies, and ultimately a phase 3 efficacy trial, would be required to address these important aspects.

The solicited local and systemic adverse reactions were not significantly different between the vaccine groups and the active control (alum) groups. This suggests that the adjuvant was responsible for the reactogenicity observed in the vaccine groups. The use of an active control agent that produces reactogenicity can be helpful for participant and investigator blinding to study group assignment, a design feature that was included in another phase 1/2 trial.

Another limitation of this report is the absence of a comparison group to provide a benchmark for the magnitude of the reported serum neutralization titers in this PRNT50 assay. Published studies of candidate COVID-19 vaccines have included the titers of serum neutralization of SARS-CoV-2 for convalescent patients who have recovered from COVID-19 illness. Although a threshold titer of serum neutralization that is associated with protection against disease has not been identified, the titers of convalescent serum samples provide an imperfect positive control benchmark. Preferably, these control serum samples would be collected from recovered symptomatic patients at 4 to 6 weeks after onset of symptoms (to approximate the timing of early post vaccination serum samples) and be identified as outpatients vs hospitalized patients.

The authors also appropriately comment on the selection of β-propiolactone as the inactivating agent and of alum as the adjuvant. Alum is an adjuvant known to induce a Th2-biased T-cell response. In earlier human trials of certain whole-virus inactivated vaccines (respiratory syncytial virus and measles), vaccine-associated enhanced respiratory disease was observed for formalin-inactivated, alum-adjuvanted vaccines, and a Th2-like response was observed when natural infections occurred after vaccination.
In the Discussion section of their article, Xia et al. noted that antibody-dependent enhancement was not observed in vivo in a vaccination plus challenge model in nonhuman primates. In the supplemental information, the authors report immunophenotyping of circulating lymphocytes and serum cytokine levels after vaccination, but determination of the Th1 vs Th2 cytokines produced after vaccination by the memory cells on re-stimulation by SARS-CoV-2 antigens in vitro is not reported and should be profiled.

In summary, this preliminary report by Xia et al. provides important interim safety, tolerability, and immune response results for a β-propiolactone–inactivated whole-virus vaccine against COVID-19. These interim data are of interest given the urgent global need for protective COVID-19 vaccines. With 7.8 billion individuals worldwide at risk for SARS-CoV-2 infection and COVID-19 morbidity and mortality, humanity needs as many safe and protective COVID-19 vaccines as possible.


Lancet Study finds Russian vaccine safe and effective

Russia’s ‘Sputnik V’ COVID-19 vaccine, approved in Russia on 26th August 2020, produced antibody response in all participants with no serious adverse events in small human trials, according to the first peer-reviewed results of the preventive published in The Lancet journal2 on Friday 4th September 2020.

Results from early-phase non-randomised vaccine trials in a total of 76 people show that two formulations of the vaccine have a good safety profile detected over 42 days and induce antibody responses in all participants within 21 days. Secondary outcomes from the trial suggest the vaccine, also produces a T cell response within 28 days, the researchers said2.

The two-part vaccine includes recombinant human adenovirus type 26 (rAd26-S) and recombinant human adenovirus type 5 (rAd5-S), which have been modified to express the SARS-CoV-2 spike protein. The adenoviruses, which usually cause the common cold, are also weakened so that they cannot replicate in human cells and cannot cause disease, according to the researchers.

These vaccines aim to stimulate both arms of the immune system - antibody and T cell responses - so they attack the virus when it is circulating in the body, and also attack cells infected by SARS-CoV-2. The trials took place in two hospitals in Russia, and were open-label and non-randomised, meaning that participants knew that they were receiving the vaccine and were not assigned by chance to different treatment groups.

The trials involved healthy adults aged 18-60 years, who self-isolated as soon as they were registered, and remained in hospital for the first 28 days of the trial from when they were first vaccinated. In the phase 1 of each trial, participants received one component of the two-part vaccine - four groups of nine participants were given the frozen or freeze-dried rAd26-S or rAd5-S component. In the phase 2, which began no earlier than five days after the phase 1 trial began, participants received the full two-part vaccine. There were 20 participants each in the frozen and freeze-dried vaccine groups, the Lancet study noted.

To compare post-vaccination immunity with natural immunity formed by infection with SARS-CoV-2, the authors obtained convalescent plasma from 4,817 people who had recovered from mild or moderate COVID-19, they said. Both vaccine formulations were safe over the 42-day study period and well tolerated, according to the study. The most common adverse events were pain at the injection site, hyperthermia, headache, weakness or lack of energy, and muscle and joint pain.
The authors note that these adverse effects are also seen with other vaccines, particularly those based on recombinant viral vectors.

Responding to the findings, Naor Bar-Zeev from Johns Hopkins Bloomberg School of Public Health, US, who was not involved in the study said\(^2\) the trial results are encouraging but small on scale. The authors note some limitations to their study, including that it had a short follow-up (42 days), it was a small study, some parts of the phase 1 trials included only male volunteers, and there was no placebo or control vaccine. In addition, they note that despite planning to recruit healthy volunteers aged 18-60 years, in general, their study included young volunteers (in their 20s and 30s, on average). Therefore, more research is needed to evaluate the vaccine in different populations, including older age groups, individuals with underlying medical conditions, and people in at-risk groups.

Explaining the next steps of their research, Professor Alexander Gintsburg, from Gamaleya National Research Centre for Epidemiology and Microbiology said the phase 3 clinical trial of the vaccine has been approved on August 26, 2020. "It is planned to include 40,000 volunteers from different age and risk groups and will be undertaken with constant monitoring of volunteers through an online application," Gintsburg added\(^2\).

From the start of the pandemic, public health officials have been scrambling to find key interventions and public health tools to mitigate the impact of COVID-19, such as lockdowns and stay-at-home mandates. As the pandemic evolved, the nature of the interventions expanded and shifted, based on the availability of real-time information and the increase in research data. Hence, increased knowledge and information on those at highest risk for hospitalization and the severity of infection, as well as the correlation to age, sex, race/ethnicity, and the presence of co-morbidities, have helped public health officials and practitioners better address the challenges associated with the pandemic.

However, more often than not, the interventions have taken a one-size fits all approach. The increase in the availability of information and research data on the science of the virus and its implications, allows for the possibility of using precision public health interventions, which may be a more feasible approach. Precision public health involves using more targeted and tailored interventions based on evidence and data, at a particular point in time. Thus, rather than relying on a one-size fits all approach, through the use of extensive population-specific data, interventions can be tailored to a certain population within a given time period. This concept is based on the same principle of precision (sometimes also known as personalized) medicine, which looks at using genomic data to allow practitioners to derive an appropriately tailored treatment for a patient at a given time.

Precision public health uses genomic and epidemiological data, as a way to define interventions to mitigate transmission patterns. For example, during the COVID-19 pandemic, the Netherlands used data from whole genome sequencing and the National Public Health response team, to drive evidence based decision making. In the study published by Munnick et al. the collection of the combined genomic and epidemiological data allowed for a better understanding of the genetic diversity of the virus during the first phase the pandemic, the extent of local and regional clusters in second phase and the transmission patterns among healthcare workers during the third phase, which complemented the data collected from contact tracing. This approach allowed for a more comprehensive assessment of the extent and type of non-pharmaceutical interventions for implementation, such as cancelation of schools, work, and large gatherings.

Beyond genomic data, for precision public health to be effective, information from public health surveillance tools are important in developing targeted interventions. This includes ensuring that location-dependent data is available on testing, such as the number of tests and positivity rate, and on the healthcare capacity, such as the number of hospitalizations and intensive care unit admissions, as well as the number of fatalities. In addition, information regarding the availability of resources, which include numbers on people and equipment, also need to be captured and accessible.

Having a comprehensive dataset, will effective in providing guidance towards designing optimal interventions based on the profile of the pandemic within a specific community at a given point in time. Furthermore, the use of geographical information systems and other technologies, will foster the type and amount of data available for decision making.

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**What does a precision public health approach look like? If the data is available, the approach would include the:**

- **Identification of hot spots of infection:** Information on the number of daily cases per 100,000 people, as well as percent positivity rate on tests that are administered, can be used to determine communities that are considered “hot spots” or dealing with high infection rates. Once the “hot spot” is identified, targeted interventions would be designed, such as testing of individuals in those communities, rather than rolling out a mass testing effort. This is particularly useful if testing resources are limited. Furthermore, knowing the number of new infections, as well as information on the healthcare capacity of the community, would also allow for real-time decision making for reopening public spaces, work, and schools. This information, for example, was used by the Atlanta mayor to base decisions on reopening.

- **Community-level interventions:** Effectively addressing high risk communities, through restricting access to nursing homes, long-term care facilities, and testing of residents within a high risk community, were shown to be effective in controlling outbreaks and ultimately reducing the number of deaths. Using precision public health, specific tailored interventions can be developed for communities of highest risk for morbidity and mortality, which will lead to greater benefits, rather than a single approach for dealing with high and low risk communities. This could mean that there are more resources allocated to the high risk communities for awareness and prevention tools, as well as tailored messaging and guidance based on the demographics of the population (i.e. specific racial/ethnic groups). Using data on infection risks based on neighborhood factors, such as lower median household income, higher employment, and household crowding rates, will also allow for targeted interventions. For example, if isolation for a patient infected with COVID-19 is not possible due close living quarters, or limited options for isolating outside the family home, then programs could be established, such as offering hotel rooms for infected individuals, as a way to decrease transmission.

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Expand the use of digital data\textsuperscript{6}: The use of technology and digital data to support predictive analyses are essential components of precision public health measures. This involves using technologies, such as cell phone mobility data, wearable devices, and geographical information systems (GIS), which can be effective for contact training, the dissemination of information and messaging for hot spot areas, as well as ensuring public compliance on mitigation strategies, such as wearing masks. In the United States, during lockdown, aggregated anonymized location data on mobility from cell phones were used to assess adherence with community mitigation measures.\textsuperscript{9} Other examples of using technological applications for mitigating the pandemic included the use of fitness trackers for tracking heart rates and assessing viral levels in sewage.\textsuperscript{10} Overall these tools could provide evidence of community nonadherence to mitigation measures, potentially predicting impending outbreaks, and fostering decisions for establishing the public health infrastructure and systems needed to limit transmission, such as adequate testing and contact tracing initiatives.

**PRECISION MEDICINE AND COVID-19**

The pandemic has also catalyzed the global health community’s acceptance and use of digital health technologies, such as telemedicine and digital therapeutics. The use of digital therapeutics, one of the emerging fields in digital health, has the ability to deliver personalized, targeted patient-centered care.\textsuperscript{11} There has been much hype, in recent years, about using precision medicine and a gene-centric approach to care, and has been considered the future of medical care. Much investment has been made in trying to deliver a precision medicine platform. The U.S. National Institutes of Health created the “All of Us” initiative in 2015, in which the goal was to collect over a million DNA samples.\textsuperscript{12}

What about the application of precision medicine to a pandemic? In relation to COVID-19, the role, so far, has been limited, mainly because a more integrated omics approach with information about societies, is needed. Furthermore, for some types of disease, such as certain cancers, the presence of certain genes indicates risk for a particular disease, but does not fully determine the fate of an individual carrying the genes. In the case of a pathogen, their genomes interact in complex molecular ways in cells they infect, and interactions between the RNA of SARS-CoV-2 and human DNA are still unknown.\textsuperscript{13} Nevertheless, there is an opportunity to begin gathering information on a pathogen, such as COVID-19, where the data could allow for a more comprehensive precision medicine approach that integrates complex interactions between genes and social behavior. This would involve analyzing the genomes of symptomatic and asymptomatic individuals, as well as those with identified risk factors that are severely or fatally ill.\textsuperscript{13}


An example of such study was completed a company called Precisionlife, where researchers mined the data of 976 genetic samples taken from known COVID-19 cases. Through their analyses, they were able to identify 68 high risk genes that were linked to poor COVID-19 outcomes. The variants were found in genes relating to the immune response pathway and cytokine production cascades, and interestingly were independent of the severity of the infection, nor associated with any co-morbidity. Several of those genes were involved in lipid programming beta-catenin and protein kinase C signaling, a calcium activated pathway involved in plasma repair, suggesting an association with several COVID-19 cases. Of those genes, 17 were considered to be good targets for therapeutics and drug development. Several of these targets were particularly enriched in specific co-morbidities, which could also be used to identify patients who are at greatest risk for contracting COVID-19; thus, developing specific targeted therapeutic strategies to enhance recovery and increase survival rates. Nevertheless, understanding the full spectrum of causes underlying their association with the disease is a process that requires times, and additional analyses.

In another study published in the New England Journal of Medicine, also found some interesting links to genetics and severity of COVID-19 cases. The study analyzed genetic samples from 1,610 hospitalized patients in Italy and Spain. Their findings showed that patients with severe disease had variants in a complex of genes on chromosome 3. These genes encode proteins called chemokines, that attract immune cells to combat infection, and it has been shown that overdrive of these proteins cause complications associated with the destruction of the lungs. The researchers found that a small change in the DNA reduces the activity of the gene that helps regulate chemokines, while at the same increasing the activity of the ACE2 gene, the gatekeeper of viral entry into cells; hence the presence of severe complications. The study considered blood type and variations in COVID-19 infections, and found that those who have type A blood, had a 1.5 times increased chance of respiratory failure, due to a stretch of DNA on chromosome 9. However, the study concluded that correlation between genes and severity of disease were mainly found on chromosome 3.

**POLICY IMPLICATIONS AND RECOMMENDATIONS**

The COVID-19 pandemic has presented an opportunity to further the evolution of precision public health, as new tools and resources begin to complement traditional medical and public health approaches to prevention and control. However, similar to precision medicine, precision public health will need a strong evidentiary foundation, which will require investment into robust surveillance infrastructures, as well as capabilities for assessing genomic, and other omics, data for building associations and correlations with public health data. Establishing a precision public health platform will also require the development of key collaborations between the healthcare sector, including hospitals and individual clinicians, and the private sector, government, and communities.

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14 Analysis of Genetic Hose Response Risk Factors in Severe Covid-19 Patients; Taylor et al. (pdf)