



COVID-19 NC Collaboratory Projects

**Final Narrative
February 8, 2021**

Burden of Respiratory Viral Illness (BRAVE)

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The “Burden of Respiratory Viral Illness (BRAVE)” clinical trial sought to enroll every patient at UNC hospitals with respiratory symptoms for SARS-CoV-2 variant analysis by next generation sequencing (NGS). The data obtained from BRAVE are linked with the patients’ medical record and they can be linked to other clinical trials that are being conducted at UNC-Chapel Hill.

Having exhaustive and detailed information about the particular SARS-CoV-2 strains circulating in NC has proven timely and almost prophetic in light of the recent discovery of the hyper-transmissible B.1.1.7 lineage first in Great Britain and now also in the US. As the SARS-CoV-2 pandemic has expanded in the past months new variants are emerging at an accelerated pace globally: in Brazil, in South Africa, and in California.

The questions about novel virus strains are always the same: (i) are they more transmissible, i.e., do more persons get infected; (b) are they deadlier, i.e., is the clinical progression for new strain variants worse than what we have experienced thus far; and (c) are they resistant to vaccines. These questions can be answered with the BRAVE trial.

WE HAVE ACHIEVED OUR PROPOSED DECEMBER 31, 2020 MILESTONES:

- BRAVE has enrolled n=327 participants and recorded their clinical progression.
- BRAVE sequenced n=253 SARS-CoV-2 isolates.
- BRAVE established the human expertise and physical infrastructure that now allows us to sequence up to 100 samples per week in an effort of ongoing strain surveillance.
- BRAVE has disseminated information to the general public in NC and around through social and commercial media (Print, TV, Radio).

Figure 1 documents the enrollment schema of the BRAVE clinical trial.

Figure 2 shows the distribution of mutations in the SARS-CoV-2 Spike protein as observed in NC.

Figure 3 shows the infrastructure developed to analyze COVID samples.

BRAVE proved that mutations in the target sites for diagnostic PCR assays are exceedingly rare in NC. Our results were congruent with other studies around the world and installed confidence into the NC testing regimen and capabilities.

BRAVE proved that mutations that affect viral fitness and visibility to the immune system are common and that the virus evolves over time. BRAVE identified one such mutation in the virus spike protein D614 to G614. This mutation has a higher binding affinity to the humane ACE2 receptor. It has become the dominant variant in the US in 2020. It is not present in the current vaccines, but luckily is still recognized by vaccine-induced antibodies.

BRAVE anticipated the need for continues SARS-CoV-2 strain surveillance as part of a broader effort to contain the COVID-19 epidemic in the US. As reported in the news “The CDC believes a minimum of 5,000 to 10,000 samples should be analyzed weekly in the U.S. to adequately monitor variants, said Gregory Armstrong”. Assuming all 50 states contribute equally, this would require NC to sequence a 100 samples per week. BRAVE does this already.

Personnel supported by the project are listed in the transaction report and include: 1 Faculty, 4 research specialists and 1 research technician.

Table 1: Public Engagement. Study results and insights being reported to the NC public
2021, Feb 9 interview CBS 17
2021, Jan 27 UNC Health Talk (*see appendix*)
2021, Jan 23, interview with WRAL

2020, Dec 22, interview with CBS 17
2020, Dec 11, interview with the Wall Street Journal
2020, Nov 6, interview with WPTF radio
2020, Nov 2, interview with CBS 17
2020, Oct 29, interview with WCHL Chapelboro radio
2020, Oct 27, interview CBS 17
2020, Oct 20: UNC Health Talk (*see appendix*)
2020, August 12, UNC Press release on Cell Reports paper
2020, July 22, UNC Health Media on You Tube
2020, July 8, Spectrum News One: Experiment testing the efficacy of Masks
2020, June 29, interview Washington Post
2020, April 5, Thermo Fischer Press Release

Links to TV interviews

<https://www.cbs17.com/community/health/coronavirus/unc-professor-outlines-whats-known-about-new-covid-19-strain-hitting-uk/>

<https://www.wral.com/coronavirus/duke-virologist-we-don-t-need-to-panic-over-new-coronavirus-variants/19486759/>

Associated National Funding:

- Received Awards during the funding period:

NA

- Pending Grants:

PI: *Dittmer*
Title/Topic: *Single Particle Diagnosis of SARS-CoV2*
Funding Agency: *NIH*
Amount (total cost): *\$450,680*

PI: *Dittmer*
Title/Topic: *Virogenomics and Biostatistics Core*
Funding Agency: *NIH*
Amount (total cost): *\$2,981,855*

- Planned Grants:

PI: *Dittmer*
Title/Topic: *R01 on SARS-CoV-2 variant of concern survey*
Funding Agency: *NIH*
Amount (total cost): *planned*

Figure 1: BRAVE enrollment exceeds the proposed milestone. This summarizes the enrollment data for the period (12/2/20-12/8/20). The trial screened around 27 new patients during this one week. Of those we enrolled 8 patients. 1 patient declined consent. We were unable to contact 6 patients and 9 patients were ineligible after screening. 3 patients died of COVID-19 prior to consent.

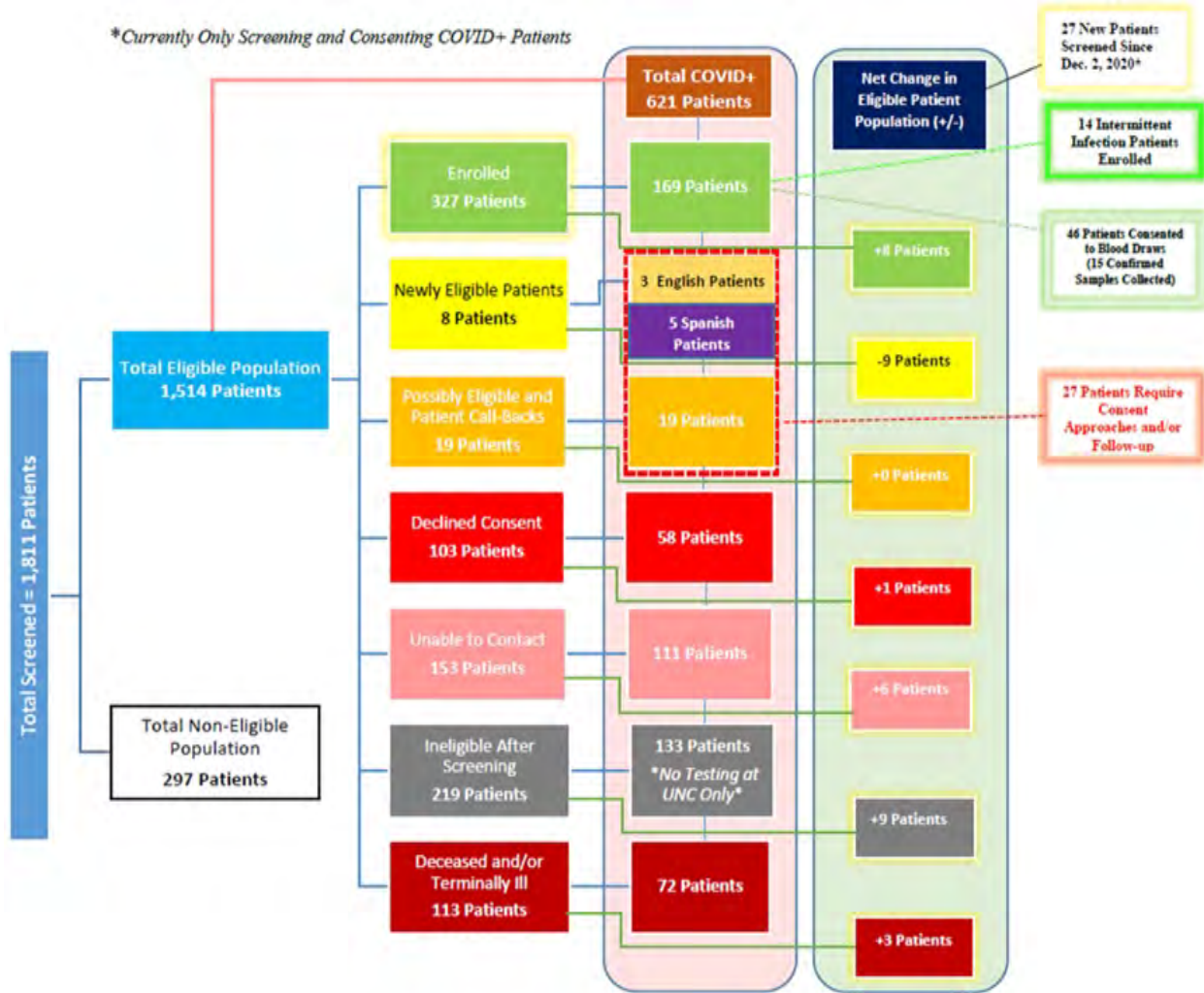


Figure 2: Distribution of mutations in the SARS-CoV-2 Spike protein in NC



253 Sequences from UNC

Figure 3: Infrastructure

Picture of a dedicated biosafety level 2 plus (BSL2+) laboratory for the analysis of COVID samples.





5 Things We Know About the COVID-19 Variants

February 2, 2021

Viruses are constantly changing, and new versions—called variants—often arise. News of variants of the [coronavirus disease 2019 \(COVID-19\)](#) virus is spreading nearly as fast as the variants themselves.

To learn more about these variants, we talked to [Dirk Dittmer, PhD](#), professor of microbiology and immunology at UNC School of Medicine.

1. When it comes to viruses, variants are common.

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[Not All Masks Are Created Equal](#)

[Nervous About COVID-19 Vaccination? Read This](#)

[The COVID-19 'Long Haulers'](#)

A genome, which is an organism's genetic material, is like an instruction manual for how the organism is made and maintained.

Early on in the COVID-19 pandemic, scientists sequenced the genome of the COVID-19 virus, meaning they determined the detailed chemical building blocks that make up the virus. This information has allowed doctors and scientists to diagnose the virus and create the COVID-19 [vaccines](#).

But like other viruses, the sequence of the COVID-19 virus genome changes, or mutates. The virus that causes COVID-19, called SARS-CoV-2, mutates neither particularly fast (such as the flu virus) or particularly slow. So scientists like Dr. Dittmer continue to study the sequence of newly diagnosed COVID-19 patients so they can watch for those changes.

"So far, all the variants we have seen (at UNC) differ by just one or two amino acids, and they have no particular clinical difference," Dr. Dittmer says.

Amino acids are the building blocks that link together to form a protein, like the spike protein that is found on the surface of the virus that causes COVID-19, and that is what is responsible for the virus entering its target cell. Over time, some of those building blocks of the COVID-19 virus change—some of these changes have no effects, while others can have drastic effects.

2. Three new variants have raised alarm bells.

Although variants to viruses are common, variants that have several (around 10 or more) changes from the original are uncommon, Dr. Dittmer says. That's why these new COVID-19 variants are causing concern.

[Variants](#) from Britain, South Africa and Brazil have multiple mutations and have changed the virus enough to alter its impact. Early research has found them to be more

contagious. For example, the variant known as B.1.1.7—first identified in Britain in December—does not appear to cause more severe disease but appears to [spread more easily](#).





“More study is needed to know about the impact of these new variants,” Dr. Dittmer says. “So far, what people have found is that these variants are more transmissible, but no one knows exactly why. Whether they are clinically worse, we simply don’t have enough data.”

3. The vaccines are still effective for the new variants.

Researchers have [found](#) that the Moderna vaccine still protects against the British variant, but it’s less effective against the one that emerged in South Africa and that shares some of the mutations with a variant that emerged in Brazil, Dr. Dittmer says.

Moderna is now working to create an “emerging variant booster candidate” against the South African variant, known as B.1.351, to determine if it will be more effective against the strain and potentially other future variants.

A recent [laboratory study](#) found that the Pfizer vaccine appeared to lose only a small bit of effectiveness against an engineered virus with three key mutations from the new South Africa variant. Its findings are limited because it does not look at the full set of mutations found in the new South African variant, and further research is underway.

    Although they may be less slightly effective, these vaccines still work, Dr. Dittmer says.

“If you’re immunized, your immune system will still take care of the U.K. variant just fine,” Dr. Dittmer says. “With the South African variant it’s about fivefold less effective. What remains is, however, still a substantial amount of anti-virus antibodies. You have to remember that an unimmunized person has no protection at all.”

In other words, if you've been vaccinated, you still are better protected against South African variant than if you are not.

4. Treatment for COVID-19 remains the same.

No matter which variant you have, you will receive the same treatment for COVID-19. People with mild to moderate symptoms who can rest and drink fluids at home will continue to do so; those with severe illness who require hospitalization will receive medications, oxygen therapy and intubation as needed.

"All the treatments that you get and all the supportive care we provide is the same, so which variant you are infected with doesn't change your clinical treatment. We don't treat specific variants at this time," Dr. Dittmer says.

5. The same safety measures you have been taking protect against the variants.

The same things you have been doing to prevent the spread of the SARS-CoV-2 virus should protect you from the new variants. This means you should wear a [mask](#), [wash your hands](#) frequently and stay [6 feet apart](#) from others whenever possible.

"If you look under a big microscope, all the variants still have the same size and have the same physical properties, and that's why these measures are effective against any variant," Dr. Dittmer says.

And while getting the vaccine is the best way to reduce your risk, you [still need to continue](#) doing those things even after you're vaccinated. Most Americans won't be vaccinated for several months, so everyone needs to keep taking precautions to reduce transmission.

Click [here](#) for the latest information on the COVID-19 vaccines or visit the [CDC website](#) and the [UNC Health](#)

[COVID-19 Resources page](#), and follow UNC Health on [Twitter](#), [Facebook](#), [Instagram](#) and [YouTube](#).

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Dirk Dittmer, PhD

Director of the UNC Viral Genomics Core





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[Dirk Dittmer, PhD](#), is the director of the UNC Viral Genomics Core and professor of microbiology and immunology at UNC School of Medicine. He leads a group of researchers at UNC in tracking the virus that causes COVID-19 by sequencing the genome of virus samples collected from diagnostic testing.






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Tracking the SARS-CoV-2 Virus with Genome Sequencing

October 21, 2020



Dirk Dittmer, PhD, professor of microbiology and immunology at the UNC School of Medicine, is tracking the virus that causes COVID-19 by sequencing the genome of virus samples collected from diagnostic testing. Using next generation sequencing on SARS-CoV-2 will help accurately diagnose the novel coronavirus, identify mutations and track its history.

CHAPEL HILL, NC – A [study published](#) in *Cell Reports* shows how next generation genetic sequencing can track mutations in the SARS-CoV-2 virus, which can in effect help with transmission tracing, diagnostic testing accuracy and vaccine effectiveness.

“Once you have the virus’ genetic sequence with next generation sequencing (NGS), then you can start asking more questions,” said Dirk Dittmer, PhD, professor of microbiology and immunology at the UNC School of Medicine, and senior author of the study. “Where have we seen this exact sequence before? Did it come from a different state or country? When did this patient travel there and who else may have it?”

Dittmer says this type of virus monitoring is also important in diagnostic testing. Much of the testing developed to diagnose COVID-19 looks for one portion of the gene sequence that causes the novel coronavirus. If that sequence mutates, the test is no longer accurate and results will be affected. Dittmer says that within their study, his team did find variations in the virus’ genetic sequence, but fortunately none of the variations were located in the portion of the virus targeted in common diagnostic testing.

“We are concerned about future mutations though,” Dittmer said. “It is inherent in a virus’ nature to mutate. Changes in other areas of the genetic sequence can not only disrupt testing, but hinder the effectiveness of vaccines.”

That’s why Dittmer’s lab has been collaborating with multiple other labs at UNC-Chapel Hill to stay up to date on what, if any changes should be made to testing protocols and possible vaccine development. Dittmer’s lab receives positive SARS-CoV-2 samples from the lab of Melissa Miller, PhD, director of UNC Medical Center Microbiology and Molecular Microbiology Laboratories, where UNC’s COVID-19 diagnostic testing was developed and put in place March 16.

“Because we are only looking at one gene sequence for the virus, we have told the FDA that we will continually monitor for changes in this gene sequence so that we can be assured that our test is still reliable,” said Miller, a co-author of the study. “NGS will help us do that.”

Dittmer’s recent study is the largest to focus on suburban and rural communities. Researchers were able to reconstruct the mutational landscape of cases seen at the UNC Medical Center in Chapel Hill, NC, a tertiary clinical care center. From March 30 through May 8, 175 samples from confirmed COVID-19-positive patients were analyzed.

Out of the samples tested, 57% carried the spike D614G variant noted in similar studies. The presence of this variant is associated with a higher genome copy number and its prevalence has expanded throughout the pandemic. The genetic variations found in these samples also support the hypotheses that the majority of cases in North Carolina originated from people traveling within the U.S. rather than internationally.

With a grant from the N.C. Policy Collaboratory based at UNC-Chapel Hill, Dittmer’s lab will continue using NGS to track the SARS-CoV-2 virus through the remainder of 2020. The goal is to enroll every patient at UNC Hospitals with flu or respiratory symptoms for COVID-19 diagnostic testing. These samples will be sequenced and compiled to form a comprehensive profile of any virus that these patients carry, information that will continue to help a community of researchers in their fight against SARS-CoV-2 and potentially novel coronaviruses.



Dirk Dittmer, PhD

Dittmer is also a member of the UNC Lineberger Comprehensive Cancer Center. Co-authors of this study include Ralph Baric, Ryan McNamara, Carolina Caro-Vegas, Justin Landis, Razia Moorad, Linda Pluta, Anthony Eason, Cecilia Thompson, Aubrey Bailey, Femi Cleola Villamor, Philip Lange, Jason Wong, Tischan Seltzer, Jedediah Seltzer, Yijun Zhou, Wolfgang Vahrson, Angelica Juarez, James Meyo, Tiphaine Calabre, Grant Broussard, Ricardo Rivera-Soto, Danielle Chappell, and Blossom Damania, all affiliated with UNC-Chapel Hill.

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