RADx-rad: The Role of Non-traditional Approaches in COVID-19 Pandemic Response

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Executive Summary

The COVID-19 pandemic presented a severe and imminent threat to lives of Americans, the healthcare system, and the economy. In response, the National Institutes of Health (NIH) launched the Rapid Acceleration of Diagnostics®(RADx) initiative to accelerate the development, commercialization, and implementation of innovative technologies for COVID-19 testing. This was no small feat, as accurate, fast, easy-to-use, and widely accessible testing was required for effective monitoring, early treatment, and prevention of the spread of COVID-19 before citizens could safely return to normal life. To accomplish these testing goals, the NIH created several programs, such as RADx Radical (RADx-rad), that made this possible.

The NIH RADx-rad program supported new, non-traditional approaches, to address the gaps in COVID-19 testing and detection. These innovative research programs included the development of devices for the rapid detection of SARS-CoV-2 and other pathogens, novel approaches for environmental detection of infectious agents including SARS-CoV-2, and the generation of tools for predicting and diagnosing severe COVID infection as well as the long-term effects of infection known as Post-Acute Sequelae of SARS-CoV-2 (PASC) infection or Long COVID. Collectively, these proposals introduced "radical" ways to predict, detect, and diagnose conditions resulting from SARS-CoV-2 or other infectious agents.

Overall, RADx-rad provided funding to support innovative research projects focused on developing novel platforms to detect infectious diseases and to evaluate community spread. Unlike other RADx programs, projects within the RADx-rad portfolio focused on new or non-traditional approaches, which may require additional time for development and could potentially be applicable to future pandemics and other health conditions.

Program Overview and Structure

In the spring of 2020, planning for RADx-rad commenced when Institutes and Centers (ICs) across the NIH were invited to submit concepts to improve testing for COVID-19. The overarching goal of RADx-rad was to support the development of novel, existing, and non-traditional approaches, and applications of tools to address the gaps in COVID-19 testing. From the initial group of proposals, the NIH leadership selected a subset of concepts to be further developed into funding announcements. Researchers from across the U.S. submitted creative applications, from which 49 awards were distributed in December of 2020. The RADx-rad program was divided into two phases, each of which is briefly described below in addition to a detailed list of all the RADx-rad funded projects.

During Phase I, an estimated $108 million was provided to support the development of new, non-traditional approaches for COVID-19 testing. These non-traditional approaches include unconventional screening, identification, and use of biological or physiological markers, development of point-of-care devices, and utilization of data science and artificial intelligence technologies. Further, RADx-rad provided an opportunity for researchers to explore and identify new approaches to understand SARS-CoV-2, which could potentially be used in the future to expedite the research response to new pathogens. These research projects were funded across the following eight categories including:

- **Automated Detection and Tracing of SARS-CoV-2**: These projects consisted of the early-stage development of an innovative platform that integrates virus-sensing elements with touchscreens or other digital devices to achieve automatic, real-time detection and tracing of SARS-CoV-2.
- **Chemosensory**: This approach consisted of the development of new, objective chemosensory tests to be used as COVID-19 screening tools for their use at home and in a wide variety of settings.
- **Exosome-based Selection**: Newly developed technologies and approaches for single exosome and extracellular RNA (exRNA) isolation and analyses were deployed for the detection of SARS-CoV-2 virus RNA and/or protein, and detection of IgA, IgG, and IgM antibodies that are part of the host response to viral infection.
- **Multimodal Surveillance**: These projects consisted of identifying existing surveillance technologies that could be rapidly deployed in communal living contexts. Additionally, this category included projects that explored novel methods of data collection,

interpretation, and use of machine learning (ML) to facilitate broad-based, real-time assessment of the needs of high risk, vulnerable populations.

- **Novel Biosensing**: This category was comprised of the development and integration of novel biosensing detection technologies with dedicated engineering and artificial intelligence (AI) systems. The goal of these technologies was to leverage the accessibility of human skin, breath, and the oral cavity to detect biological, chemical, and other biometric signatures of COVID-19.
- **Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds)**: This opportunity was created to support the development of novel, unique, and non-traditional approaches to identify and characterize the spectrum of SARS-CoV-2-associated illnesses, such as Multisystem Inflammatory Syndrome in Children (MIS-C). Algorithms generated through this research were used to predict the longitudinal risk of disease severity after a child has been exposed and infected with SARS-CoV-2 to tailor their treatments and optimize their health outcomes.
- **Screening for COVID by Electronic-Nose Technology (SCENT)**: Electronic nose and gas chromatographic technologies were developed to monitor the onset, progression, and resolution of COVID-19. These technologies used highly sensitive olfactory biosensors to detect volatile organic compounds (VOCs) which are produced in the host as a response to a pathogen or other insult. These steps included detection of the compounds, identification of a signature that reflects COVID-19 variants and/or severity of disease, and then integration of this into a detection platform. The VOC signatures of COVID-19 could be detected in human skin, breath, and the oral cavity. Technologies based on gas chromatography were also developed into portable VOC (odor) breath analyzers for their application in intensive care units, emergency rooms, and ambulatory clinics.
- **Wastewater Detection of SARS-CoV-2:** Wastewater-based detection (WBD) platforms provided a detailed mapping of the extent and spread of SARS-COV-2 in communities. WBD was shown to precede outbreaks of infection as detected in the clinical samples.

The community wastewater analysis method served as a complementary approach to individual-level testing and screening.

In addition, RADx-rad was supported by a Data Coordination Center (DCC) which provided management, direction, and overall coordination across RADx-rad awardees in areas such as data collection and sharing (e.g., data upload to the NIH RADx Data Hub), data management standards and terminologies, and provided standardized viral samples and testing protocols.

Following the initial set of awards, the RADx-rad program launched Phase II in the spring of 2021, which provided an additional ~$75 million in NIH funding (including access to RADx core resources and entrepreneur consultation, as well as additional funding support for assistance to projects that demonstrated the potential for commercialization). The Long COVID Computational Challenge (L3C) launched during Phase II aimed to support creative, data-driven solutions to advance the current understanding of the risks of PASC/Long COVID. The goal of L3C was to support development of AI or ML models to determine the likelihood of patients infected with SARS-CoV-2 of developing PASC. Six prizes totaling a purse of $500,000 were awarded, and the winning algorithms were shared as open-source software to enable further development by the scientific community.

Program Accomplishments

The RADx-rad program demonstrated the value of a collaborative system to develop novel platforms and methods to detect SARS-CoV-2 and monitor community spread. Over the course of the program, RADx-rad published 13 funding opportunity announcements and awarded 49 projects. Some highlights from the program are:

- The RADx-rad WBD researchers were able to detect COVID-19 variants in various wastewater collection sites and the same variants in clinical samples using improved technologies for collecting and managing the samples to minimize human contact, and transport and processing of the samples.
- The RADx-rad PreVAIL kIds researchers developed various algorithms based on standard emergency department lab tests and clinical observations. These processes

enabled physicians to differentiate between serious childhood diseases such MIS-C, Typhus, Kawasaki disease, and other febrile diseases within a 24-hour period, thereby preventing discharge of individuals who require more intensive treatment.

- Researchers developed a rapid saliva-based test that can differentiate between gram positive and gram negative-bacterial infections and viral infections. This test has broad implications for public health in combatting the emergence of antibiotic resistant pathogens by allowing clinicians to tailor the use of antibiotics for bacterial infections and eliminate the inappropriate provision of antibiotics for viral-based conditions.
- RADx-rad researchers used AI and ML technologies to determine that VOC signatures in breath significantly differed in response to variants of COVID-19 in the host. Early results showed a difference in VOC biomarkers between children and adults with COVID-19. Currently, scientists are exploring the patterns of VOCs in PASC.
- RADx-rad researchers developed biosensing technology for rapid and ultrasensitive SARS-CoV-2 detection capitalizing on the trimeric assembly of viral surface proteins. Its simplicity and specificity made it promising for on-site testing in various settings, including airports and clinics. The study also explored its adaptability for detecting other viruses and potential use in diagnosing Long COVID, showcasing its significance in infectious disease diagnostics.
- Scientists developed and validated new objective chemosensory tests that are affordable, highly scalable, self-administered and globally deployable as screening tools for COVID-19. This was especially relevant to viral variants that frequently resulted in loss of taste and/or smell and is now being applied to other neurological conditions.
- RADx-rad researchers integrated radical ideas in virus sensing and device designs to develop several prototype devices for SARS-CoV-2 detection, ranging from an environmental detector, breathalyzer, touch surface detection, to pocket-sized devices that can be coupled with a contact tracing application. These innovative platforms can enable automatic real-time virus detection and tracing, which will prepare us to face the challenge of viral outbreaks in future pandemics. High innovations of these virus detection platforms have attracted private investments to develop some of these

technologies with multiplexing capabilities further towards commercialization for preparation for future pandemics.

- During Phase II, L3C was a community-based challenge which supported the development of creative data-driven solutions that meaningfully advance the current understanding of the risks of developing PASC. The top three winners for the challenge were:
    - First Place: University of Chicago’s Convalesco team built a real-time monitoring system based on LightGBM and XGBoost that updated a patient’s risk for developing PASC/Long COVID as new clinical events occurred. Clinical features for this model included conditions from the acute phase that are associated with PASC (such as fatigue, pain, weakness, and dyspnea) as well as prior viral exposure of any type, bloodwork, oxygen saturation, and certain drug exposures.
    - Second Place: Geisinger AI Lab built a portable, efficient, and accurate model using fewer features than the competition, resulting in a translational PASC/Long COVID prediction clinical decision support tool that included EHR-ready summary visualizations for clinician interpretation.
    - Third Place: University of California, Berkeley team built a clinical prediction model that combined many smaller prediction models (this combined model was known as an ensemble or a super learner). The model used various aspects of a patient’s health such as their cardiovascular health, respiratory health, history of hospital use, and age to predict the patient’s risk for developing PASC/Long COVID.

Throughout the RADx-rad program, 32 projects filed patents or released as open-source, one project submitted an Emergency Use Authorization (EUA), seven projects submitted pre-EUAs, 23 projects met with the Food and Drug Administration (FDA) for authorization of their products for emergency use, 26 projects teams submitted primary publications, and 10 projects were awarded commercialization support. Overall, the accomplishments of the RADx-rad program

emphasized the potential of these innovative methods to be applied to other and future pathogen detection, surveillance, and diagnostics.

Community Engagement

Because COVID-19 disproportionately affected the most vulnerable populations, a critical component of the pandemic research was to involve the community and collaborate with other scientists to improve health outcomes. RADx-rad funded 49 extramural research projects at 45 unique institutions across 20 states. Ninety-six teams registered to participate, and 35 teams submitted completed models as part of L3C. In combination, the teams represented academic institutions, medical centers, technology and data firm industry partners, and a private-public partnership.

Throughout the RADx-rad program, awardees had the opportunity to interact with the community. For example, the WBD category funded seven projects throughout the U.S., which focused on using wastewater to estimate population-level data within communities and to reduce COVID-19 spread throughout. During these projects, researchers had the opportunity to collaborate with local governments in both urban (e.g., New York City, New York; Tempe, Arizona) and rural communities (e.g., mobile vans which serviced counties in Kentucky), universities, such as those with contained wastewater systems, Tribal communities, and private sector partners to conduct their studies. The new community collaborations helped to identify the circulation of new variants prior to clinical detection. Furthermore, PreVAIL kId’s funded eight projects, whose goal was to develop prognostic algorithms to predict disease severity of COVID-19 in infants to adolescents. Across each of the eight studies, researchers partnered with over 45 domestic sites and nine international sites, which contributed to the enrollment of over 8,000 participants. By fostering and sustaining new academic- community partnerships to carry out this meaningful research, the innovative and novel applications developed during the RADx-rad program can be applied to future pandemics and public health emergencies.

Impact and the Path Moving Forward

As the post-pandemic world continues to take shape, it is important to apply the lessons learned over the past few years. Several processes have been proven beneficial to the ongoing success of the program. First, the RADx-rad program established a working group of committed Program Officers. Clear, early guidance helped resolve Common Data Elements (CDEs) in advance of application receipt which ensured data quality and consistent data collection. Second, the program tailored its support and funding to the needs of the investigators. The program partnered with the NIH Small Business Education and Entrepreneurial Development (SEED) Office to support the investigators as they worked to bring their products to market. Finally, the program provided opportunities for investigators to engage with the FDA prior to the submission of their applications for authorization. Some investigators are continuing to work with the SEED office as their projects move closer to commercialization. Lessons learned on navigating and expediting the regulatory process from FDA officials, and bringing a product to market from the SEED entrepreneurs in residence as well as the various core supports has positioned both individual investigators and the NIH as a whole to tackle future health emergencies. Overall, the RADx-rad program brought together academics, industry partners, and community members from across the U.S. to develop innovative approaches and reimagine uses of existing tools to detect and combat the SARS-CoV-2 virus, its variants, and emerging infectious diseases.
The project teams are continuing to collect longitudinal data and develop their technologies to be used in detecting other diseases. Notable among future plans are:

- SCENT is exploring the use of breath analysis for rapid screening of illicit drugs, and for the detection of PASC, Diabetes, Respiratory Syncytial Virus (RSV), Influenza, and Lung Cancer
- The Chemosensory Testing teams are assessing how to encourage the routine testing of loss of olfaction function, which can be a symptom of viral infections, brain injuries, and neurodegenerative diseases such as Parkinson’s and Alzheimer’s

- The Exosome-Based project teams are working to develop technologies to be used for detecting multiple viruses, characterizing cancer biomarkers, and predicting response to therapies
- The WBD teams are expanding their testing to other viruses, bacteria, and illicit drugs.
- Multimodal Surveillance project teams are collecting longitudinal data on COVID-19 outcomes, including mortality and hospitalization rates
- The Novel Biosensing teams are working to develop a multiplexing test for COVID-19, RSV, and Influenza
- PreVAIL kIds teams are working to implement the new KIDMATCH algorithm which calculates a risk score for the development of MIS-C and Kawasaki disease
- Automatic Detection and Tracing teams are improving the accuracy of the testing and are planning to expand to include the detection of other viruses such as Human Immunodeficiency Viruses, Influenza, RSV, and Dengue Fever

Overall, the novel concepts developed from the RADx-rad program will provide an array of devices and strategies to tackle the next pandemic as well as inform the detection and treatment of other health conditions.

Conclusion

In summary, the RADx-rad program provided a mechanism to support innovative projects to complement other research regarding detection and testing of SARS-CoV-2, and to improve diagnosis of acute and long-term conditions associated with COVID-19. Using a variety of technologies such as nucleic acid driven micromotors to AI generated algorithms, RADx-rad funded applications showed the various ways technology and informatics can be used to support public health responses to future pandemics. Furthermore, RADx-rad illustrated how a broad range of scientific collaborators across various sectors and engagement with community members can leverage technologies and informatics to develop new tools or improve existing ones for improved detection and testing during a pandemic. Although, the RADx-rad program is scheduled to conclude by the end of 2024, the tools developed during the program and the lessons learned will be used to address future public health crises.