1) Protocol Title:

Pilot randomized clinical trial of multi-respiratory pathogen testing versus usual care in emergency department (ED) patients with upper respiratory symptoms

Version Date: February 23, 2018

2) Objectives

To prospectively evaluate the effect of rapid, multi-respiratory pathogen molecular testing vs. usual care among patients being evaluated for influenza like illness (fever or cough and sore throat; ILI) and/or upper respiratory infection (nonspecific upper respiratory symptoms without fever; URI) in the emergency department (ED) setting. Specifically, we will evaluate the impact of having the rapid, multi-respiratory pathogen molecular test results on the frequency of respiratory pathogen detection, clinical treatment and outcomes among patients. To do so, we plan to conduct a prospective, patient-oriented, pilot randomized clinical trial of the BioFire FilmArray Respiratory Panel (FilmArray RP) from clinical nasopharyngeal swab viral transport media versus usual care (which may include but is not limited to no testing or targeted influenza molecular testing *Alere I Influenza A & B*).

Our study has two hypotheses:

1) Rapid, FilmArray RP testing will increase the proportion of ED patients with a specific respiratory virus detected and decrease the proportion of ED patients receiving unnecessary antibiotics for viral infection, relative to patients receiving usual care.

2) Rapid, FilmArray RP testing will increase the frequency of a confirmed influenza diagnosis and improve overall anti-influenza medication use (composite rate of anti-influenza treatment in positive patients and non-use of anti-influenza treatment in negative patients) in ED patients, relative to usual care.

3) Background

ILI and URI are a frequent cause of ED visits but most patients of have a viral infection, which resolves without treatment and does not need specific treatment or antibiotics. Influenza and Respiratory syncytial virus (RSV) are the most common cause of ILI and URI during the winter respiratory season; Rhinovirus/Enterovirus infections predominate during summer and fall. Other viruses such as human Parainfluenza viruses, Adenovirus and human Metapneumovirus (hMPV) are less common but account for a sizable proportion of patients in aggregate. Most symptoms of ILI (cough or sore throat and fever) and URI (cough, sore throat, runny nose, and sneezing without fever) are non-specific. The current standard of care for ILI and URI does not typically include microbiologic testing and test results are often not available until after the patient has left the ED, when they are obtained. Thus, patients are often treated presumptively with antibiotics or hospitalized unnecessarily due to physician uncertainty and lack of rapid and comprehensive microbiologic tests. This leads to antibiotic overuse, excess healthcare costs, and antibiotic resistance among other things.

Recent improvements in molecular diagnostic tests and the development of rapid, multi-respiratory pathogen tests provide an opportunity to identify viruses and viral infections like ILI and URI during the ED visit and potentially improve patient management. The FDA-cleared FilmArray RP provides results for 20 different respiratory pathogens in approximately 1 hour with 85-100% sensitivity and 90-100% specificity. However, the clinical utility and impact of rapid, multi-pathogen testing on patient management, physician decision-making and patient and system-level outcomes has not been rigorously evaluated, especially in the ED setting. This creates challenges for physicians, laboratories, and hospitals in justifying the cost of instruments and tests and lack of guidance regarding optimal use. Hence, this study will evaluate whether rapid, multi-pathogen detection can have a significant impact on outcomes in the ED setting that might make tests like this become standard of care. This study will provide important preliminary data to guide larger pragmatic outcomes-oriented clinical trials.

4) Inclusion and Exclusion Criteria

All UC Davis ED patients who are being evaluated for ILI or URI by an ED physician and who agree to having a nasopharyngeal swab sample collected for the study will be eligible for recruitment. Since this procedure poses minimal risk to individuals and no risks to an embryo or fetus should the patient be or become pregnant, we will not exclude pregnant women from this study.

Our study will also include children (individuals below 18 years old) since the collection of the nasopharyngeal swab sample poses minimal risk to them. Informed consent will be obtained from the children's parents, legally authorized representative or guardian before the child is enrolled. In addition, should an adult be incapable of giving informed consent, consent will be obtained from the individual's legally authorized representative.

Spanish speaking patients will also be included. We plan to translate our informed consent documents into Spanish after IRB approval and a translator will be present in the ED to allow proper communication between the patient and ED research coordinators, ED nurse, or physician throughout the study. Other non-English speaking patients will be excluded.

We will also exclude those patients who are prisoners or are currently taking antibiotic or antiviral medications.

5) Study Timelines

The study will begin upon IRB approval and continue until December 2017. Eligible patients will be identified by ED research coordinators or EMRAP students and will be approached by ED Research Coordinators and asked for consent to enroll. The patient will continue to be a part of the study throughout their time in the ED. Additional follow up data collection and analysis of results will be performed for 1-5 years after completion of the active enrollment phase.

6) Study Endpoints

Patients may be recruited until the end of December 2018 while primary data analysis will be

completed within one year after patient recruitment ends.

7) Procedures Involved

All UC Davis ED patients who are being evaluated for ILI or URI by an ED physician during the study period will be eligible for recruitment. Once the ED research coordinator or EMRAP students identify an eligible patient, the patient will be approached by the ED Research Coordinator and asked for consent to enroll. After obtaining informed consent, patients will be randomized to one of two arms: multi-respiratory pathogen testing together with usual care or clinician directed standard of care (which may include but is not limited to no testing or targeted influenza molecular testing *Alere I Influenza A & B*) using a simple randomization scheme. In this study, the randomization scheme we are planning to use is individual randomization. To ensure that the study population includes patients treated as outpatients vs. admitted, patients will be recruited from the 'up front care' treatment area (urgent care unit for ED patients expected to be treated as outpatients), in addition to our main emergency department area.

A brief demographic and symptom questionnaire will be administered to all subjects (see attachment). If patients are assigned into the control group, they will receive clinician directed standard of care (which may include but is not limited to no testing, point-of-care influenza molecular testing *Alere I Influenza A & B,* or multi-pathogen respiratory viral panel testing at off-site laboratory performed 3-4 times weekly in scheduled batches). Conversely, patients randomized to receive the rapid FilmArray RP, will receive usual care plus have a nasopharyngeal swab collected by an ED nurse or ED physician for FilmArray RP testing. The nasopharyngeal swab will be transported to the CLIA-certified clinical laboratory located one-floor above the ED where a licensed Clinical Laboratory Scientist (CLS) will perform the FilmArray RP test in real-time. Once the test is completed, FilmArray RP results will be reported in EMR via standard procedures and be available to ED physicians for use in patient management. ED physicians are free to decide how the test results will impact their treatment decisions and whether they would like to share these results with their patients. To ensure that results are available before ED physicians make treatment decision, we will encourage the ED triage physician to order the test before patients are put into ED rooms and ensure that FilmArray RP results are reported within 2 hours of sample collection.

In order to evaluate the impact of having rapid FilmArray RP results on clinical treatment, outcomes, and costs among ED patients, we will collect additional clinical and administrative data from EMR, laboratory, and UCDHS administrative databases. These data may include but are not limited to demographic characteristics, ICD10, CPT, and DRG diagnosis, procedure, and billing codes, charge and cost data, admission source, discharge disposition, clinical signs and symptoms of respiratory or other illness, relevant laboratory and radiology results, medications, antibiotics, antiviral and other respiratory treatments (e.g., oxygen, nebulizers and inhaled treatment) 30 days before, during, and after the ED episode of care, length of ED encounter, and data for any hospitalization, ED, or outpatient clinic visits within 30 days. These additional data collection and analysis of results will be performed for 1-5 years after completion of the active enrollment period (December 2017).

8) Data and/or Specimen Management and Confidentiality

Power Analysis - Based on existing literature and baseline data, we anticipate approximately 50% of patients with the diagnosis of ILI or viral URI in the control group will receive antibiotics, whereas 10% with confirmed influenza will receive antivirals. Based on the effect sizes, anticipating significant improvement in detection rates for influenza and other viral pathogens, and hypothesizing a 15 percentage point decrease in antibiotic use for patients with ILI or URI from 40 to 25% in the multi-respiratory pathogen test group, we plan to enroll approximately 304 – 325 patients over 12-18 months (June 2016 – December 2017). A sample size of at least 152 enrolled patients in each of the control and intervention arms will provide > 80% power to detect any true 15 percentage point difference between the multi-respiratory pathogen test and usual care arms.

Data for this study will be collected from the patient questionnaire, electronically in bulk from EMR, administrative and laboratory databases, and from individual patient charts in EMR. Entry into individual patients charts (EMR) will be used primarily to clarify responses to the patient questionnaire, evaluate physician awareness of and utilization of FilmArray RP results and decision-making (e.g. to determine how the results from the rapid, multi-respiratory pathogen testing influences physicians' decision to prescribe antibiotics, to obtain respiratory radiology results), and clarify gaps in the bulk electronic data.

All data will be maintained for 5 years after completion of this project. All data will be maintained in password-protected spreadsheets/databases located on a secure UCDHS server. Patients' PHI will be removed and data assigned a unique study identifier as soon as possible after extraction and electronic matching. Access to databases with identifiable electronic data will be limited to authorized investigators, study personnel, research coordinators and analysts directly involved in the study. All signed HIPAA Authorization forms granting research personnel permission to use PHI for research will be kept in a locked cabinet in the office of the principal investigator or in a lockbox in the ED for 5 years. Any unauthorized entry into individual EMR patient records (e.g. to identify potential subjects and before the HIPAA Authorization form is signed) will be documented and reported to the UCDHS compliance office via Break the Glass on EMR.

9) Data and/or Specimen Banking

Samples – Remnant nasopharyngeal swab samples in viral transport media will be labeled with a non-PHI containing code number and kept in an access-controlled UC Davis laboratory freezer for 5 years after the active study period for potential repeat, confirmatory, or additional respiratory pathogen testing. Access to the laboratory freezer will be limited to authorized investigators and research personnel. Only authorized investigators will be allowed to request further testing on these samples.

Data – All subjects' questionnaires and signed consent forms will be kept in locked cabinets in the office of the principal investigator or in a lockbox in the ED. Patient test results (which includes both the clinician directed standard of care and the rapid, FilmArray RP testing) will be documented in the laboratory LIS and EMR as per routine procedures. All extracted and collected data will be maintained in password-protected spreadsheets/databases located on a

secure UCDHS server and will be coded (e.g. stripped of PHI and assigned a unique study identifier) as soon as possible after extraction and electronic matching. Data will only be accessible to trained project personnel. Coded data will be maintained for 5 years after the study is closed.

10) Withdrawal of Subject

The investigator can decide to withdraw subjects from the study at any time due to reasons such as missing information, collection of a sample inadequate for testing or because the entire study is terminated. Subjects are also free to withdraw from the study whenever they want.

If a patient withdraws from the study, research personnel will discard the patient's remnant nasopharyngeal swab sample and no longer obtain new clinical and administrative data about the patient from EMR, laboratory and UCDHS administrative databases. However, already collected data relating to any subject who chooses to withdraw will be retained and analyzed to maintain the integrity or reliability of the research.

11) Risks to Subjects

This study poses minimal risk of harm or discomfort to subjects. For patients assigned to receive the rapid FilmArray RP test, it is possible that the collection of the nasopharyngeal swab sample may make some of them feel uncomfortable. However, there is little or no risk of injury as the swab will be administered by trained ED personnel and there should be no lasting physical or emotional harm associated with the procedure. This procedure also has no risks to an embryo or fetus should the patient be or become pregnant.

There will be no risk to patients placed in the usual care control group since they will receive the clinician directed standard of care (which may include but is not limited to no testing, point-of-care influenza molecular testing *Alere I Influenza A & B,* or multi-pathogen respiratory viral panel testing at off-site laboratory performed 3-4 times weekly in scheduled batches); patients will receive similar treatment should they decide not to be enrolled in this study.

12) Potential Benefits to Subjects

Patients who are assigned to receive the rapid FilmArray RP test may or may not benefit directly from participating in the study. There are no guidelines on how physicians should utilize the results; instead, physicians are free to decide how the results will impact their decision-making. Depending on how physicians use the results, a possible benefit these patients may have is not receiving unnecessary antibiotics for viral infection.

Patients placed in the usual care control group will receive no direct benefit from this study. However, we expect general benefits to the public as our study results may have the impact to change the clinical paradigm and testing/treatment strategy when diagnosing IRI or URI in ED patients.

13) Community-Based Participatory Research

This study is limited to UCD Emergency Department patients; there will be no community participation.

14) Sharing of Results with Subjects

The rapid FilmArray RP test results will be released by CLS and reported to physicians through EMR. Physicians may decide if they would like to share these results with subjects.

Results from clinician directed standard of care test results will also be released to physicians through EMR as per standard hospital protocol.

15) Prior Approvals

This clinical trial is sponsored by BioFire Diagnostics and thus the contract between BioFire and UC Davis Health Systems must be approved before this study is conducted.

16) Provisions to Protect the Privacy Interests of Subjects

An ED research coordinator will be present to educate and clarify any questions or uncertainties the patients might have about the study before they sign the informed consent form. The ED research coordinator will also emphasize that none of the patient's identifiable information will be released and that all responses and results will be kept confidential and used for research purposes only. All patient enrollment, completion of the questionnaire and collection of the nasopharyngeal swab sample will be done in a private room in the ED.

17) Economic Burden to Subjects

As part of the agreement with BioFire Diagnostics, the UC Davis ED will be provided two FilmArray instruments and approximately 900 FilmArray respiratory panel reagent pouches. Hence, subjects who are assigned to the rapid, multi-respiratory pathogen testing will not incur any additional costs.

18) Consent Process

Once an eligible patient is identified, the patient will be approached by an ED Research Coordinator and asked for consent to enroll. Consent will occur after recruitment, but prior to any research activities. Consent will also occur face to face in a private room in the ED. Prior to obtaining consent, ED research coordinators will describe the study protocol and the possible risks and benefits and also address any questions or concerns the subject may have about the study. Patients will be provided with the IRB approved informed consent document to read given ample time to read the document and decide if they want to participate. After this point, eligible patients will sign the consent form. The signed consent form will be copied and the copy of the signed consent form will be given to the patient for personal records while the original will be kept by the ED Research Coordinator for the research record. After all research activities are completed, all data collected will be entered into a database. Hard copies of the consent forms and questionnaire will be stored in a lock box in a secure location in the ED. Contents of the lock

box will be collected by study personnel when necessary and transferred to a locked cabinet in the principal investigator's office.

For patients who are children (individuals below 18 years old), informed consent will be obtained from one of the child's parents, legally authorized representative or guardian before the child is enrolled. In addition, should an adult be incapable of giving informed consent, consent will be obtained from the individual's legally authorized representative.

19) Drugs or Devices

√ I confirm that all investigational devices will be labeled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

The BioFire FilmArray RP test and instruments are FDA-cleared/approved for diagnostic use. The device will be labelled in accordance with FDA regulations and will be stored in a clinical laboratory located one-floor above the ED where only laboratory personnel and authorized investigators are allowed to enter. The device will be used only on enrolled subject samples and used only by trained CLS and authorized investigators. The FilmArray instrument and respiratory panel reagent pouches will be maintained and stored as instructed in the instrument's manual.