Part 1

Surveillance of Wastewater and Prevention Platform (SWAPP): A Case Study of Digital Public Health and SARS-CoV-2

By **Corina J Shtir, Austin D Swafford and Jeremy E Ellis**

Abstract

COVID-19 caused unprecedented disruptions across healthcare systems and global economies, exposing an unmet need for precision public health (PPH) measures. Incidence and prevalence rate estimates rely on seamless delivery of relevant information when and where it is needed most. Wastewater-based Epidemiology (WBE) complements clinical COVID-19 testing via a cost efficient and scalable approach. Digital health (DH) provides the catalyst for WBE stakeholders to support healthcare practitioners and affiliates.

In this article we summarize the elements necessary to support PPH via WBE, and illustrate the roadmap addressed via SWAPP (Surveillance of Wastewater and Prevention Platform), a dynamic, cloud-based DH platform, developed by InterOme. Collaborative synergies between InterOme, University of California San Diego, and Fry Laboratories are detailed, all of which

are necessary for robust PPH efforts. We describe the WBE scope of work necessary for multiple WBE healthcare stakeholders and how SWAPP is designed to address the expanding lens of PPH for the SARS-CoV-2 pandemic. We present the architecture of SWAPP and illustrate the critical role of multi-omic advanced analytics. While the goal of WBE is to collect analytical measurements of the viral concentrations within wastewater, the goal of SWAPP is to convert these results, align other data sources, and contextualize the integrated data package into tractable knowledge.

Even after the COVID-19 pandemic, we anticipate an ongoing and substantial demand for DH to improve management of infectious diseases, and ultimately diseases in general. SWAPP serves as a foundation for future applications that will accelerate the progression from monolithic approaches (e.g., clinical, genomic, proteomic) to more consolidative models essential for PPH.

I. Public Health Challenges and Opportunities.

Efficient public health surveillance and disease prevention programs rely on robust and scalable solutions that can rapidly gather data, predict outcomes, and recommend interventions via seamless delivery of relevant information when and where it is needed most. The ongoing COVID-19 pandemic has served as a powerful example of the costs, both human and capital, that come from a lack of access to up-to-date, reliable, contextualized, and actionable information. According to the American Hospital Association, across a span of four months, from March to June 2020, when US COVID-19 cases started to spike, hospitals and health systems lost an estimated $202.6 billion. The global burden of this pandemic has surpassed many trillions of dollars, and more pressing, efforts aimed at managing public health (PH) remain inefficient in their ability to surveil the onset of outbreaks and take steps to preserve quality life years. This challenge is exacerbated by broad variation in biological risks and predispositions, complex demographics, environmental interactions, and ineffective data aggregation or interpretation across multiple disciplines.

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Even before COVID hit the US healthcare systems, the inefficiency of finding the necessary information or inability to successfully connect the innumerable and ever-increasing datapoints ultimately contribute to US healthcare costs. *Total* US healthcare industry expenses in 2018 alone amounted to approximately $3.6 trillion, averaging $11,000 per person. Estimates given by the Centers for Medicare and Medicaid Services project that by 2028, healthcare costs will climb to $18,000 per person, for a total of $6.2 trillion, and will represent about 20% of GDP.[1] Although much infrastructure, devices for testing, and public awareness have now been developed, these resources have created a new set of challenges in the form of unprecedented amounts of disorganized, sometimes conflicting, information ('data overload') at the local, regional, national, and global level. By isolating information in independent healthcare silos,

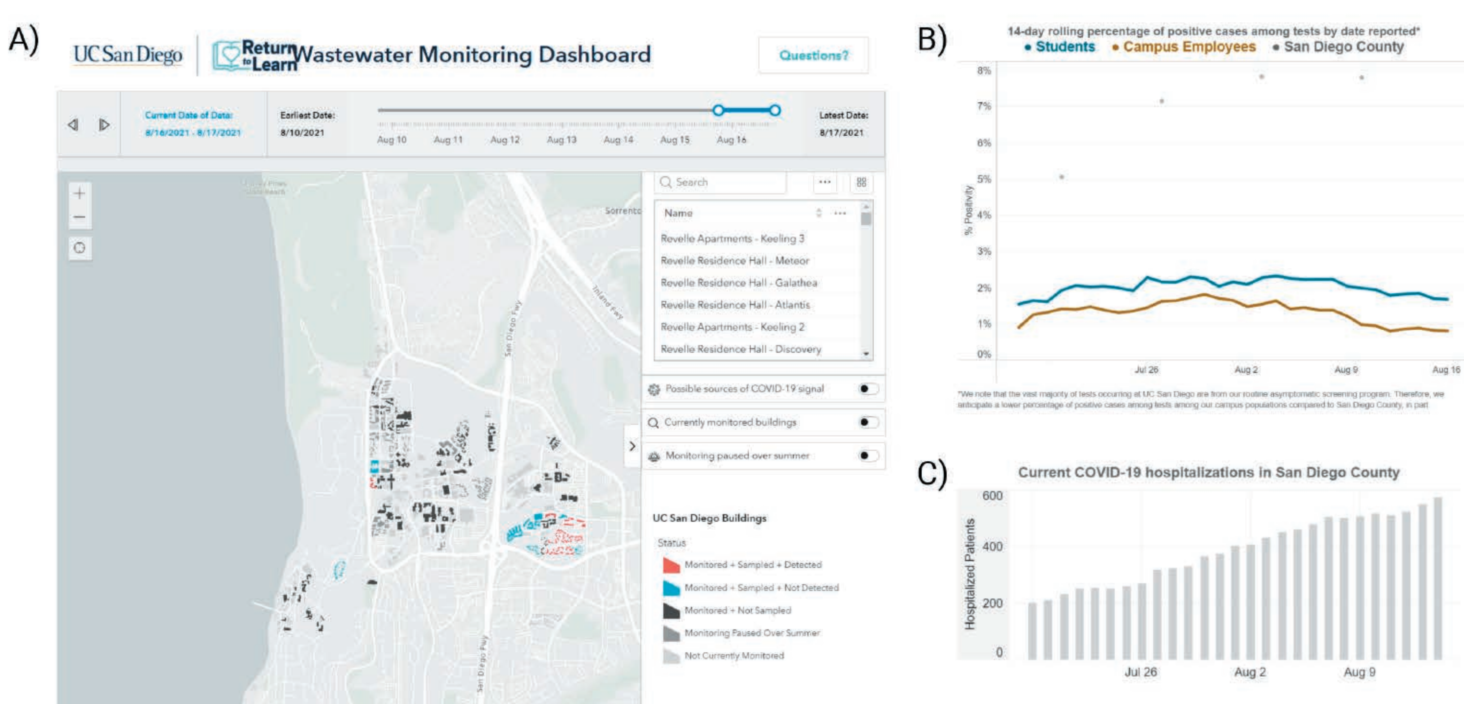

Figure 1: Highlight from the UC San Diego Return to Learn (RTL) Monitoring Dashboard.

A) An interactive map of the locations and statuses of buildings as assessed by wastewater monitoring for SARS-CoV-2 provides timely spatially-coherent information on the patterns of viral detection and spread on campus. B) The 14-day rolling percentage of positive cases for UC San Diego student and staff in the context of similar data reported by San Diego County for the period of mid-July to mid-August 2021. C) The number of patients in San Diego County hospitalized with COVID-19 over the period of mid-July to mid-August 2021 reflecting the broader rise in cases and hospitalizations from the delta variant (B.1.617.2) of SARS-CoV-2.

the risk of being too slow to respond to a new or prolonged pandemic remains unnecessarily high. Management of a prolonged SARS-CoV-2 pandemic or an entirely new pandemic will become increasingly difficult for a healthcare system stretched to the breaking point driven by an unprecedented increase in devices and tests, interventions compounded by independent, unintegrated, and potentially conflicting healthcare practices.

Unmet Need for Precision Public Health Solutions

The current pandemic unequivocally revealed an unmet need for better management of assessing risk for a developing disease. A DH platform that supports data integration and interpretation at the individual and PH level ideally addresses four main areas in PH management:

1. exponential information growth via new parallel and orthogonal devices and tests
2. inefficiency of multidisciplinary data aggregation
3. the pace of discovery exceeding decision making and
4. limited remote access to expertise in routine clinical practice.

DH is well-suited to collect, count, catalogue, categorize and organize information in ways and at scales that exceed human capacity. This includes the capacity to assimilate and integrate structured and unstructured data from public databases, datasets, and biomedical literature by use of machine learning (ML) and natural language processing. The outcome is the ability to provide (1) explanatory and predictive summaries that inform on the type of measures that can improve wellness, and (2) automate data quality control, which in turn advances implementation of standardized processes. The final purpose of digital health is to transform data into knowledge via data integration and advanced analytics. Efficient integration of information and data has the potential to extend these gains to support both population-scale and targeted prevention efforts. Moreover, the population-aware contextualization and integration of information supported by DH platforms can form the avenues that combine precision medicine (PM) and PH efforts into precision public health PPH initiatives.

> *"Precision medicine is focused on improving wellness by leveraging large amounts of datapoints to improve diagnosis and treatment of disease for a patient population with the aim of giving the right treatment to the right person at the right time."*

PM and PH endeavors have for most part been operating at opposite ends of the healthcare spectrum. Precision medicine is focused on improving wellness by leveraging large amounts of datapoints to improve diagnosis and treatment of disease for a patient population with the aim of giving the right treatment to the right person at the right time. At the other end of the spectrum, public health utilizes a few datapoints to apply solutions across large populations through preventive approaches and timely interventions. With the surge of Big Data and the rise of the COVID-19 pandemic, the convergence between precision medicine and public health has been cemented, resulting in PPH, a sector which leverages biological, demographic, environmental, and genetic factors supported by population-scale data. Chokwanyun et al. defined PPH's aim as

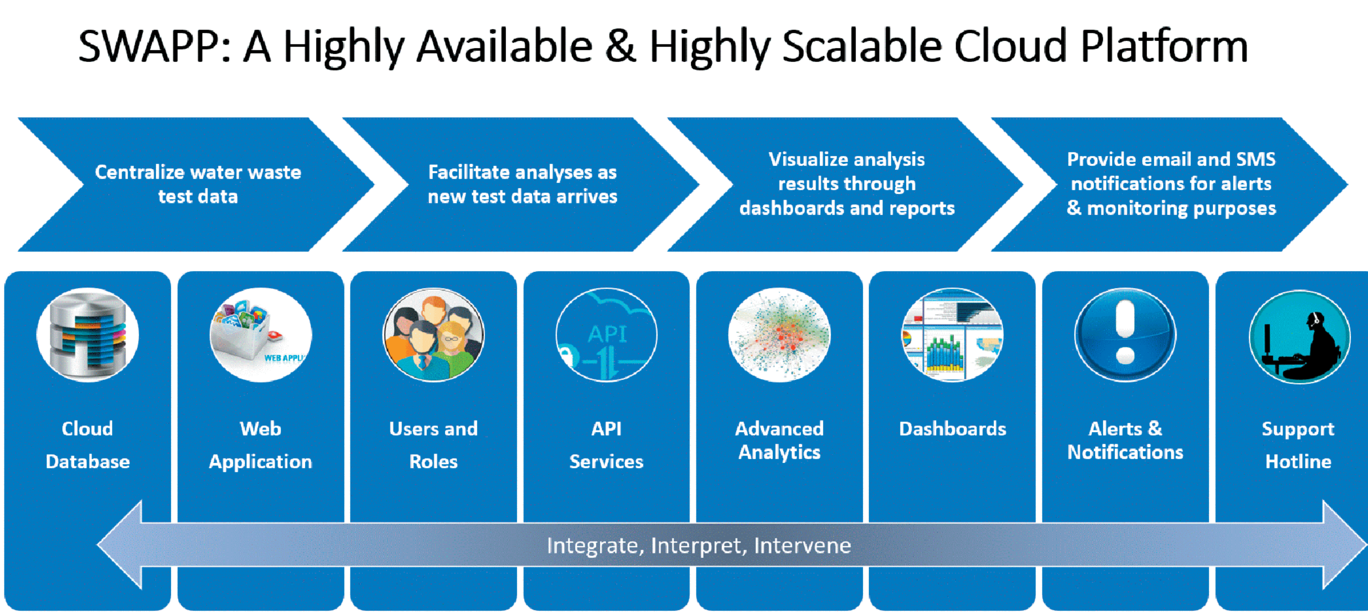

Figure 2: Surveillance of Wastewater and Prevention Platform (SWAPP).

SWAPP is an extensible and scalable cloud-based platform for wastewater monitoring tracking, reporting, analysis, visualization, and interaction to support critical decision-making efforts for many types of end users and organizations. Main characteristics for each component are as follows: 1) Cloud Database facilitates storage of data and groups sites into organizations to allow analysis at site level as well as organizational or regional level, 2) Web Application enables system, user, and data management and configuration, access to data monitoring dashboards, and reporting, 3) Users and Roles setup via a privilege-based system, 4) Application Programing Interfaces (APIs) Services automate the receiving of data via an 'always-on' connection, 5) Advanced Analytics, via multi-omic, explanatory, or predictive modeling, 6) Dashboards monitor and track the status of selected metrics and are customized for particular use cases, 6) Alerts and Notifications by email and/or text messages, 7) Support Hotline provides backing for API services as well as for general web application use.

"using all available data, coupled with advanced analytics and technologies, to improve population health"[2] which aligns with the vision of Khoury *et al.*[3] that "PPH can expand understanding of health disparities, advance strategic public health science, and demonstrate the need for innovation and workforce development." Good health is fundamental to a good life, and the power of PPH to reshape the health of individuals and communities provides a powerful motivation for investment of time and resources to turn these visions of DH-powered PPH into reality.

II. Building the Infrastructure for a Large-scale Surveillance of Wastewater and Prevention Platform (SWAPP).

We describe in this paper the collaboration at InterOme, with academia, private labs, and citizens at large to develop a DH platform that supports healthcare practitioners and affiliates to manage large-scale surveillance and prevention of COVID-19 via wastewater testing. We illustrate the necessary ecosystem required to generate meaningful integration and automation of information, and to facilitate symbiosis between regional and population or global-scale efforts. Further, we illustrate the different perspectives from each of the main players, their challenges, and the interdependencies that drive the expansion of such a DH platform. Ultimately, we describe, from a DH platform perspective, the challenge of building an infrastructure with functionalities that address one or multiple correlated issues or symptoms. This challenge is defined by a multidimensional matrix, which is the main reason why such efforts are still in development or in research mode and not yet widely adopted for routine practice, either at large-scale or across a variety of regional strata.

We also emphasize our efforts to reduce the incurred costs on PH management and improve quality of life regardless of time, location, and sufficiently staffed facilities. The current pandemic related PH ecosystem revealed that most requirements do not have a one-to-one relationship with a specific digital function. Rather, we observe a one-to-many or many-to-many mapping both ways; a given datapoint (coming from the wastewater, lab, or other origin) invokes multiple functions within a DH system, while a single DH functionality often maps into multiple and potentially correlated PH variables or issues. Characterizing and defining this matrix alone requires deep understanding and communication between all players. Furthermore, solving it necessitates a strategic, collaborative, and phased approach that works in tandem with the accumulation of multiple datapoints, and with validation of results across different scenarios.

We describe at a high level in this article the scope of work necessary for multiple healthcare stakeholders to engage in development of a PPH initiative, and how SWAPP is designed to address the expanding lens of PPH for the SARS-CoV-2 pandemic via four main areas of parallel development:

1. multi-omic advanced analytics,
2. explanatory and contextualized analysis,
3. automation of data QC, and
4. continuous assimilation of demographic, environmental and other data, via advanced prediction modelling.

In this paper we present the SWAPP architecture and multi-omic advanced analytics approach. A second paper will follow with inclusion of the remaining areas, along with related data. Finally, we describe a framework that includes precision medicine to support a fully realized PPH. We note that a DH platform entails not only generation of data outcomes, but advanced management of data quality itself, with automated QC surveillance and monitoring at all steps throughout the journey of a sample. SWAPP implements this two-pronged approach – automated QC of data and an engine that generates outcomes to safeguard adequate generation and adoption of standardized protocols. In return, advanced DH-based QC models can enhance all systems incorporated within a PH operation.

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The SWAPP platform will serve as the foundation for many additional future efforts, including PM applications. Eventually, digital health platforms such as SWAPP will close the link between PM and PH applications into PPH and enable the progression from individual genomic-based models to more consolidative models that include social, demographic, and environmental factors. Notably, failure to facilitate mechanisms that influence and improve individual behavior that contributes to better health of populations will prevent successful implementation of PPH broadly.

III. Wastewater-Based Epidemiology: Opportunities, Perspectives and Challenges.

As the majority (~80%) of individuals infected by SARS-CoV-2 do not exhibit clinical manifestations or only experience mild symptoms,[4] a critical need persists to improve the surveillance system for monitoring PH. Recent studies demonstrated that while SARS-CoV-2 is primarily a respiratory virus, it also replicates in the gastrointestinal track and is excreted into the feces of infected individuals,[5-7] making wastewater-based epidemiology a feasible model for PH surveillance and for implementation of prevention programs. Furthermore, Barcelo *et al.*[8] presented a WBE mechanism for surveillance of viral spread within communities. These authors demonstrated how wastewater-based monitoring can provide an essential surveillance tool that can aid the spatial and temporal mapping of viruses. In addition, WBE presents a more cost-efficient method of estimating the true number of infected persons, as the number of reported clinical tests is usually limited to symptomatic individuals and is delayed by the number of days required for infected people to develop symptoms. In contrast, rising levels of viral isolate detected over time by WBE is a reliable predictor of overall infection rates within the population from which the wastewater is derived, regardless of the reported incidence of the virus as detected by individual testing and reporting.

In addition, wastewater analytics can predict outbreaks or hotspots, and through inclusion of regional and temporal assessment, evaluate the effectiveness of PH intervention or alternatively viral spread where measures were not implemented. Xagoraraki and O'Brien[9] presented a WBE system model and defined conditions under which we could improve detection and prediction of viral outbreaks. In addition to WBE's use as an early warning for an outbreak, it could be used to generate spatial and temporal heat maps detailing the dissemination of viral variants in a community, as was the case with the near universal and rapid displacement of all previous COVID variants by the Delta variant from June to August of 2021.

WBE monitoring could predict the prevalence and distribution of any variant over time, enabling directed PH measures to slow the spread and protect vulnerable populations within affected areas. Similarly, besides proving the cost efficiency of high throughput WBE testing versus individual and repetitive clinical testing, Hart and Halden[10] and Knight *et al.*[11] explored modes though which WBE can quantify the viral spread and estimate the number of asymptomatic infections. Investigating further, Daughton[12] described three types of WBE test models, depending on the level of available information:

1. a qualitative method to assess presence or absence of infection,
2. a semiquantitative method that measures relative levels of infection across different regions within a community, and
3. a quantitative method to evaluate absolute infection levels in different zones within a community, and relative to other communities.

Several studies of WBE for COVID-19 validated the utility of these models, including Wurtzer *et al.*[13] who accurately forecasted the cumulative number of COVID-19 cases as early as 8 days before other methods, and Karthikeyan *et al.* who demonstrated the prediction of total caseloads in San Diego County via total wastewater samples collected from the Point Loma location.

As an example of public dashboards, the Return to Learn (RTL) work at UCSD, supported by UCSD and independent of SWAPP, was able to show how PPH can be deployed at a single location using WBE to perform daily monitoring of more than 100 wastewater manholes to triage screening, testing, and intervention efforts for students and staff.[14] More recently we have even been able to extent this to determine which students were the source of detected viruses in a specific building and predict how soon they would appear in the hospital.[14] Our UCSD RTL Dashboard is updated daily to provide summary statistics on our campus COVID status as well as timely information on potential exposures, based on wastewater testing (**Figure 1A**). Additional statistics and visualizations are provided to give some broader context by placing our student- and staff-test positivity rates in the context of San Diego County data (**Figure 1B**), as well as to provide information on the COVID burden across our local hospital systems (**Figure 1C**).

Links to additional information, including agent-based models developed in partnership with Mathematica (https://college.covid19.mathematica.org/) can also help assess the impact of campus-wide policy efforts, however, users interacting with the tools can only perform limited operations to re-visualize or examine the data. At this time, UCSD users cannot set custom rules for notifications or updates, neither access external tools that help in the interpretation of the results for themselves or their organization. For example, if vendors are considering an on-campus visit to one or more research buildings and note that the campus positivity rate is on the rise, yet less than the overall rate of the county, while at the same time noticing that the number of COVID hospitalizations is rising, how should they use this information to determine how to act? Predictive, AI-driven analytics, and user-driven interactions and queries, all part of a PPH DH tool, could enable them to better assess the risk of their planned behaviors and activities, and therefore to aid in decision-making.

The expansion of such efforts across whole regions with integration of information via a robust DH platform could enable healthcare systems to efficiently allocate and mobilize resources with precision while simultaneously supporting contact tracing both at the social and molecular levels, as detected strains can be mapped to their sources of origin. Thus, WBE integration via DH can assist PH stakeholders to prioritize their efforts and resources and depending on a given geospatial location and demographic profile, to better control parameters that influence viral spread.

"It is incumbent on digital health platforms to allow for access to information, not just to those within the expertise strata, but to the community stakeholders."

Monitoring wastewater encompasses different approaches, all of which play a distinct and complementary role in the overall endeavor. The range of assessments that affect the overall workflow of WBE includes the wastewater companies, testing laboratories, end-user customers (nursing homes, schools, organizations, etc.), governments, hospitals, researchers, individuals within the community at large, and within the PPH sector, the inclusion of pharma and healthcare providers.

In the following sections we focus our attention on the perspectives and challenges faced by wastewater companies, testing laboratories, and end-user customers, in addition to the full development scope that a DH platform needs to undertake. It is incumbent on digital health platforms to allow for access to information, not just to those within the expertise strata, but to the community stakeholders. To distribute knowledge efficiently, local, and global community efforts should be engaged during the project inception. This early engagement will ensure that all our efforts are encouraging behavioral attitudes and, where needed, policy changes, that will cumulatively lead to improvement in individual and public health.

A variety of evaluations will not be covered at this time, such as the governmental and regulatory perspective of WBE, wastewater drainage basins and their effects on viral decay, or the implementation of various water treatment tests that have not yet been sufficiently tested, validated, or incorporated in the mainstream of WBE programs. These topics will be deferred for a later publication, as such elements will naturally become part of the growing environment of PPH wastewater management.

For the reasons mentioned above, InterOme has established SWAPP as a highly accessible and scalable cloud platform that allows for the centralization of wastewater test data, automates QC of data, facilitates automation of analysis as new test data arrives, provides comprehensive visualization through dashboards and contextualized reports, and provides email and SMS notifications for alerts and monitoring purposes. InterOme makes managing and interpreting Big Data more tractable by analyzing and presenting information in a format for actionable decisions (**Figures 2**). Through our collaboration with academia, we constantly include relevant research initiatives to investigate ways in which we can use these data to:

1. to study the variety of different organisms that may be appearing in a sample of feces and that may influence the outcome of our interpretations,
2. to include demographic and environmental aspects of PM and PH in algorithms that support PPH at the population level, and
3. to improve models aimed at predicting better responses.

We note that lessons learned during the process of developing SWAPP alerted us to a primary need for DH companies to take the time to understand all necessary components and variables that influence the outcome of WBE testing, and to nurture their development via multifaceted collaborations. This is an essential prerequisite for building a successful infrastructure that includes a secure, flexible, and scalable system.

To better illustrate the views of the central players, we detail in this paper the main steps involved in the wastewater testing process

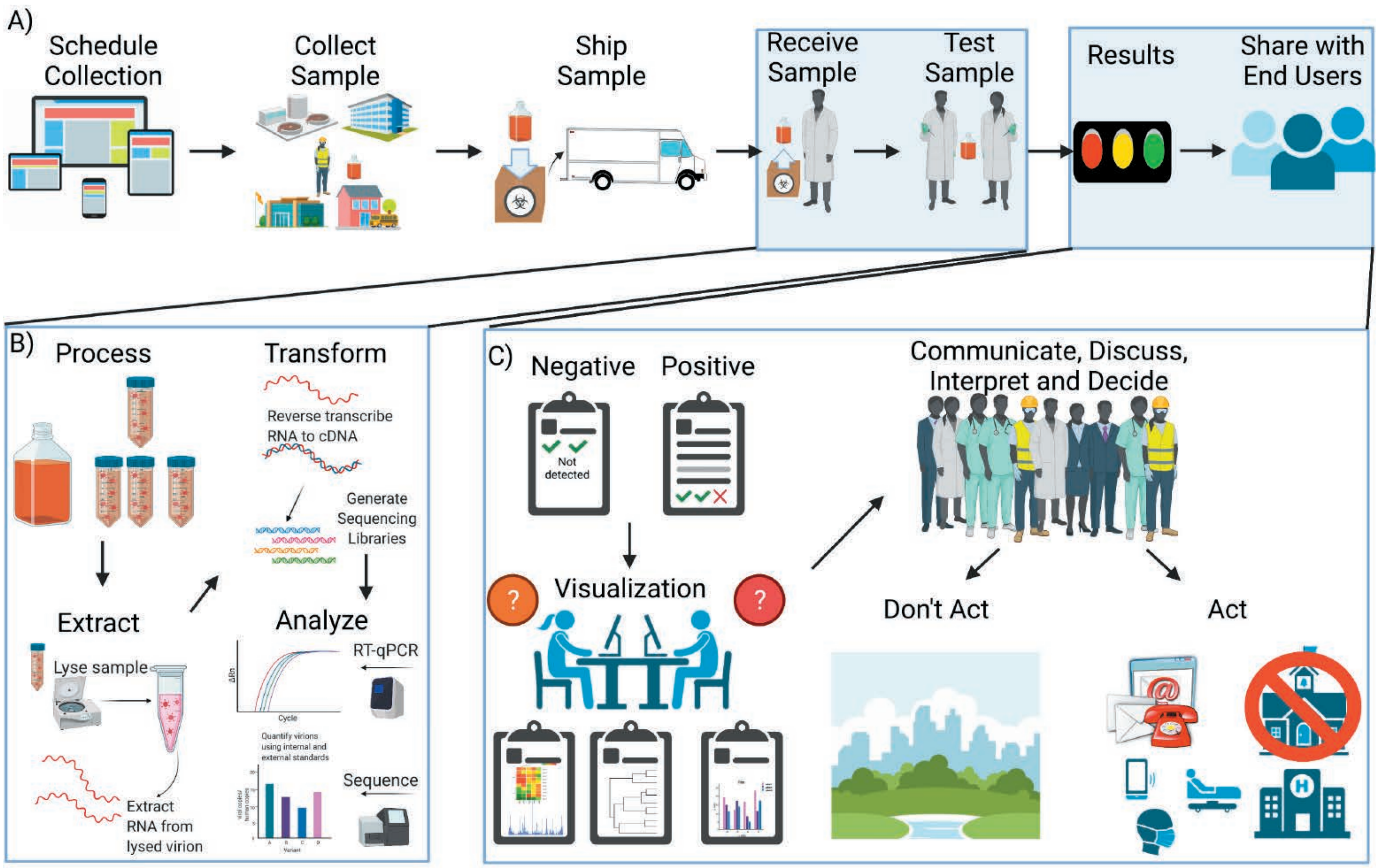


Figure 3: Wastewater-based Epidemiology Perspectives

A) From the perspective of a wastewater company, the monitoring effort for a pathogen such as SARS-CoV-2 should be a straightforward set of actions that begins with a scheduled collection and ends with the straightforward reporting of results to the customers or end users based on the testing activities of a contracted laboratory. B) From the perspective of a wastewater testing laboratory, many steps to generating the result are needed each of which comes with associated protocols, data, and metadata about the protocols that are crucial for quality-control efforts and improving workflows. C) From the perspective of the customer, the process of wastewater monitoring does not conclude with the receipt of the results as negative and positive results will have different information content which may need to be incorporated into visualization for communication, discussion, and interpretation to inform actions.

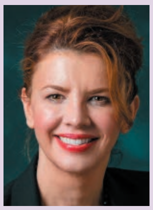
across wastewater companies, laboratories, and end-user customers, as summarized in **Figure 3**. Each decision process relies on multiple triggers dependent on different steps or outcomes. This workflow establishes the baseline for the type of processes that must be addressed by an integrative DH platform, not only for data monitoring and advanced statistics, but to ensure operations run efficiently, automatically, and at large scale.

Wastewater Surveillance Company Perspective

From the perspective of a wastewater company (**Figure 3A**), a viral monitoring process is straightforward. The scope-of-work consists of scheduling sample collection(s), dispatching team member(s) to perform the sample collection from one or more wastewater sites, shipping samples via a preferred provider to a testing lab, receiving results, and finally sharing them with their end-users/customers. In addition, other significant factors relate to location where to sample from, sampling frequency, mapping of sample flow-path to relevant buildings, multiple sampling strategies, chain of custody of sample and data, GLP (Good Laboratory Practices) sample tracking through the process, and association of sample result with time and sampling location. While the process workflow itself is simple, each step and related option can introduce an opportunity for degradation of biological material, e.g., viral particles, that could potentially affect the test outcome and confidence in the results. For example, sample collection is based on a variety of existent protocols that safeguard against spilling and is dependent on the type of container utilized and on the type of wastewater tested. Also, the sampling step involves a variety of volume extraction requirements, depending on the site location and sample type.

The wastewater company may also encounter factors that are environmentally induced, such as temperature at the wastewater site, system flowrate, or bulk materials that have unexpectedly entered the flow system. Additionally, the GPS location of the sampling site is a required parameter to safeguard against incorrect prediction of a potential outbreak source, a task that can be addressed through a DH support application. However, the GPS location only indicates the most available site necessary to harvest a sewer sample from. A sewer map is also required to determine the source and elevation map, to establish flow direction.

The individual and cumulative effect of these steps influences the viral (and data) integrity. A multitude of metrics must be implemented as part of the QC workflow, within lab reports, and as weighted scales within DH algorithms that focus on creating prediction models. Many of these parameters are well established; however, many other parameters remain to be addressed by scaling up studies and to learn more about the WBE process and variables that can introduce inaccuracies. From the wastewater company's perspective, the remaining system could well be treated as non-surveyable "black box" that ends with analysis and data generation. Wastewater surveillance for COVID is the main element included in the SWAPP target application. We pick up this story in Part 2 with the Laboratory Perspective, Customer Perspective, and detail about SWAPP. JoPM



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Dr. Corina J Shtir is CEO and Co-Founder of InterOme Inc, a global digital health company that aims to make complexity simple by developing and placing digital healthcare tools in the hands of healthcare practitioners, for the purpose of enabling profound assessment of wellness, disease, and treatment. Dr. Shtir has a PhD in Biostatistics with applications in Statistical Genetics and Epidemiology, and (2021) Distinguished *"Public Health Hero"* Award by the US USC Keck School of Medicine University, (2013-2109, Thermo Fisher Scientific), VP, Global Head of Precision Medicine. Dr. Shtir led the global expansion of the company's precision medicine platform and led the growth of Thermo Fisher's Precision Medicine segment into an operation encompassing 200+ large or national-scale programs with a presence in 100+ countries.

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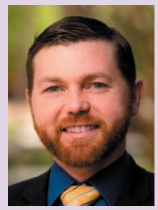

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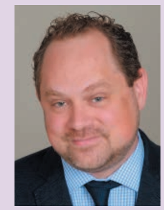

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Jeremy Ellis, Ph.D. is the Chief Scientific Officer at Fry Laboratories, LLC and BioID Genomics, Inc. Fry Laboratories is an independent clinical diagnostics and research laboratory based in Scottsdale, Arizona; while BioID Genomics is a biotechnology spinoff company used to distribute innovative technologies developed in the clinical laboratory. Dr. Ellis is responsible for evaluating and translating high value biotechnologies to clinical use in addition to developing novel technologies that support next-generation DNA sequencing. He is an author of several recent patents regarding an ultra-rapid next-generation DNA sequencing technology and associated computational analysis methods. Dr. Ellis received his bachelor's degree in microbiology from the Arizona State University and completed his Ph.D. studies in developmental and cellular biology at the University of California, Irvine. As an industrial scientist, he has focused on the development of clinically compatible comprehensive microbiology laboratory solution across all disease types enabled by cutting edge bioinformatics, targeted sequencing methods, and the sequence-based analytical definition of microbial taxonomy. More recently, Dr. Ellis has led the development and the EUA submission of a high-throughput SARS-CoV-2 detection assay using next-generation DNA sequencing methods. This assay development project is a result of an ongoing collaboration with Beckman Coulter Life Sciences.

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Part 2

Part 2 of this article will be published in the December Issue of *Journal of Precision Medicine*.