COVID-19
Evidence Wins the Game

by Kelie Williams Luby, VP Clinical Trials Software at Mint Medical

We are now firmly entrenched in the second year of a worldwide pandemic of COVID-19. A second year of lockdowns, social distancing, online school and remote work. We've witnessed the tremendous strain felt by the healthcare infrastructure and workforce, economic stress (to put it mildly), and the unfathomable loss of human life. While we have experienced the hard line now of 'before' and 'during' the pandemic, we are now seeing the potential for 'after', particularly in some areas where we begin to see the possibility of a win against the pandemic.

At the time of this writing, I have not seen my colleagues in Germany at Mint Medical in person for over 16 months. The last time with my teammates in person was also the last time I've traveled for business – February 2020. At the time, I had just come back to the US from two weeks in Germany. The news was definitively heightened for the growing concern over a novel corona virus in the start of the New Year, but even in retrospect, I think it was so unprecedented that I, like many others, didn't quite know how to respond or what that meant to respond if we did. I am not sure if even now, I fully appreciate the depth of my own misconception of what this would be, what it would mean globally, and how we are, in many ways, still also learning how to respond.

As it were, going into the end of February 2020, I was at a conference in NYC, and for certain, the news was amplifying each day with growing concern. There were about 75,000 cases at the time which seems just impossible to believe considering where we are now and there were about 1,000 cases outside of China at this point (from what we understood at the time). It was at this conference when a colleague proposed we at Mint could do something to support the growing threat of COVID-19.

My own recollection of these discussions was that personally, I wasn't yet convinced that COVID-19 was

potentially going to lead to a pandemic - a memory I now cherish of my own misconception of COVID-19's potential to wreak havoc in the way in which it has. However, there was worrying potential for this that could not be ignored. If it did indeed become a global threat, then it warranted the need for a global response. A global response would mean knowledge transfer and data collection across countries and borders.

The proposal in this case from Mint was a comprehensive reporting template for CT scans and the related clinical information that would collect not only the structured radiology assessments but also patient treatment, history, clinical values, comorbidities, demographics and clinical symptoms. At this point in time, it was still not known what would be relevant to first simply understand the nature of COVID-19 but also what was needed for a true evidence-based approach to treat affected patients and also contain the further spread of the virus. At the forefront of the development of this template was the goal to identify as much information of relevance that could be connected and curated in a structured format and made comparable.

Part of why I joined Mint almost 5 years ago now was because I believed in the product. I knew personally the unmet need it fulfilled for clinical research: the efficiency of having a verified read-ready platform for clinical trials, the structured reporting and configuration flexibility, and the means to achieve high-quality data with integrity. The very same holds for clinical routine with read-ready reporting templates for structured, comprehensive imaging evaluation during screening and staging. This is what we do best at Mint. It's the premise behind the product and what motivates and drives our team to go further and do better: Ask for more, leave no data behind. Connect, curate, structure and make mobile the imaging data, the assessments, meta-data and the images themselves.

So, when a colleague proposed that we respond with a read template in mint Lesion™ to support the growing evidence that imaging played a central role in the support of COVID-19 response, the question was not can we do it, the question was rather should we. Responding with a read-ready template in a short period of time was in many aspects a business risk.

There is the basic business risk question that is always considered in any endeavor of *"What if we invest the time and resources into this and it's not utilized or it doesn't meet the need?"*

The larger risk was that this was February 2020. We still didn't know enough about the virus, the manifestations of disease it would cause or even what information would become relevant and necessary on the longer term. The phrase 'rapidly evolving situation' took on new meaning, I think, for the world at large with COVID-19. The question at hand was more importantly, *"Do we have enough information to make a meaningful template based on what we know now and how do we mitigate the evolution of this for what we know we just cannot see now and need to adapt later?"*.

What was significant here, was that the goal was not to address the immediate need to diagnose COVID on CT or even to replace PCR testing for COVID. The goal rather was to provide a means for high-quality, comprehensive data analysis, so that the information collected and reported could become a route to evidence-based interpretation of treatment effects. In other words, what we all wanted were answers and solutions – these are topics only solved by evidence and data, since only the controlled interpretation of data with an evidence-based approach provides answers and solutions.

A radiological reading of a chest CT scan for possible diagnosis or evaluation of COVID-19 disease extent is not necessarily a time intensive evaluation, but a very important one, since it determines what further action is taken for the patient. For example, based on the radiological evaluation of a chest CT scan for COVID-19, could evidence enable or refine a predictive model for which patients would benefit from ventilation and ICU care?

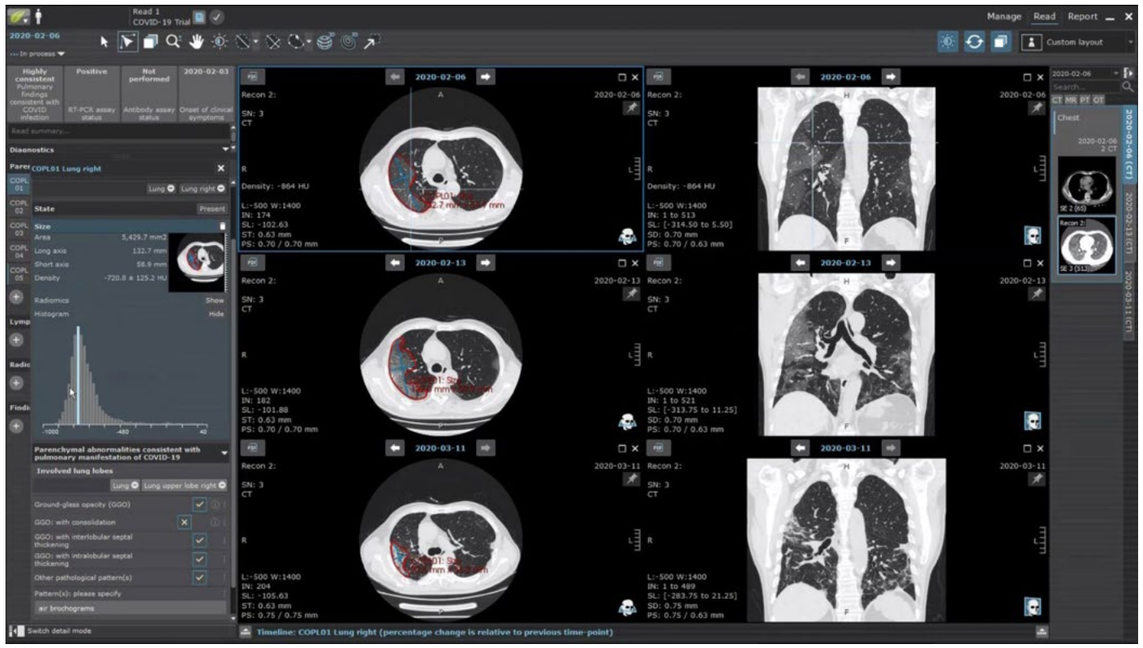
The urgent need in this case was organized data collection that encompassed epidemiological, clinical and imaging data for COVID-19 so that evidence-based medicine had the framework to do what it does best: connecting clinical expertise and experience with clinical evidence based on systematic research in order to add value to patient treatment as well as research. While this may sound like the obvious approach to tackle COVID-19, the impending pandemic at the time made this more challenging than we imagined. For me personally and what I estimate is the view of many, once you have seen the true power of evidence-based medicine to address an unmet need, it's nearly impossible to envision any other approach.

As we at Mint evaluated the question of should we, let me give some precedence for the answer by quoting a globally renowned German literary figure, Goethe[1]: "Daring ideas are like chessman moved forward. They may be beaten, but they may start a winning game." The collective debate was not what if we do but rather what if we don't. The answer was easy – of course we do this. What happened next and where we are now at the time of this writing is, to me, the most exciting part of this story: my colleagues demonstrated not only a possible contribution that Mint could offer to the global health challenge of COVID-19, but they did so in record time, with scientific integrity and flexibility in every step of the way.

Timeframe: By late March 2020, the international public, government and healthcare sectors had largely accepted that COVID-19 posed a significant threat and the world at large was waiting for the path to resolution – the resolution being deeply dependent on science to make recommendations and formulate an escape plan. There was tremendous pressure on the medical and scientific community to provide information that manifested by way of an urgency to publish results, generate data, make recommendations and provide the needed key to the continually unfolding worldwide crisis.

Meanwhile, by the first week of March 2020, Mint Medical developed a class 2b certified solution as a context-sensitive electronic data capture (EDC) template that enabled systematic large-scale data acquisition to provide an optimized digital platform to gather and aggregate multidisciplinary scientific evidence on COVID-19. By mid-March this was deployed to university hospitals and healthcare providers in multiple countries, including severely affected regions of the USA, Italy, Tyrol in Austria, and the majority of the university hospitals in Germany.

As a basis for the template features, a systematic review and meta-analysis was performed of data pooled from 13 studies to provide evidence on the radiological features of pulmonary manifestations of COVID-19 in chest CT. The



resulting mint EDC not only supports a structured method for evaluating the pulmonary involvement, but also quantitative assessment of the progression of the disease, both in clinical trials and in daily clinical routine, where it is cleared as a medical device.

However, there were operational considerations beyond just data generation that needed to be addressed – namely, users had to become quickly familiar with the reporting frame work and begin performing evaluations in record time, in the midst of a global health crisis. By nature, the mint Lesion™ software implements all read templates with guard rails in the form of sophisticated edit checks and guided assessments for the user and automatically generates reports.

Another challenge was that not all institutions accomplish their work in the same way – meaning, the flow of patient

[1]As an aside, Goethe was not only an accomplished writer, philosopher, politician amongst other roles but he was also a brilliant scientist. He was the first to systematically study color theory with organized data collection and reporting which led to the color template we now refer to as the Color Wheel. Johann Wolfgang von Goethe (August 28, 1749–March 22, 1832) 1810 Publication Theory of Colors.

evaluation is very organization-centric. Think of it as the way our individual households function from a workflow perspective – perhaps the end goals of our day to day lives are the same but the means by which we journey through our days are not. Workflows vary across institutions and while the end goal of patient evaluation and reporting may be universal, being able to adapt the workflow for organization-specific clinical practices and business rules, so to speak, requires a flexible framework. mint Lesion™ is framed on the concept of a workflow engine to accomplish this dynamically.

Lastly, information on COVID-19 was changing daily. The data collection in the mint EDC had to be actively adaptive to the latest scientific evidence – in other words, it was created to adapt to new requirements for data collection and reporting as the COVID-19 situation itself evolved. Keep in mind this was March 2020 and only three months later in June 2020, there were upwards of over 25,000 COVID-related publications and more than 2,000 clinical trials. Medical science was tasked with a mission in a race against time to deliver solutions and, more critically, data.

We all know this story by now of what occurred: Collectively, we globally understood (or began to understand) that data does not equate to credibility. Data, even great data, bore the risk of being mis-interpreted, mis-construed and hastily exposed to the world at large. While so much data was being generated, data and information sources were bogged down by design. The result was a multiplicity of redundant clinical trials, known and unknown data bias, single arm trials without control groups, conflicting endpoints, and patient sample sizes that were simply too small to draw meaningful conclusions. While we had an abundance of data being generated, it was tangled in an assortment of varied outcome measures from all-cause mortality, to time to sustained recovery, hospitalization rate, number of hospitalization days and so on, as well as discretionary arrays of exclusion/inclusion criteria in the patient populations: age, early vs. late state disease, symptomatic vs. asymptomatic, co-morbidities and disease severity amongst others.

This is where structured data then realizes its value and its importance. Because the mint EDC is integrated with mint Lesion™, mineable data are obtained in a semantic data model with a HIPAA- and FDA CFR Part 11-ready audit trail – a necessity for clinical trials and medical research and the support needed for the very essence of evidence-based medicine. Furthermore, the data are exportable in various human- and machine-readable data formats, such as comma-separated values (.csv) for external analysis. All image annotations can be exchanged in open formats, such as NRRD, or as DICOM-compliant annotations (DICOM RT, DICOM Segmentation Objects). Interfacing with other information systems, such as hospital information systems (HIS) to include clinical data, is possible through standardized interfaces, such as HL7 FHIR and HL7 CDA Level3.

But how did we know if this would provide relevance on a large scale, a global scale? In order to validate this approach, 283 patients based on anonymized data who had either suspected or confirmed SARS-CoV-2 infection from eight European medical centers were aggregated in data analysis dashboards. This data was then compared to key findings of landmark research literature. In March of 2021 (one year later) this concept has been chosen as starting point for the national COVID-19 response of the radiological departments of all university hospitals in Germany.

The next part is what is really important: What this COVID template model demonstrated is that structured data acquisition for clinical research can be achieved within a structured reporting routine workflow with equivalent time expenditure. Furthermore, what the concept of this platform provides is not limited to COVID-19. This offers the underpinning methodology for supporting evidence-based medicine with an efficient, agile, and dynamically adaptable framework for the conduct of clinical trials at large in a master protocol concept. This is what we at Mint and the broader scientific community know is required to achieve success in evidence-based diagnostic and therapeutic discoveries.

Before the pandemic, I can fairly say that while I knew evidence-based research was the only path to what I consider reliable information, I also saw this as a route that takes time. Perhaps because I also believed that to conduct a well-designed trial, setting up the operational infrastructure to collect high quality, reliable data of integrity was a time intensive part of the process. It was non-negotiable – it just took time and I rather accepted this. I now know this is not always true.

Not only is it possible to conduct large-scale evidence driven approaches with integrity in crucial timeframes to solve health challenges, we've seen the evidence that it works with the remarkable vaccine development. As we now see the proverbial light at the end of the tunnel of the pandemic, and we reflect on many of the lessons this provided, one of the most important ones I gained was that we do not have to compromise what we know works: ***evidence wins the game.***

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To read more on the COVID-19 read template and platform:
Salg, G.A., Ganten, MK., Bucher, A.M. et al. A reporting and analysis framework for structured evaluation of COVID-19 clinical and imaging data. npj Digit. Med. 4, 69 (2021). https://doi.org/10.1038/s41746-021-00439-y