

## **BRAVE: RESPIRATORY VIRUS TRACKING (INCLUDING SARS-COV2) IN NC**

### **Team**

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The “Burden of Respiratory Viral Illness (BRAVE)” seeks to enroll every patient at UNC hospitals with flu or respiratory symptoms for SARS-CoV-2 testing. BRAVE collects both sera for antibody testing and nasal swabs for actual virus testing. BRAVE is forward-looking as it will sequence every virus that causes someone in NC to be admitted to a hospital and it will compile a comprehensive profile of antibodies to any virus that these individuals carry.

BRAVE started several years ago as a survey of respiratory viruses and bacteria in patients admitted to the intensive care unit ICU at UNC Hospitals (1). Since then, the UNC viral genomics core has perfected coordination with clinical trials at UNC and around the US, and we have validated robust, reliable, reproducible methods to identify and characterize new viruses. The data obtained from BRAVE can be linked with the patients’ medical record and they can be linked to other clinical trials that are being conducted at UNC-Chapel Hill.

To date, we have sequenced ~100 SARS-CoV-2 genomes from COVID patients in NC. These sequences will allow us to trace outbreaks, e.g. among nursing home populations, and it will allow us to verify that the current tests recognize the particular strains of SARS-CoV-2 that circulate in North Carolina. This information is particularly important should we experience a second wave of infections in the fall.

Having exhaustive and detailed information about the particular SARS-CoV-2 strains circulating in NC today, will help us model future outbreaks and prepare for a potential “second wave” and beyond. Current tests were developed quickly. They represent a first pass at the problem and operate under EUA only. Since the SARS-CoV-2 virus mutates constantly, current tests may or may not recognize new SARS-CoV-2 strains. According to the GISAID database (2020-05-09) 2.7% of strains circulating worldwide have mutations in the test target site and thus would escape detection. BRAVE will determine if current and future PCR tests recognize the particular strains of SARS-CoV-2 that are circulating in NC.

Scientific evidence is beginning to emerge that some strains of SARS-CoV-2 cause more disease as others, they lead to longer hospitalization rates and increased need for ICU capacity. This is not uncommon for viral infections. We have detected that a substantial fraction of SARS-CoV-2 strains in NC carry a mutation, G614, in the virus Spike protein, which is circulating at UNC Hospitals. This changes the biology of the virus and leads to worse clinical outcomes. Knowing the proportion of G614-SARS-CoV-2 variants will aid in predicting ICU needs. Testing by sequencing will also allow us to determine if some strain variants are more transmissible than other, e.g. by being more resistant to heat or more effective at escaping the body’s initial immune response.

By comparing blood serology data to virus tests on the same patients, BRAVE will determine if patients that have antibodies to SARS-CoV-2 can still get sick and can still infect others and we can ask what is special about these patients where immunity fails. This, in turn, will inform vaccine design. Vaccines are generally directed against the virus Spike protein. For RNA viruses, so-called antibody-escape

mutants are common and, similar to the annual flu vaccine, any future SARS-CoV-2 vaccine has to be matched to the strains that are most prevalent in the US and NC. These are slightly different than the initial strain that emerged in China. BRAVE will generate a database of SARS-CoV-2 variants that are circulating in NC and that database will be updated in real-time and shared with the NC State health department, the CDC and vaccine manufacturers.

In the broader sense BRAVE protects our nurses and doctors, so they know each week which bacteria and viruses are circulating at UNC Hospitals, if SARS-CoV-2 has become resistant to vaccines or drugs, and if perhaps there is an entirely new virus emerging in North Carolina.

(1) Sellers et al. In [Influenza Other Respir Viruses](#). 2020 Mar 9. doi: 10.1111/irv.12734.

## **IMPACT TO THE STATE (300 word limit)**

- *Description of the problem or challenge being addressed and how the problem impacts those in the state of North Carolina*
- *Describe how the proposed research will provide impactful solutions to the described problem to help the state of North Carolina*

The “Burden of Respiratory Viral Illness (BRAVE)” is enrolling every patient with respiratory symptoms at UNC Medical Center for SARS-CoV-2 sequencing and comprehensive virus profiling. All viruses, including SARS-CoV-2, are constantly evolving.

Current tests represent a first pass. They are far from optimal. BRAVE will determine if current, future CDC, and commercial PCR tests recognize the particular strains of SARS-CoV-2 that are circulating in NC. It will determine if any new strains emerge in our hospital. According to the GISAID database (2020-05-09), 2.7% of strains circulating worldwide have mutations in the test target site and would escape detection. UNC recently received a request to consider sequencing patients at the US Army Ft Bragg installation, particularly those with severe disease returning from world-wide assignment to NC.

By sequencing viral strains circulating in NC, BRAVE will ensure that future vaccine designs protect the people of NC. For example, if there exists a mutation, G614, in the virus Spike protein, which is circulating at UNC Hospitals. It is essential to include this and other NC variants that BRAVE will detect in future vaccines.

UNC Medical Center is a tertiary hospital. BRAVE will sequence not only SARS-CoV-2, but all virus in the sickest patients. Some COVID patients also have other infections and the same G614 mutation mentioned above confers more mortality than other SARS strains. BRAVE will help predict how many more ICU beds are needed in NC based on the makeup of SARS-CoV-2 strains circulating in out hospitals.

All data generated by BRAVE will be shared with the NC State health department, the CDC and vaccine manufacturers. It will also ensure that the PCR based tests used in NC have the same sensitivity to detect SARS-CoV-2 strains that are part of a potential “second wave” as they have for the original SARS-CoV-2 strains.

## **MILESTONES (300 word limit)**

*Description of what will be accomplished and what can be delivered by August 31, 2020, and by Dec. 31, 2020. The start date will be June 1, 2020.*

For any cohort study the milestones are enrollment and results, in this case the number of SARS-CoV-2 genome sequences generated.

BRAVE is continuously increasing enrollment by adding more recruitment sites at the Chapel Hill hospitals and removing barriers to trial access. For instance, BRAVE now provides a Spanish language consent, as >30% of COVID patients in NC are members of the Latinx community and we are seeking to expand to UNC Children's and NC Cancer Hospital. There is evidence that children, while not becoming very ill, nevertheless transmit large amount of virus and there is evidence that cancer patients, due to their weakened immune system and specific cancer, e.g. lung cancer, are at high risk.

BRAVE has fully validated its methods, particularly the accuracy of virus sequencing, the sensitivity of isolating viral nucleic acids from any sample, and the validity of our bioinformatic analysis. Now it is a question of scaling up and capturing as much NC-specific information about SARS-CoV-2 as possible. The same technology that is used to understand patients' samples can be used to investigate environmental samples, i.e. virus isolated from water or surfaces or the workplace.

### **August 31,2020 Milestones**

- 1) Have >100 participants enrolled into the BRAVE trial.
- 2) Deliver 200 whole genome SARS-CoV-2 sequences from NC. At present we are sequencing ~32 samples per week. The requested equipment will increase that capacity to 48 samples/day. Thus, we are able to capture multiple timepoints (day of admission and day of release) as well sample types from each patient: saliva, nasal swab, blood, stool.

### **December 31, 2020 Milestones**

- 1) Have >300 participants enrolled
- 2) Deliver >400 whole genome SARS-CoV-2 sequences from NC
- 3) Provide a final, comprehensive analysis to the stakeholders around NC, the scientific and general public.

## **BUDGET JUSTIFICATION** (200 word limit)

*Funds are limited. We encourage all teams to revisit their budget and determine if it can be reduced.*

**Total budget= \$717,300**

The BRAVE budget has three components.

### **Personnel**

\$199,890

This budget covers clinical personnel to ensure continued, representative, and expanding enrollment into the trial. The budget requests the minimum of resources to maintain current staffing levels and thus rate of enrollment. This includes 4 screeners from the SOM Department of Medicine, who work 7 days a week to consent people to the BRAVE trial. It includes people fluent in Spanish.

All laboratory and bioinformatics personnel are supported by UNC Chapel Hill (Vironomics Core). Bioinformatics and other infrastructure will be supported by UNC Chapel Hill Lineberger Comprehensive Cancer Center.

### **Equipment**

\$354,000

This represents essential hardware to achieve the sequencing throughput needed to complete the project by Dec 31. This includes the Genexus sequencer that is optimized for the particular chemistry used to sequence the virus and a plate reader needed to determine neutralizing antibodies to SARS-CoV-2.

All ancillary equipment, e.g. for quality control and sample processing will be supported by UNC Chapel Hill (Vironomics Core).

### **Supplies**

\$163,410

Supply costs are budgeted to deliver 500 full-length SARS-CoV-2 genomes at a cost of \$325/ finished genome, which is possible due to efficiencies provided by the hardware upgrade.

## Personnel Table

EHRA Salaries	\$ 51,858
SHRA Salaries	\$ 87,745
Grad Student	\$
Temps	\$
Fringe Pool	\$ 48,872
Non-Personnel expenses	\$ 528,825
<b>TOTAL</b>	<b>\$ 717,300</b>