PANDEMIC Supermind Activation

FINDINGS

MilliporeSigma

MIT Center for Collective Intelligence

community biotechnology

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FIRST FINDINGS

The MIT Center for Collective Intelligence, MIT Media Lab's Community Biotechnology Initiative, and MilliporeSigma—the life science business of Merck KGaA, Darmstadt, Germany—convened more than 180 experts and global leaders in science, healthcare, public policy, and other sectors for a three-week exercise to address the following challenge:

How can we develop pandemic resilience—the ability for society to recover quickly from global disease outbreaks—both in resolving the current COVID-19 pandemic and in building the public health and other infrastructure to prepare for future pandemics?

We activated our expert group—or 'Supermind', "a powerful combination of many individual minds" (Laubacher et al., 2020)—to share their ideas on how to address this challenge in five domain areas: (1) diagnostics and monitoring; (2) viral transmission control; (3) therapies and vaccines; (4) validating, sharing, and communicating scientific insights; and (5) pandemic preparedness.

Our experts submitted more than 200 contributions—ideas that covered a wide spectrum of topics, from identifying emerging, disruptive technologies to suggesting new modes of global, cross-sector collaboration that could strengthen healthcare systems. Using facilitated dialogue and natural language processing, and with an emphasis on impact and feasibility, we clustered these contributions into emergent, actionable themes, several of which we have highlighted within the document:

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Early warning signs of disease spread can be found in sewers, genomes, voices, internet searches, and other digital health breadcrumbs.

Robust and reliable monitoring of infectious disease can provide the advance warning necessary to control and prevent outbreaks. The Supermind identified several surveillance methodologies that can provide the timely information needed to save lives. Analyzing the genomic content from our sewer systems can provide as much as a seven-day leading indicator of disease spread. Studying sewage from planes, trains, and other transportation could signal the need for passenger testing and tracing. A widespread sewage monitoring program could help establish a critically needed population baseline to help us identify new pathogen threats. Genomic epidemiology can help detect the emergence of viral variants that may be evading population herd immunity to motivate the development of new treatments and vaccines. Phylogenetic network analysis of viral genomes could help identify unreported cases in a population. Voice acoustics change when disease impacts respiratory function, so smartphones could be potential COVID-19 respiratory monitoring tools. A host of digital breadcrumbs—from internet searches to networked digital thermometers and device data from wearables—could be integrated into systemic "disease forecasting" approaches to detect community spread days or even weeks early.

Digital contact tracing with privacy protections could suppress the pandemic.

Our mobile phones could contain the data necessary to trace and rapidly identify the contacts of infected individuals so they can isolate themselves from the population, halting spread of the disease. If every adult carried a device with digital contact tracing enabled, such an approach, combined with cutting edge privacy protections, could single-handedly control the pandemic without mass lockdowns or masks. The Supermind proposed several ways to enhance the impact and adoption of digital contact tracing. Data standards could be implemented to create interoperable, privacy focused contact tracing applications that share community data and update in real time. Tracing could be done "bi-directionally"—notifying both people who were recently exposed, along with the infected individuals—which, when done with digital exposure notification, could triple the probability of controlling outbreaks relative to current practice. Giving phones to every adult could not only increase the efficacy of digital contact tracing, but would also help bridge the digital divide for low income communities.

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Accelerate therapy and vaccine clinical trials.

The COVID-19 pandemic will ultimately be controlled with effective therapies and vaccines. Research suggests that only 10% of drugs make it to market after an arduous trial process which often takes decades (Bio, Biomedtracker, and Amplion, 2016). The experts proposed ways to accelerate clinical trials through global, harmonized protocols. Competitive barriers can be removed when possible to encourage the broad sharing of antiviral and vaccine candidate clinical trial data. Data standards should be unified to facilitate cross-institutional agreements. New safety testing methods could be conducted, for example using proteomics to detect warning signs of adverse immune responses, potentially markedly reducing the duration of clinical trials.

Create resilient supply chains.

Manufacturing and supply chains matter. From personal protective equipment (PPE) to diagnostic tests, therapies, and vaccines, our ability to stockpile and rapidly produce the necessary materials, ingredients, and reagents is essential for resilience. Our experts emphasized employing decentralized manufacturing modalities and creating regional and local production hubs for stockpiling and emergency production. Critical materials should have manufacturing redundancy with multiple factories. In the event of emergency, flexible manufacturing is necessary:plans and standards should be in place to pivot production lines or re-purpose existing factories.

Include and empower marginalized and vulnerable communities.

Marginalized communities—including ethnic minorities like African Americans, Latinx, American Indians, immigrant workers, and other indigenous groups—are not only disproportionately impacted by the pandemic, but have also historically been under-represented in pharmaceutical clinical trials and benefited least from translational research. These systemic problems require systemic solutions. The Supermind proposed building equity considerations into all pandemic research funding and implementation and ensuring representation from these communities in randomized clinical trials (RCTs). Community mobilization and education should be participatory at the grass-roots level and involve engagement with trusted local leaders. Effective implementation of policies and programs, like contact tracing, should be done collaboratively and with respect to cultural perspectives and communal needs and priorities. Communication strategies need to be community specific and foster equitable discussions amongst healthcare, governmental, and other stakeholders, taking into account language and accessibility needs.

Build better behaviors.

Non-pharmaceutical interventions can save lives and can, in lieu of an effective therapy or vaccine, control the pandemic. Our experts proposed ideas to change public behavior, like encouraging mask adoption by partnering with fashion forward designers and influencers to make mask-wearing culturally normative. Education programs could be deployed to teach the public basic sterile techniques regarding PPE like masks and gloves. Campaigns to address major risk factors for COVID-19, like obesity, should be launched. Technologies should be developed to encourage good hygiene, like preventing face-touching and avoiding contact with commonly shared surfaces. Social scientists, psychologists, and cultural anthropologists should be mobilized to help shape messages and interventions in ways that people will hear, trust, and follow.

Build trust and dispel fear.

Controlling outbreaks requires trust at multiple levels—among the public, government, public health experts, scientists, and other stakeholders. Successfully empowering the public with trustworthy, accurate, and scientifically validated information can help dispel fear and promote the social cohesion and actions necessary to control the pandemic. Our experts proposed myriad strategies for building trust amongst stakeholders. Participatory research methods could be used to incorporate the perspectives, needs, and concerns of community members. Multi-generational engagement could be fostered by empowering communal youth networks for outreach and distribution of information and services. Concerted efforts should be made to develop reliable, continuous communication methods with vulnerable communities that may, for example, have accessibility issues like poor access to internet or smartphones. National and global institutions that can communicate scientific facts, guidance, and advice should be established or reformed. Scholarly articles could include plain language summaries for the public. Visual designers could collaborate closely with researchers to help demystify scientific findings. Public health officials should have platforms to regularly engage with the public and help manage expectations.

We will expand upon and explore these themes in greater depth, in the context of a series of upcoming reports we will release that correspond to the domain areas listed at the opening of the brief.

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Appendix 1: Methodology

The Pandemic Supermind was activated as a crowdsourcing platform for collective thinking, created as an enabler to help identify critical, unmet needs to address COVID-19 and future pandemics. The platform engaged participants online over a three-week period, allowing a diverse and geographically separated group to work together conveniently, cost-effectively, efficiently, and rapidly.

By bridging specialties, disciplines, industries, and geographic boundaries with technology, the Pandemic Supermind Activation aimed to deliver deeper insights and more useful and trusted information to contribute to the current and future role of life sciences in pandemic resilience.

The process used natural language processing (NLP), in addition to facilitated dialogue, to identify themes in experts' contributions. These themes informed questions and prompts throughout the process, ensuring there were not any gaps during the three-week discussion and discovery period.

Week 1: Experts were asked to submit contributions in their domain areas, i.e., areas in which they were most comfortable. Even if a participant brought a perspective that was outside of the life sciences (say for example they were a tech writer), they were asked to weigh in on areas that they might know more about from the news, life experiences, or how their field could intersect or inform the domain.

Week 2: Members of the Supermind were then asked to submit contributions outside of their domain areas. They were prompted to think creatively, and suggest ideas that were outside of the box. The hope was that this would expand the breadth of ideas and push the boundaries of domain bias.

Throughout the process, participants were asked to like and comment on others' contributions to highlight areas of opportunity or signify their support.

Week 3: Participants had the ability to vote on groups of contributions created by clustering the ideas generated in weeks 1 and 2. Prior to the start of week 3, the contributions created during weeks 1 and 2 were clustered into groups. This was done by first using natural language process (NLP). The results of the NLP analysis were then reviewed by members of the CBI/CCI staff and a scientific advisory committee from MilliporeSigma, and 15 meta topics or categorizations were parsed out using two NLP methodologies: 1) topic modeling, and 2) word to vector (word-2-vec). Topic modeling looks at the frequency of words and phrases used, and clusters according to semantic patterns. Word-2-vec takes a large corpus of text, and by noting which words occur close together, is able to represent each word as multi-dimensional vectors. It can take new strings of text and assign them a position in the multi-dimensional space. Text strings can then be clustered with like groups based on their proximity. By doing an initial pass with topic modeling and then comparing this result with word-2-vec, we were able to get our final 15 groups of contributions. The advisory committee then created a description and title for each of these clusters.

The Supermind participants voted on which clusters they believe would have the most impact in building pandemic resilience, both in resolving the current COVID-19 pandemic and in building public health and other infrastructure to prepare for future pandemics.

Throughout the process, we also created social network graphs, which looked at participants by their sector and analyzed what contributions they were commenting on and liking. An interesting insight from this analysis was that participants were liking and commenting on not only contributions within their sector, but also contributions outside their own. Thus, there was significant cross-pollination between sectors.

Appendix 2: Pandemic Supermind Activation by the numbers

Total Contributions: 243
Total Supports (Likes): 413
Total Comments: 152
Total Votes: 1,267

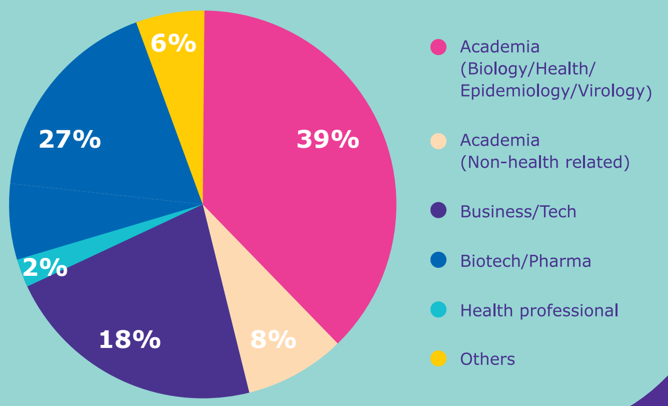
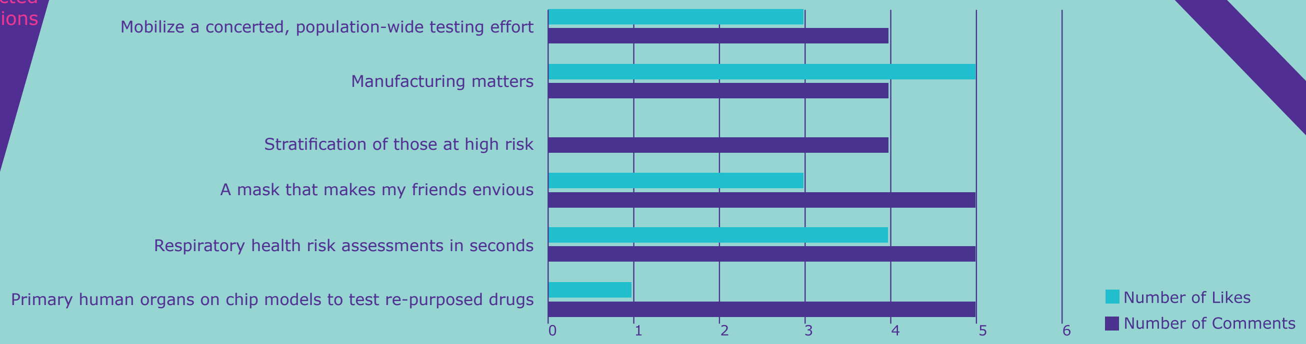


Figure 1:
Participants by sector

Figure 2:
Most interacted with contributions



Most impactful & feasible groups of contributions for present pandemic

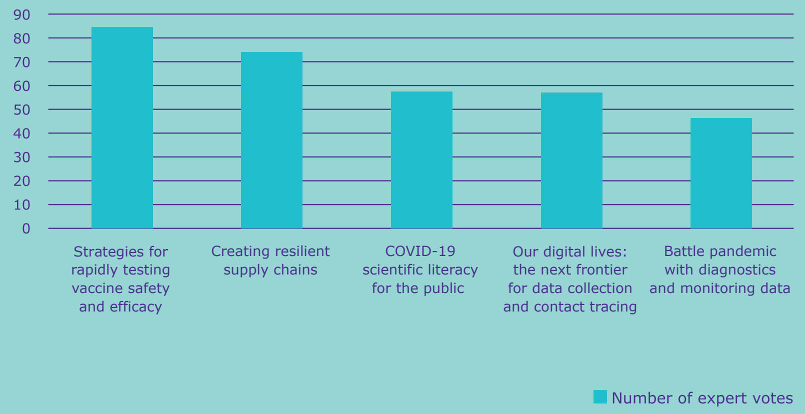


Figure 3:
Most impactful & feasible groups of contributions for the present pandemic

Most impactful & feasible groups of contributions for future pandemic resilience

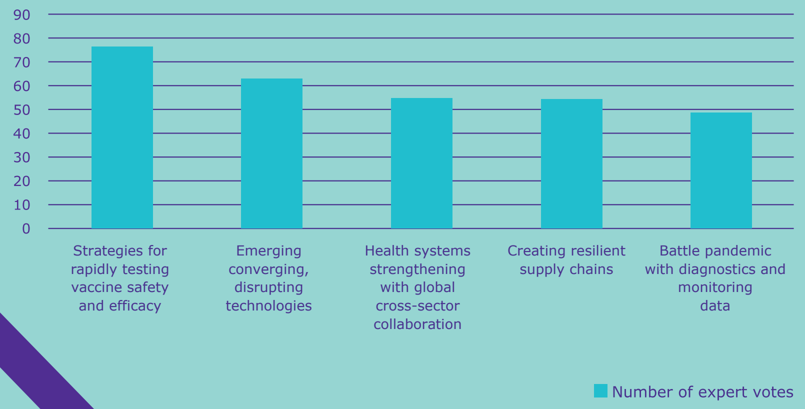


Figure 4:
Most impactful & feasible groups of contributions for future pandemic resilience

Appendix 3: Short list of Institutions of the Participants

- BI Lahey Health
- Boston Medical Center
- Stanford
- Brandeis University
- Institute of Natural Material Technology, TU
- Lysogene
- Wyss Institute
- University of Ghana
- MIT
- University of Iowa
- Longview Analytics
- University of Cambridge
- Takeda
- Deloitte
- Columbia University
- GenPact
- Boston Children's Hospital
- University of California San Diego
- Tel Aviv University
- University of Melbourne
- AAFOA
- Sonde Health
- MilliporeSigma

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Diagnostics & Monitoring

The MIT Center for Collective Intelligence, MIT Media Lab's Community Biotechnology Initiative, and MilliporeSigma—the life science business of Merck KGaA, Darmstadt, Germany—convened more than 180 experts and global leaders in science, healthcare, public policy, and other sectors for a three-week exercise to address the following challenge:

How can we develop pandemic resilience—the ability for society to recover quickly from global disease outbreaks—both in resolving the current COVID-19 pandemic and in building the public health and other infrastructure to prepare for future pandemics?

This chapter covers insights generated from the Supermind related to diagnostics and monitoring for controlling the pandemic.

INTRODUCTION

Methodologies for widespread and rapid testing and disease surveillance, such as digital contact tracing, can play a crucial role in suppressing the pandemic. The Supermind proposed novel modalities for how to detect COVID-19, including identifying novel biomarkers; where to look for signs of the disease, including in the air, in the sewers, and in our "digital health breadcrumbs," and also how to quickly build new testing labs and infrastructure. The Supermind also focused on aspects of smart phone technologies for contact tracing, known as digital contact tracing: how to ensure equitable access and increase efficacy and interoperability, while critically protecting privacy.

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"Data from over 45,000 volunteers ... indicates that voice acoustics could be used to detect and monitor various health conditions

Digital health breadcrumbs: digital signals that can provide health surveillance data for tracking infectious disease

Detecting COVID-19: Novel biomarkers in our voices and in digital health breadcrumbs

The bedrock of public health response for mitigating and suppressing the spread of infectious disease involves widespread and rapid testing. The most common method for detecting active cases of COVID-19 has involved analyzing patient samples for the presence of viral RNA, usually through variants of polymerase chain reaction (PCR). There are, however, other types of biomarkers that could indicate the presence of an infection.

For example, an ongoing clinical study of digital biomarkers involving data from over 45,000 volunteers across the United States and India indicates that voice acoustics could be used to detect and monitor various health conditions affecting brain, respiratory, and motor functions required for healthy speech. In response to the COVID-19 pandemic, respiratory-responsive vocal biomarkers (RRVB) have shown promise to detect and measure COVID-19 associated respiratory impairments that also could be tracked over time to understand disease status and symptom severity. Furthermore, because the methods used to collect and analyze speech samples could be gathered from smart phones, such detection could reduce infection risks by eliminating the need for close contact with healthcare workers. Detecting vocal biomarkers using smart phones could provide cost-effective and near universal access to diagnostics and monitoring, making the allocation and use of these resources more timely and efficient and providing valuable assessment and risk stratification capability when gold standard tools, like viral RNA detection, may not be available or are too slow.

Biomarkers for COVID-19 can also be found in our "digital health breadcrumbs," or digital signals that can provide health surveillance data for tracking infectious disease. Some of these include search history keywords for symptoms; networked digital thermometers tracking fever trends; device usage changes correlating to cognitive, behavioral, and mental health changes that occur with infectious disease; and acoustic biomarkers as described above. Such bio-surveillance techniques have been successfully used to track the flu, including FluNearYou and Healthmap. It is possible that an integrated and systemic approach, fusing complementary digital signals with advanced machine learning and artificial intelligence techniques, could provide a robust monitoring system that could detect community spread of COVID-19 days or weeks earlier than current timelines for testing and patient notification. Current approaches can take longer than a week, rendering diagnostic tests largely useless for containing outbreaks.

Making diagnostic tests and labs accessible and scalable

The lack of sufficient COVID-19 diagnostic testing is still a significant problem in the United States and globally. The Supermind emphasized the critical importance of massive-scale testing to enable the isolation of asymptomatic individuals and proposed several approaches to make viral testing more accessible and scalable.

With tens of thousands of COVID-19 cases confirmed per day in the United States alone, and the significant rate of transmission by asymptomatic individuals that one study estimates to be between 6% to 41% of cases (Bradshaw et al., 2020), universal testing is desired. Large-scale detection of infected individuals without symptoms (either pre- or asymptomatic) is incredibly challenging without ubiquitous testing. An additional benefit of universal testing is the ability to relax social distancing measures, enabling the return of socioeconomic activities while limiting future outbreaks (Bradshaw et al., 2020).

"**Large-scale detection of infected individuals** ... is incredibly challenging without ubiquitous testing

One approach to scale the number of tests conducted is to pool samples from multiple patients in a single test. In such a scenario, a negative test result indicates that no viral RNA was detected in any of the patient samples, thus returning valuable data on multiple patients with only a single test, thus enabling large-scale screening. If, however, a positive result was returned, subsequent rounds of pool testing or testing of individuals from within the pool would be required to determine whom was infected. Pooling samples is particularly effective when rates of community transmission are low.

The Supermind proposed generating the necessary data standards and guidelines for how best to pool samples based on the type of diagnostic test and their prevalence to facilitate regular population-level screening. Such approaches have been successfully conducted in parts of the world, including in China, for example.

Other approaches the Supermind highlighted to make testing more accessible include developing rapid tests that could be conducted at home using saliva samples, which can be easier to collect than, for example, nasopharyngeal swab tests, which require specialized training. The Supermind also pointed to the recent FDA emergency use authorization (EUA) approval to Rutgers Clinical Genomics Laboratory to permit testing of samples self-collected by patients using saliva (Giordano et al., 2020). University of Colorado, Boulder has also recently developed a saliva test with a 45-minute sample-to-results turnaround (Meyerson et al., 2020).

Finally, the Supermind also acknowledged that collecting more samples alone is insufficient; infrastructure to conduct the tests also must be scaled. In the United States, for example, numerous outbreaks across the country during the summer of 2020 have overwhelmed centralized testing facilities, causing a processing backlog. To address this challenge, the Supermind proposed designing highly automated units, like 20-ft. shipping containers, that could be self-sufficient, containing a small number of staff with automated testing solutions capable of handling different diagnostic tests. For example, Open Cell, an organization in London, has designed a bio lab in a shipping container. These mobile labs could be deployed quickly to hot spot areas in close proximity to locations where samples could be collected (e.g., subway stations, hospitals, large factories) to augment existing testing infrastructure.

Similarly, more modular, reagent-agnostic testing systems could provide flexibility and remove points-of-failure in supply chains that potentially rely on single, large manufacturers. The Supermind pointed to entities like OpenTrons, who make open source pipetting robots, along with the Global Biofoundry Alliance and the London Biofoundry, which are also working on developing systems to automate lab protocols and diagnostic testing. Such modular and automated systems would be ideally suited to operate in mobile testing labs that could also be deployed to offer testing for underserved populations like the homeless, or in rural areas that are experiencing outbreaks and require additional infrastructure.

> **Understanding airflow dynamics**
> ...
> is critical for designing circulation systems that refresh air and dilute the presence of any viral particles

COVID-19 surveillance for the air, sewage, and our genomes

AIR MONITORING

One area the Supermind identified that requires significant research and study is the analysis of viral prevalence in air, both indoor and outdoor. A recent article from The Atlantic (Tufekci, 2020) similarly highlighted this need. The Supermind proposed rigorous analysis of outdoor transmission in settings like golf courses, outdoor markets, restaurants, and learning environments for schools, for example. A deep understanding of these dynamics could play a critical role in designing public policies for many socio-economic activities that potentially could be conduced safely outdoors.

Similarly, for indoor transmission, rigorous analysis of air filters or air monitoring devices in schools, workplaces, or transportation systems could also provide critical data, which could influence public health policies. Such monitors could be placed strategically with either sample collection or molecular diagnostics tools in situ. Understanding airflow dynamics inside buildings and ventilation systems is critical for designing circulation systems that refresh air and dilute the presence of any viral particles. Finally, the Supermind highlighted the need to understand the particle sizes and concentration in exhaled breath of COVID-19 infected individuals to elucidate the infection dynamics of aerosol transmission.

SEWAGE SURVEILLANCE

Sewage can be an early indicator of epidemics. The Supermind proposed developing a monitoring program based on metagenomic sequencing of all nucleic acids found in sewage that could establish a baseline against which novel pandemic zoonosis (the process of a virus infecting humans from animals) could be detected. Moreover, particularly dangerous engineered viruses are likely to have telltale signatures of alteration by humans, and those changes could be detected by automated algorithms. This type of sewage monitoring could be done not only in municipal sewer systems but also in transportations systems like airplanes, ships, or trains, which, when coupled with pool testing, could trigger targeted testing and contact tracing.

Such systems could provide a vital early warning, with studies showing that sewage screening could provide communities as much as a week's early notice of a COVID-19 outbreak (Peccia et al., 2020). When coupled with exposure notification and contact tracing technologies, local outbreaks could be controlled before they became pandemics. Furthermore, the existence of such an early warning system may provide the additional benefit of deterring malevolent actors from making engineered bioweapons.

> **The Supermind proposed developing a monitoring program**
> ...
> to sequence all nucleic acids found in sewage that could establish a baseline against which any novel pandemic zoonosis...could be detected

Digital contact tracing is sensitive to uptake, but powerful if universal

One of the most promising technology solutions for suppressing the pandemic is digital contact tracing (DCT). Such technologies rely upon individuals having contact tracing applications installed on their smart phones that through, for example, blue-tooth technology, enable the logging of close proximity contacts. In the event of a positive test, all potentially exposed individuals could be instantly contacted so they can then be tested and potentially isolated. Models predict that, if such digital technologies were universal, the pandemic could be controlled without requiring lockdowns or face coverings (U.S. Food & Drug Administration, 2020). However, strong privacy protections would be required for adoption to succeed, particularly in liberal democracies where installing such applications would be largely voluntary.

To help adoption, the Supermind proposed, for example, buying every adult in the United States an inexpensive smartphone with a basic data plan that is DCT-enabled. This could cost approximately $4.2b. Such an approach could also help provide low income communities and frontline workers access to low cost technologies to help keep their families safe while bridging the “digital divide” that has exposed profound inequities in society, including access to life-saving digital tools. DCT applications could also be enabled with “bidirectional” contact tracing, which is predicted to reduce the effective reproductive number (Reff) of SARS-CoV-2 by roughly 0.3 (U.S. Food & Drug Administration, 2020). Finally, to manage the complexities of multiple DCT applications (potentially a unique app for each state in the United States or each country in Europe), particularly when individuals cross state or country borders, the Supermind proposed using interoperable data standards to prevent data silos and to enable connected systems updated in real time.

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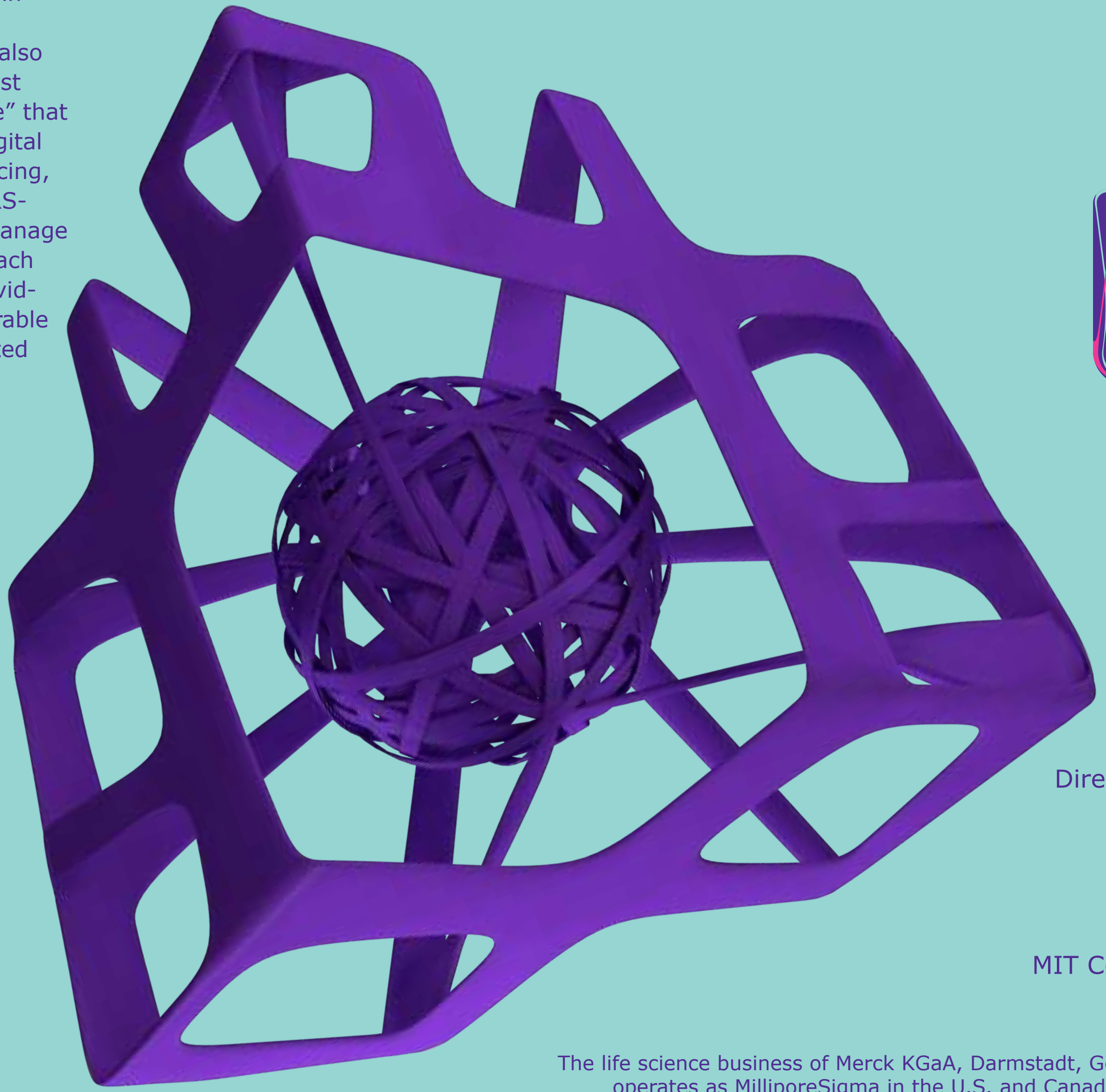

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THERAPIES & VACCINES

For effective therapy and vaccine discovery and development, it is critical to understand the molecular basis of COVID-19 pathogenesis in terms of mechanisms of viral entry, replication, and host responses. The Supermind proposed approaches in computer-aided rational design and development of safe and effective broad-spectrum antivirals or repurposing known drugs with antiviral activity to combat the next pandemic, and development of antivirals to families of viruses that jump species. The Supermind also focused on various aspects of vaccine development including utilizing adjuvants that lower vaccine doses, inhalation-based vaccines, and approaches to fast track vaccine safety and efficacy evaluation and new ways to conduct clinical trials. Finally, the Supermind proposed ways to create more resilient supply chains for the various reagents and materials critical for manufacturing therapeutics and vaccines.

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Advances in patient treatment

Since March 2020, physicians’ tools have improved considerably with significant advances in treating COVID-19 patients with multiple treatment regimens. These include:

- The antiviral drug Remdesivir, which has become a standard of care, and other repurposed antiviral drugs such as Kaletra (liponavir/ritonavir) and Tamiflu;
- Dexamethasone, a common corticosteroid used in autoimmune conditions and allergic reactions;
- Transfusion of convalescent plasma from recovered patients with high antibody content to treat active coronavirus infection;
- Acterma (Tocilizumab), a drug approved for rheumatoid arthritis which works by blocking interleukin-6 (IL-6), a protein involved in causing overactive immune system that could result in a cytokine storm, a potentially fatal problem where the immune system malfunctions and inflammation goes out of control;
- Monoclonal antibodies generated against portions of spike proteins, which are currently in clinical trials to see if they could provide short-term protection (until vaccines become available) from SARS-CoV-2 by binding directly to portions of the virus that are used to attach and enter host cells, preventing them from initiating the infection cycle.

Antivirals to families of viruses that jump species

Viruses like parvoviruses, coronaviruses, influenza viruses, parainfluenza viruses and arthropod transmitted viruses have shown a propensity to jump species, also known as zoonosis. Viruses jump species in two ways: the first is as a spillover event when humans become exposed to zoonotic viruses that they normally do not encounter. Forest clearances and dam building are examples of these events as they affect vector populations. In the second type, viruses mutate or undergo recombination or re-assortment, altering their ability to infect a variety of hosts.

Each of these virus families have points in their replication cycle that are targets for antivirals. For instance, for influenza viruses, the “M2 protein” has been a main target, but resistance has been developed to a class of antiviral medications known as “adamantanes.” Combination therapy is required to reduce establish-ment of resistant mutants, ideally via rational design based on the 3D crystal viruses that have jumped species, followed by in vitro selection with selected molecules to predict escape mutants and then designing drugs for escape mutants and combination therapy to reduce their establishment.

Search for broad-spectrum antiviral drugs

Unlike broad-spectrum antibiotics such as penicillin, available to treat multiple bacterial infections, we currently do not have any broad-spectrum antivirals to treat respiratory track diseases arising from various viral infections. The Supermind proposed screening novel molecules through computer-created virtual libraries and the libraries of known drug compounds for their ability to inhibit viral replication through either viral protease or polymerase inhibitors or by preventing viral entry into the host cells by specific host enzyme inhibitors. This approach has potential for pan-pathogenic applications to develop broad-spectrum antivirals to combat future pandemics.

Next-generation adjuvants for scalable vaccine production

While the United States Food and Drug Administration (FDA) has traditionally been cautious around the adjuvants used in vaccines, the Supermind proposed utilization of novel, next-generation protein-based adjuvants that may reduce the effective dose of the vaccine by a factor of 10–100, and vastly accelerate manufacturing and scale-up. Additionally, long-term protection may require a more powerful immune response than can be achieved using traditional vectors. The fastest vaccine modalities are nucleic acids (DNA and mRNA) which are traditionally not very immunogenic—but they also make it very easy to co-deliver adjuvants in gene-encoded form.

Designing an inhalation-based vaccine

The Supermind proposed novel methods for improving delivery of a mRNA vaccine for SARS-COV2 to the lungs. Through the design of an efficient and rapid process to generate biomolecule-carrying aerosols with minimum disruption to their internal structure, this concept could provide a method that minimizes waste of important vaccine biomolecules. While other nebulization processes can destroy biomolecules, a major breakthrough for biomolecule delivery could be deliverings directly to the lungs. If successful, it would provide validated technology to produce an optimized mRNA vaccine for SARS-CoV2 for delivery to the lungs. As such, this inhalation-based vaccine technology could offer several advantages including being non-invasive, direct delivery and reduced cost, resulting in improved access to potentially life-saving formulations.

Approaches to fast track vaccine safety and efficacy evaluation and new ways to conduct clinical trials

Vaccine trials often take a long time to uncover serious adverse effects. The Supermind has suggested the application of modern biotechnology tools to detect the adverse events early, to allow vaccine trials to proceed more quickly and safely with tools like modern proteomics.

The safety risks for SARS-CoV-2 vaccines fall under three broad categories: 1) *Acute anaphylaxis* in response to the antigen or the adjuvant; 2) *Vaccine-induced allergies* or *autoimmune diseases*; and 3) *Antibody-dependent enhancement* (ADE) effects that can make future SARS-CoV-2 infections worse.

Acute issues typically occur within minutes of vaccination, and therefore can be rapidly identified in Phase I and Phase II trials. Determining adverse reactions due to allergies and autoimmune disorders are the main reason that trials take a long time. However, it should be possible to detect warning signs of adverse immune response without actually causing them in people. For instance, allergen tests can be carried out before and after vaccination to identify unexpected shifts in allergen profiles. Proteome protein arrays and mass spectrometry methods can be used to detect the development of autoantibodies, allowing potential autoimmune issues to be identified in early vaccine subjects who do not go on to develop any diseases. These data can then be used to build custom assays for early diagnosis of potential side-effects in Phase III trials, eliminating the potentially lengthy follow-up period.

Antibody-dependent Enhancement (ADE) has been observed in Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS). In cats, for example, a feline coronavirus produces a mild disease, but if re-infected with a variant virus a fatal autoimmune disease can occur which, in part, is associated with ADE (Vennemma et al. 1990; Vennemma et al. 1998; Corapi et al. 1992; Hohdatsu et al. 1998). The Supermind proposed an assay to test ADE by comparing virus entry in three engineered cell types, all based on a common parental cell. These cell types would be designed to have variations of the "FC receptor," a protein found on immune cells, and the "angiotensin-converting enzyme 2" (ACE2) receptor, which is utilized by the SARS-CoV-2 virus to infect cells. By infecting these cell lines and testing their responses, one could identify an ideal vaccine candidate that elicits high neutralizing activity while having no or little infectivity on a cell line expressing FC receptors but not ACE2 receptors.

Accelerating and improving clinical trials

The Supermind also proposed a novel approach to speed up Phase III clinical trials for vaccines, using population-level statistics. One could capitalize on the high prevalence of SARS-CoV-2 in many American communities, such that an effective vaccine would be expected to shift the dynamics of local spread. The vaccinated subjects may develop a strong Immunoglobulin G (IgG) response within a few days, enabling efficacy measurements as early as five weeks into a clinical trial. In contrast, traditional clinical trials rely on measuring the protection conferred to each clinical trial subject, which may require more than one year of observation to obtain sufficient statistical validity.

In a pandemic crisis situation, traditional processes must be accelerated. There is a need to implement new thinking in clinical trial processes—like real-world trials, Bayesian Statistics, etc.—on an emergency basis, in parallel with the traditional Randomized Clinical Trial (RCT) approach to collect data very broadly across candidates, by removing competitive barriers, both geopolitical and institutional.

The Supermind noted pros and cons regarding the ethical dilemma of accelerating vaccine trials by infecting healthy volunteers with SARS-CoV-2 virus following vaccine administration. Instead of vaccinating hundreds to thousands of people and waiting to see if they naturally catch the virus and whether the vaccine would be effective in neutralizing the virus, the idea would be to purposely infect a smaller number of healthy vaccinated volunteers with the virus in a controlled setting to see if a vaccine offered protection (Lambert, 2020). If successful, such studies could fast-track vaccine evaluation, as well as our understanding of COVID-19 immunity. Arguments for and against this "human challenge trial" approach need to be evaluated and a decision would need to be made by regulatory authorities.

Finally, the Supermind noted that communities of color have historically been excluding from pharmaceutical clinical trials. Given the disproportionate impact the virus is having on communities of colors, the clinical trial programs for promising therapies must include adequate representation from those communities to ensure we are developing treatments that are efficacious for those hardest hit by COVID-19 (CDC, 2020).

Creating resilient supply chains

The Supermind noted that the development of therapies and vaccines will only make a significant impact if sufficient manufacturing capacity exists and can be rapidly deployed. For example, when the antiviral drug Remdesivir was approved by the FDA for "emergency use authorization," there were only enough doses to treat 5,000 patients and the pharmaceutical supply chain was not equipped to deliver the drug in sufficient quantity (Gilead, 2020). Similarly, raw materials for the SARS-CoV-2 diagnostic kit manufacturing were also in short supply, resulting in large delays in viral RNA testing.

The push for vaccine development on an accelerated timeline has resulted in multiple modalities being pursued simultaneously, including RNA vaccines and antigen (recombinant) based vaccines, each of which has different manufacturing requirements. The Supermind proposed ways to improve supply chain resiliency by increasing local capacity to produce some of the most commonly used reagents and ingredients in a selected number of regional hubs. The Supermind also proposed the development of "innovation teams" that could be assembled under emergency conditions that could be connected to existing "maker" or grassroots innovation communities to aid in local production. Existing manufacturing capacity could also potentially be re-purposed, if relevant standards could be made available along with operating procedures and expertise. This type of flexible and decentralized manufacturing, along with manufacturing redundancy with multiple factories for critical reagents and ingredients, could significantly increase supply chain resiliency for therapeutic and vaccine deployment.

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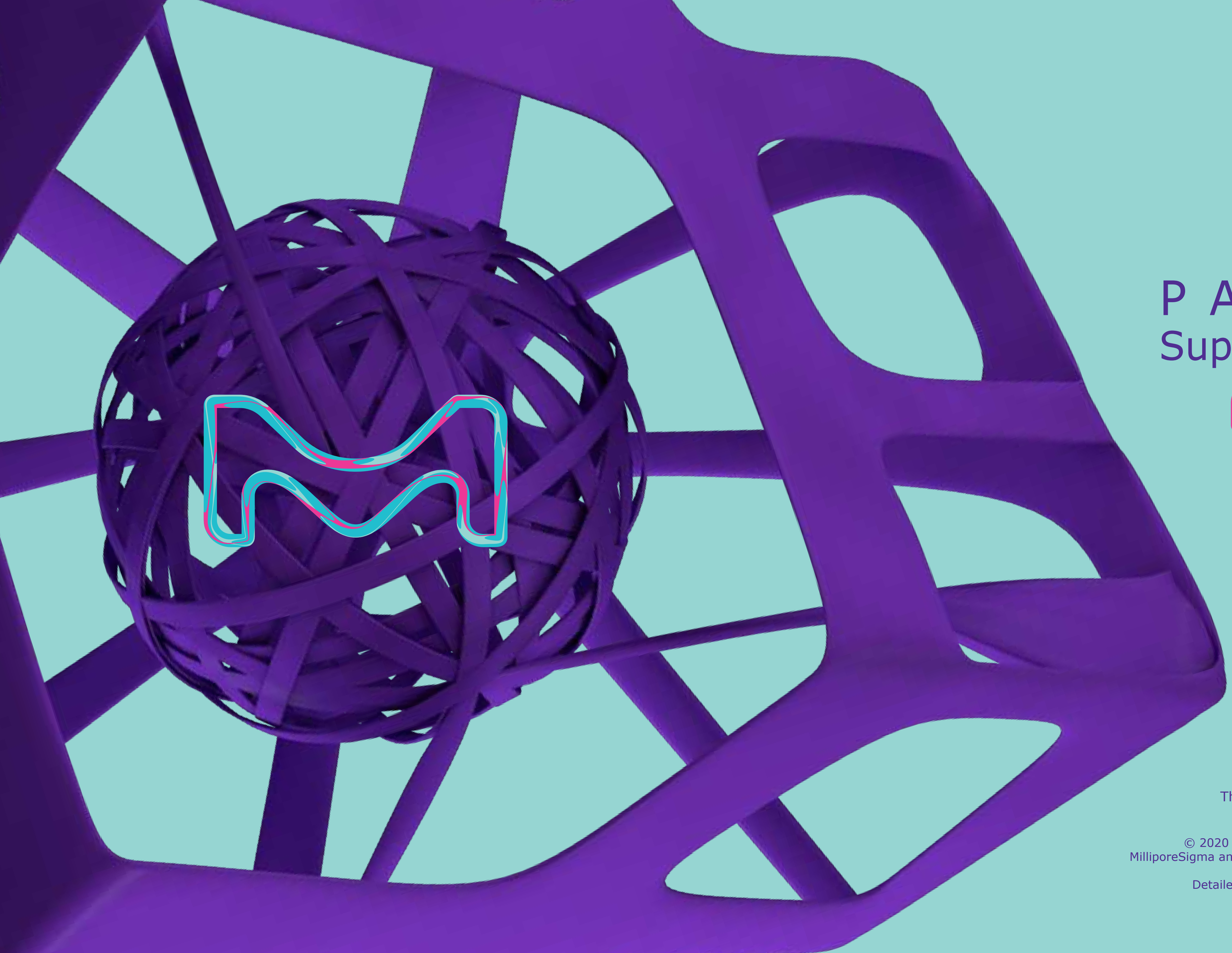

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