REAGAN-UDALL FOUNDATION FOR THE FDA

Practical Applications of Real-World Evidence to Enable Regulatory Submissions

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Optimal use of real-world data/evidence (RWD/RWE) in research and regulatory science will enable all stakeholders to improve the use, interpretation, and performance of diagnostic tests – a process that ultimately improves the medical products available to patients and enables critical public health decision-making. The Reagan-Udall Foundation for the FDA sponsored a research program to evaluate real-world performance for two types of diagnostic tests (antigen and molecular) and to determine how RWD/RWE can be leveraged for Emergency Use Authorizations (EUA).

Below is a summary of some of the research findings as well as the potential practical use of these findings for regulators and manufacturers. Of note, this commentary is based on a review of the publicly available executive summary only.

IDx20

Many of us who took home antigen tests during the height of the pandemic really wanted to know if we were contagious. Many of us also noticed when we had COVID that the at-home lateral flow antigen test seemed to turn vividly positive early on in our course; and when we were recovering, if we still tested positive, it would be a fainter line. However, most of us thought this was just an incidental finding as there was no science behind it. The IDx20 team asked many questions, including the one we all wanted to know: what does the intensity of the line on my at-home test mean? Understanding if one was contagious, or even what the correlation to viral load was could have clinical significance in how patients are managed, including implications for return to work. The project also aimed to create tools for quantifying and comparing the real-world performance of different COVID-19 antigen tests.

Key Findings:

The clinical study employed computer image processing and mathematical probabilistic modeling techniques to quantify test results. Key findings from IDx20 were that signal intensity (how vivid the line was) can be leveraged to develop an algorithm to obtain quantifiable limits of detection (the concentration of virus that can be detected with 95% confidence) and assess test performance. In addition, the research team developed a digital reporting system for collecting and reporting test results in real-time. The digital reporting platform allows users to log their antigen test results, review testing history, and provides various reporting options – thereby supporting clinical care and public health surveillance.

Limitations: One of the largest limitations is that viral load does not always equate to contagiousness (given whole live virus vs. particles/fragments of virus that result in viral load), so this study cannot be translated into practice to definitively claim that someone is contagious.

Beth Israel Deaconess Medical Center

Clinicians managing patients during COVID often wondered what some of the differences were that made some people sicker than others. The information many wanted was what patient characteristics are significant in changing outcomes and how do these characteristics differ across patient groups. One of those characteristics is viral load. Given that COVID-19 viral loads can vary from person to person, clinicians did not know if viral load differed by patient demographics, especially race. Beth Israel

Deaconess Medical Center investigators hypothesized that most groups exhibit the same range of viral loads. If true, then home antigen tests for COVID would be equally effective for most groups. If not, then certain groups might require separate trials to get the most benefit from antigen tests.

Key Findings:

A public web application (https://arnaoutlab.org/coviral/) was developed to share graphic outputs from data generated from this research. The website includes: 1) estimates of viral load derived from cycle thresholds across patient groups (e.g. race, gender, presumed circulating variant); 2) the p-values for the difference in viral loads across different groups; 3) measures of sensitivity and specificity from paired samples that underwent both OTC antigen and PCR tests; and 4) predictive modeling results for contagiousness. Viral load distributions from different patient groups were found to be similar and the sensitivity and specificity of the two antigen tests were similar across patient groups. These results suggest little variation across groups and that separate trials focused solely on patient variation may not be necessary for evidence-based approval of COVID antigen tests.

Disseminating information via a public portal helps to dispel misinformation about test performance and gives access to results to patients, clinicians, and public health officials. This research helps set the stage for future expansion and further development of such tools.

Limitations: This current example is only applied to COVID-19 and we do not know how it would perform with other infectious diseases tested in similar modalities. Meta-data about the tests (e.g., reference ranges for each test) were missing from the website and having such information available for review would advance public trust of RWE for regulatory decision making. Finally, as with IDx20, viral load doesn't always equate to infectiousness/contagiousness.

Conclusions:

Overall, these projects demonstrate techniques for evaluating the performance of COVID-19 antigen tests. These techniques may offer advantages in comparing data among different clinical trials and assessing the performance of lateral flow at-home antigen tests in real-world conditions. Knowledge of the antigen test performance across different groups may inform the need for (or obviate the need for) further clinical validation studies. As the COVID-19 testing landscape highlighted, different tests are needed in different environments. The gold standard, the molecular test, is still something that will be essential, but at-home testing will have a role in a public health response and from an access and convenience standpoint.[1] In addition, if there is a predictive model that can be used to estimate the level of contagion, that could be clinically useful and demands further study.

Both projects highlight areas of interest for further investigation. Currently, the results from these studies might be leveraged to speed regulatory submissions from SARS-CoV-2 IVD manufacturers for EUA to full market approval by obviating the need for clinical trials on subpopulations for market approval or to speed clinical trial completion in other ways. The speed-to-trial completion will be helpful to regulators and manufacturers, and ultimately patients as they would have access to needed tools sooner. These incremental findings, that the intensity of a result line on a lateral flow test might be leveraged for measuring viral load or perhaps be a proxy for "contagiousness" and that, in the case of COVID, specific

[1] A molecular test (often referred to as PCR, generally done in a laboratory) detects the SARS-CoV-2 virus's RNA. An antigen test (often lateral flow test), detects pieces of protein from the SARS-CoV-2 virus (or that the virus produces).

populations need not be studied, are helpful for hypothesis generation when approaching new and emerging pathogens.

One area that might have broad applicability across disease states is the use of a public web application (e.g., https://arnaoutlab.org/coviral/) that would collect and report out on the real world data collected. Key here is publicly reporting these data and results so that they might be compared easily and replicated, as well as standardizing and harmonizing tools for capturing these data across all labs doing this work. Creating a learning health network (LHN) leveraging the collective talents and data in the LHN would be useful for clinical trial tool development and clinical operations, advancing regulatory science, and ultimately, for regulatory review. Ensuring critical data elements needed for a public health response were included and leveraging this concept with that of MakeMyTestCount, the NIH effort to report at-home tests, would allow for improved public health action.

Though more work needs to be done, this research did increase knowledge of real-world diagnostic test performance with respect to certain test characteristics and findings. It also highlighted the need for having public websites for people doing at-home tests to report their data elements. If we might shorten trial times, create better ways to gather data from the public via an on-line portal in real time, and share these data widely, the public's health would benefit.