Improvements Through the Use of a Rapid Multiplex PCR Enteric Pathogen Detection Kit in Children with Hematochezia

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1 Introduction/Significance

This document is a clinical research protocol and the described study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated Federal regulations (i.e. Health Canada), and all applicable institutional research requirements.

Approximately 22,000 STEC infections occur in Canada annually at a cost of $404 million. [1] The effects of an *E. coli* O157 infection (O157 is the most common and virulent STEC pathogen) range from asymptomatic to lethal with ~15% of infected children developing HUS 5 to 13 days after diarrhea onset. [1] HUS is defined as the presence of azotemia, thrombocytopenia and anemia. In a recent study of 770 children with HUS, 57% of children required dialysis, 93% received transfusions, and 3% died. [2] Among HUS survivors, 12% develop end-stage renal disease [3] and in children with prolonged anuria, 100% suffer from chronic kidney disease. [4] Currently, most STEC infections are diagnosed microbiologically several days after they present for care when they suffer from bloody diarrhea. Because of the time lag to diagnosis as well as development of HUS, monitoring of renal and hematologic parameters is recommended to enable the early identification of children who are developing HUS. Our team has recently quantified this time lag in Alberta's children (Appendix 1). [5] We have also published guidelines that have been distributed by Alberta Health Services indicating the importance of repeating the blood tests until the HUS window has passed and of the importance of preventing dehydration (http://www.albertahealthservices.ca/assets/info/hp/diseases/if-hp-dis-ecoli-stec.pdf).

The prevention of dehydration in children with STEC infection is gaining prominence due to recent publications that associate early intravascular volume expansion with improved outcomes. [6-9] It is important to note that **no therapy has been proven to prevent HUS [10] or reduce kidney injury severity after HUS is established.** [11] To address this gap experts recommend the administration of intravascular volume expansion to all children with bloody diarrhea while awaiting culture results. [12] The rationale for this approach builds on evidence that **in children with HUS, volume expansion may improve outcomes [6,7,9] and that dehydration and hemoconcentration are associated with adverse outcomes [2,8,13-15] including death (OR=5.1; 95% CI 1.5, 17.6)**. [16] Therefore, the ability to rapidly and reliably identify children with STEC infection, and to identify other pathogens with alternative treatment, public health, and follow-up implications, has the potential to dramatically improve the care of children with hematochezia.

The **BioFire Gastrointestinal Panel FilmArray®** [17] is a multiplexed nucleic acid (NA) based device that simultaneously identifies 22 enteric pathogens. It specifically tests for the presence of Shiga toxin and for O157. It requires 2 minutes of hands-on-time, returns results in ~1 hour, and is Health Canada and Food and Drug Administration approved. The device, which has been validated, [18-21] hopefully will enable the early identification of infected children and initiation (or withholding) of interventions directed by previously unavailable clinical data. It will enable us to bring a precision medicine approach into ED care. Our proposal is the first attempt to evaluate the ability of this technology to minimize testing and treating to those most likely to benefit. Such an evaluation that is needed by knowledge users to justify integration into care.

2 Knowledge Gaps

Each year, in the United States, 31 pathogens cause 9.4 million episodes of foodborne illness, 55,961 hospitalizations, and 1,351 deaths. [22] While a small proportion of this overall burden is due to STEC infection, 3% of all children with diarrhea associated HUS die. [2] In a study that included over 30,000 participants, STEC accounted for 39% of all bacterial pathogens identified [23] and children 5 – 9 years of age were the group with the highest prevalence of STEC infection. [23] We are targeting children with bloody diarrhea as *E. coli* O157:H7 infection is 59 times more common (95% CI, 37 to 96) in visibly bloody stool specimens than in non-bloody specimens. [23] Lastly, this issue is of paramount importance to Southern Alberta as the incidence of diarrhea-associated HUS is two to threefold higher than other parts of Canada, North America and Europe. [24]

We intend to determine new knowledge:

1. If use of the **BioFire FilmArray,** a rapid, multi-analyte enteric pathogen detection device, reduces resource utilization in a pediatric ED when employed on children with bloody diarrhea. **We hypothesize that use of the test combined with behavioural changes by physicians will reduce the use of baseline blood tests, the administration of intravenous fluids and future health-care resource use** (children are often brought back for repeat blood tests and fluids while awaiting culture results).

2. If satisfaction is higher in individuals randomized to testing with the BioFire FilmArray arm compared with children in the standard care arm.

Potential child health improvements:

1. **Children with STEC infection will be rapidly identified:** We have shown that in the 2014 STEC outbreak in Alberta, the median time from initial health care presentation to stool sample collection was 7 hours (IQR 2, 28) and to sample receipt at the laboratory was 33 hours (IQR 18, 42). Even more concerning is that the time from initial health care encounter to positive culture was 120 (IQR 86, 205) hours. By collecting rectal swabs at the point of care we will initiate specimen processing an average of 30 hours earlier. By employing the BioFire FilmArray we will reduce stool processing time by over 80 hours.

2. **Children with STEC infection will have dehydration reversed rapidly and they will be closely monitored:** Following the rapid identification of children with STEC infection, all such children will be managed in accordance with a protocol developed by the APPETITE team for Alberta Health Services (http://www.albertahealthservices.ca/assets/info/hp/diseases/if-hp-dis-ecoli-stec.pdf), which includes the performance and monitoring of serum biochemistry and hematologic profiles and the prevention of dehydration. It is believed that the early administration of intravascular volume expansion has the potential to reduce the morbidity of HUS in affected children. [6,7]

3. **Children who do not have STEC infection will avoid unnecessary blood tests, intravenous fluids and repeat visits:** As ~10% of eligible children will have STEC infection, [25,26] the routine performance of blood tests, administration of intravascular hydration, and frequent monitoring is unnecessary in the vast majority of children with hematochezia. As such, knowledge that a result will be rapidly available will enable clinicians to confidently discharge children without performing unnecessary procedures. Those who test positive can be recalled to the ED for the appropriate management.

4. **Children will have alternative etiologies identified rapidly:** The BioFire FilmArray will also enable the rapid identification of other pathogens, some of which will require immediate therapy such as *Shigella sp.*, *Clostridium difficile*, and others that have public health implications such as *Salmonella sp.,* and norovirus.

5. **Children who do not have infectious gastroenteritis will be rapidly identified:** Children with a negative BioFire FilmArray will also be identified. This would raise the suspicion for alternative etiologies.

6. **Transmission will be reduced**: The rapid identification of infected children has the potential to reduce spread, which is common and occurs early in the course of disease. Transmission might be reduced by separating infected index cases from their at risk siblings. [27]

3 Study Objectives

The rapid identification of STEC-infected children will enable the provision of appropriate and timely care to such children. The rapid identification of other enteric pathogens (bacteria, virus, parasite) will enable the provision of targeted therapies as appropriate and the withholding of avoidable interventions. It will also provide information for clinicians to consider alternate, non-infectious etiologies as appropriate. We hypothesize that the **BioFire FilmArray can be used selectively in children with hematochezia to identify children with STEC infection and therefore will expeditiously identify children in need of therapeutic interventions and those for whom blood testing, intravenous fluids, and follow-up visits are unnecessary.** Knowledge of the etiology early in the course of disease will enhance the provision of a patient-level precision medicine approach to what is otherwise an ill-defined symptom.

Research Questions

1. Do individuals randomized to testing with the BioFire FilmArray undergo fewer procedures (i.e. blood tests, intravenous fluids) and repeat healthcare visits compared with children in the standard care arm?

2. Are patient and caregiver satisfaction higher in individuals randomized to testing with the BioFire FilmArray arm compared with children in the standard care arm?

Primary Objective

1. To determine if **use of the BioFire FilmArray in children with hematochezia results in a reduction in resource utilization.** Primary outcome – any blood tests (dichotomous with sub-analysis by specific blood tests); secondary – intravenous fluid administration, ED encounters.

Secondary Objectives

1. To quantify clinical outcomes – development of HUS, acute kidney injury, need for renal replacement therapy, turnaround time from BioFire result relative to stool culture result.
2. To determine if use of the BioFire FilmArray is associated with greater family satisfaction with care.
3. To determine testing criteria to optimize the clinical improvement emerging from use of the BioFire FilmArray (i.e. predictors of bacterial etiology).

4 Patients and Methods

4.1 Study Design

We will prospectively identify children who present with hematochezia. Potentially eligible subjects will be identified by our Pediatric Emergency Medicine Research Associate Program (PEMRAP) and the Pediatric Emergency Research Team (PERT) nurses (ED coverage 14 hours per day). Eligible children will have ≥3 episodes of diarrhea within the preceding 24 hours and will have had blood identified in the stool (by physician, nurse or parent). Eligible subjects will be approached by a PERT team member to obtain consent (and assent when appropriate). Once consent has been obtained, study participants will be randomized by a REDCap randomization tool to ensure allocation concealment (i.e. research team, ED physicians will be unaware until after enrolled into the study and randomized). In order to optimize participants who have consented/assented to be contacted in the future regarding additional research studies as well as follow up, we will collect the following information at the initial point of contact: home, cell, work and alternate telephone numbers as well as e-mail address.

Children randomized to the standard of care arm will have demographic and clinical information collected and the treating physician will be informed to proceed as per their usual practice and treatment patterns. If stool is unavailable a rectal swab will be collected and sent to Calgary Laboratory Services (CLS) for routine culture. A routine stool specimen for back-up culture will still be requested as per standard of care. Home stool collection will be performed for those unable to provide a sample at enrolment and will be achieved by providing families with collection kits. Following the completion of the visit, data regarding all testing, procedures, and medications administered will be collected. The family will be contacted 14 days later to collect outcome information (clinical and health resource use) and satisfaction. The medical

records and select administrative databases may be reviewed to ascertain and confirm outcome data on Day 28.

Children randomized to the BioFire FilmArray arm will have the same data collected, but stool, if available, will be sent STAT to Calgary Laboratory Services (CLS) for the performance of the BioFire FilmArray test and routine culture. If stool is unavailable, a rectal swab will be performed and sent to CLS for the performance of the BioFire FilmArray test and routine culture. A routine stool specimen for back-up culture will still be requested as per standard of care once it is available. The result of the BioFire test will be printed and brought to the ED where it will be provided to the ED physician for immediate review and management as appropriate. The result will be included in the ED chart for documentation purposes. Education regarding the interpretation of BioFire FilmArray results will have been performed in advance to all faculty members and a research team member will be available to answer any questions should they arise. We have worked with leaders at CLS including Drs. Gregson, Berenger and Vanderkooi who believe we should be able to receive a result within 2-3 hours of receipt of the specimen at CLS. Treatment decisions will be at the sole discretion of the ED treating physician who receives the result. Following the completion of the visit, data regarding all testing, procedures, and medications administered will be collected. The family will be contacted 14 days later to collect outcome information (clinical and health resource use) and satisfaction. The medical records and select administrative databases may be reviewed to ascertain and confirm outcome data on Day 28.

All children 6 months – 18 years of age will be eligible for participation (STEC infection is exceedingly rare in children < 6 months of age). Children previously enrolled in the study will be ineligible to participate.

For those who decline consent, we will request consent to access select administrative data, Netcare and/or access to the child's medical records related to the illness to document interventions and outcomes in order to be able to assess bias by comparing participating and non-participating children in this study.

Biofire FilmArray™: The Health Canada and Food and Drug Administration-approved, multiplex Biofire FilmArray™ Gastrointestinal Panel can detect 22 analytes: *Campylobacter* (*C. jejuni, C. coli, and C. upsaliensis*), *Salmonella, Shigella/*Enteroinvasive *E. coli* (EIEC), *Vibrio (V. parahaemolyticus, V. vulnificus*, and *V. cholerae*), *Yersinia enterocolitica*, Shiga-like toxin-producing *E. coli* (STEC) stx1/stx2, Enterotoxigenic *E. coli* (ETEC) lt/st, *E. coli* O157, *Clostridium difficile* (Toxin A/B), *Plesiomonas shigelloides*, Enteroaggregative *E. coli* (EAEC), Enteropathogenic *E. coli* (EPEC), norovirus GI/GII, rotavirus A, adenovirus F40/41, astrovirus, sapovirus (I, II, IV and V), *Cryptosporidium, Entamoeba histolytica, Giardia lamblia*, and *Cyclospora cayetanensis*. A single instrument can test one stool sample in approximately 1 hour with 2 minutes of hands-on time. After adding 200 µL of stool specimen in Cary Blair and hydration solution to the FilmArray pouch, the system performs nucleic acid extraction, nested multiplex polymerase chain reaction and lastly, endpoint melting curve analysis with the

FilmArray software. For this study, the BioFire FilmArray will be run as a research test at CLS and it will not go through full verification and implementation procedures at CLS. The product insert recommendations will be followed for verification purposes.

Rectal Swabs: The APPETITE team has been evaluating the use of rectal swabs for over two years now and we have demonstrated that rectal swabs are a suitable alternative specimen when stool is unavailable. [28] In brief, we insert a sterile flocked rectal swab (FLOQSwab, Copan Italia, Brescia, Italy) into the rectum. It is then rotated a full circle once and then transported in modified Cary-Blair media. The current APPETITE protocol employs the Luminex xTAG Gastrointestinal Panel Platform and requires a full day for extraction (hence the switch to the Biofire FilmArray for the current study proposal). When compared with paired stool samples on 1142 children, overall agreement is 90% (95% CI: 88, 92) with positive test result agreement of 98% (95% CI: 96, 99). As it relates to bacterial pathogens the overall agreement is 93% (95% CI: 92, 95) with positive bacteria test result agreement of 81% (95% CI: 74, 86). These results were achieved through the use of a specimen procurement approach that would be replicated in the current proposal.

In a 3-centre project currently underway in the U.S. employing rectal swab analysis on the Biofire FilmArray platform they have found performance of the rectal swab to be comparable to stool for detection of pathogens.[29] Importantly, there were no discrepancies for bacterial or STEC targets. They concluded that rectal swab collection at the time of the patient visit enables rapid testing and the generation of actionable results in the acute care setting when a stool specimen cannot be provided.

4.1.1 Outcome Variables

We will track the following on all participants:
Primary Outcome Measure:

1. Blood test performance, any blood testing performed within 72 hours of randomization;

Secondary Outcome Measures:

2. Intravenous fluid administration, children administered IV fluids identified by chart review;
3. Total physician visits (ED and non-ED), children visiting additional health-care practitioners identified by chart review;
4. ED length of stay, ED length of stay during enrollment visit determined by chart review;
5. Antibiotic use, antibiotic use identified by chart review;
6. Hospital and intensive care unit admission, hospitalization identified by chart review;
7. Diagnostic imaging performed, diagnostic imaging performed identified by chart review;
8. HUS, children with HUS identified by chart review;

9. Acute kidney injury, based on chart review in accordance with KDIGO guidelines;
10. Need for renal replacement therapy, renal replacement therapy identified by chart review; and
11. Caregiver and patient satisfaction, satisfaction of care received during ED visit answered in Day 14 follow-up form on a Likert scale

4.2 Subject Selection and Withdrawal

4.2.1 Inclusion Criteria

Eligible children will:

1. Be aged 6 months – 17.99 years of age
2. Have ≥3 episodes of diarrhea within the preceding 24 hours and have blood identified in the stool (by physician, nurse or parent)

4.2.2 Exclusion Criteria

Children with any of the following will not be eligible:

1. Previously enrolled in the study
2. Unavailable for Day 14 follow-up
3. Currently (most recent complete blood count) known to be neutropenic (Neutrophils <1000), or at high-risk of being neutropenic (receiving chemotherapy) at present
4. Known to be STEC positive (stool culture, PCT, or toxin)
5. Language barrier that prevents the ability to obtain informed consent and assent (when appropriate)

4.2.3 Study Withdrawal and Discontinuation

Subjects will be withdrawn if:

1. If it is deemed by the investigator or treating physician that the child's health may be jeopardized by continued participation in the study (prior to sample collection)
2. The patient's caregivers wish to no longer participate and withdraws their child for whatever reason
3. The patient wishes to no longer participate and withdraws themselves for whatever reason
4. The assented child wishes to no longer participate and withdraws for whatever reason

If the patient, patient's caregiver or the assented child respectively chooses to withdraw the participant from the study, they will be provided with a choice regarding their exit from the study:

A. The patient, caregiver or assented child may choose to withdraw the participant from the study, as well as all data collected from their participation in the study. In this case, all

data will be excluded from analysis and not incorporated into the study. The data will also be destroyed in accordance with local data destruction policy and TCPS2 guidelines.

B. The patient, caregiver or assented child may choose to withdraw the participant from the study; however they will allow continued use of study data collected from their participation in the study.

Subjects will discontinue the study if:

1. If it is deemed by the investigator or treating physician that the child's health may be jeopardized by continued participation in the study (following sample collection)

4.3 Study Procedures

Children randomized to the standard of care arm and the BioFire FilmArray arm will have clinical data collected:

1) Day 0 – ED enrollment visit (In person): At the initial screening visit, the research assistant or research nurse will explain the nature of the research project to the family. Informed consent, and assent if applicable, will be obtained. A detailed medical history will be documented to ensure the subject's eligibility for inclusion in the study. Parents will be asked to participate in a standardized 10 minute survey administered by study personnel. The survey will collect descriptive data regarding current medical history (i.e. diarrhea – frequency/duration/blood; vomiting – frequency/duration; fever; pain; health care use; treatment required/procedures performed), previous medical history (i.e. investigations), household pets, and childcare arrangements. The information will be entered in our electronic data capture system (REDCap), and all charts will be reviewed in the ED.
    a. Specimen Collection: Subjects who qualify for the study will have a stool sample collected, or a rectal swab specimen will be collected if stool is not available for either cohort (Standard Care and BioFire). Children who have a rectal swab collected at this visit will be requested to submit a stool specimen for culture after the ED visit.
    b. Letter to parents: Only subjects randomized to the BioFire FilmArray arm will be given a letter. The letter outlines their assignment to the BioFire arm and what that means.
2) Day 14 Follow-Up: Data regarding ongoing symptoms, any hospital visits/admissions and locations of the respective hospital visits/admissions, testing and procedures conducted as well as parental satisfaction of the experience at the ED will be collected. Parental reports will act as source documentation for data that is related to any additional healthcare visits as well as care in relation to the respective visits not associated with the Alberta Children's Hospital. At the initial point of contact, we will collect the following data: home, cell, work and alternate telephone numbers. For phone follow-up, we will call all numbers provided at least once daily (maximum 5 attempts). Study participants will not be identified by name on study document except the Contact Sheet.

All standardized surveys employed in this study will consist of a series of single-and multiple-select closed-ended items. We will also allow for the selection of a residual "other" category. In cases in which the respondent feels that his or her response does not correspond to one of those already listed (ie. he/she selects "other"), the respondent will be asked to elaborate on his or her answer in full text.

3) Day 28: The medical records, Netcare and select administrative databases may be reviewed to ascertain and confirm outcome data on Day 28. This chart review will collect descriptive data regarding subsequent hospital visits and/or subsequent hospital admissions. Variables such as date and time of visit/admission, discharge diagnosis, investigations completed, complications or procedures performed and medications administered will be collected. Chart reviews will serve as source documentation for all data that is related to the Alberta Children's Hospital.

4.4 Statistical Plan

4.4.1 Sample Size Determination

The desired sample size – 54 subjects – was calculated employing a baseline blood testing rate of 60% in the control group, a power of 80%, type I error of 5%, and a minimally clinically important difference of 40% in the proportion of children who experience **the primary outcome** (i.e. have any blood testing performed within 72 hours). Thus, we hypothesize that 20% of children in the intervention arm will have blood testing performed. The estimation of children having any blood testing performed within 72 hours (i.e. meeting our primary outcome measure) is based upon data from the APPETITE study (currently 62% among children with hematochezia). Based on previous experience we estimate that 10% of subjects will be lost to follow-up; hence the final sample size is 60 in total. Sample size requirements will be recalculated after the enrollment of 30 children. Based on the enrollment into APPETITE of 935 children at ACH since April 2015 and the presence of hematochezia in approximately 5% of children (23/506 on whom these data were collected), we anticipate that through the identification of potential participants outside of research coverage hours, we should be able to recruit our cohort over the span of 12 months.

4.4.2 Statistical Methods

All analyses will be undertaken by the intention-to-treat (ITT) principle. Patients who drop out or crossover will be followed and included in the ITT analysis. All statistical tests will be two-sided. Baseline characteristics will be analyzed and compared. Sensitivity analyses will be performed to assess the possibility and consequences of non-random loss to follow-up. The proportion of children who have any blood testing performed within 72 hours of randomization, the **primary outcome**, will be analyzed by comparing proportions utilizing a Fisher's Exact test. We will use an alpha level of 0.05 for statistical testing.

The overall significance level for statistical tests on the **secondary outcomes** will be set at 0.05 with adjustment for multiple comparisons performed using a Bonferroni correction.

Dichotomous outcomes to be evaluated include 1) intravenous rehydration, 2) ED revisits, 3) any healthcare revisits and 4) hospitalization within the subsequent 14 days. Clinical outcomes will also include development of 5) HUS, 6) Kidney Disease Improving Global Outcomes Stage 2 or 3 creatinine based acute kidney injury,[31] 7) antibiotic use, and 8) diagnostic imaging.

Recursive partitioning analysis will be employed to identify clinical features that select candidates for BioFire testing that maximize specificity and sensitivity to identify STEC patients. Analyses will be performed blinded to allocation assignment.

5 Adverse Event Reporting

Anticipated disease outcomes (listed below) are sought to be a natural continuation of the disease and as a result, the following will not be reported to REB:

1. IV insertion
2. Blood tests
3. Abdominal pain
4. Fever
5. Vomiting
6. Diarrhea
7. Bloody stool
8. Dialysis
9. Renal abnormalities
10. Hematological abnormalities
11. Biochemical abnormalities
12. Transfusions
13. Seizures
14. Hospital admissions
15. Other known complications of STEC infection

6 Data Handling and Record Keeping

Patients will be assessed and treated by ED staff without any regard to this study. Stool specimen testing will continue as per standard of care. Once the inclusion criteria are confirmed and parental consent is obtained (and child assent when appropriate) an enrollment ID number will be assigned. Recruitment and specimen collection will commence after ethics approval is obtained.

We may need to contact subjects in the future regarding research questions which that may be discovered from the data collected in this study. Select administrative data may also be accessed to allow linkages beyond study collected outcomes.

6.1 Confidentiality

Data collected on paper will be stored in a locked cabinet in a locked office of a securely accessed building.

Data will be entered from paper to REDCap, or entered directly into REDCap, which is a data capture system that has been validated by Health Canada. REDCap access will be determined based on project involvement. Only the investigators and research staff listed on the ethics submission will have access to data. Additionally the data management team will have administrative access to the database and the servers on which it resides. The data management team will only access study data as required to perform maintenance and support duties.

The database contains sensitive patient information as well as personal identifiers however, each patient is assigned a study ID that is used to communicate about the patient. Information from the database will be coded and stored into the secure server. The database will have robust and modern security principles enforced in an auditable fashion as outlined in the Health Information Act and in most cases in line with the guidelines set out in the FDA's CFR Part 11 Guidance document.

Deidentified data may also be stored on secure network drives including Alberta Health Services, University's hydrogen drive and computers on the ProvLab Laboratory Information System. Authorized access will be granted to relevant research team members and requires a specific user ID and password.

Because this study will recruit participants in an ED setting, the likelihood of one study participant speaking with another is very low. These participants will likely only have one visit, at which time they will be enrolled. All follow up will be done confidentially over the phone or by secure email.

6.2 Records Retention

Name of patient is collected and kept for future contact after data collection has been completed only if the patient consents to contact for a future research study.

6.3 Regulatory Binder

A regulatory binder containing all information pertinent to the study will be kept.

7 Budget

PEMRAP	**$2,500** – coordination, training, supplies, data collection
CLS	$100/test x 30 = **$3,000**

Flocked Rectal Swabs	$0.75 x 30 = **$23**
Study Coordinator	Start-up: $40/hr x 37.5 hrs/wk/FTE x 0.5 FTE x 8 weeks x 1.23 (benefits) = **$7,380** Ongoing: $40/hr x 37.5 hrs/wk/FTE x 0.1 FTE x 52 weeks x 1.23 (benefits) **$9,594**
Database/randomization	**$2,500** – database creation, design, logic, limits, and computer based randomization
Statistical Analysis	**To be done by Dr. Stephen Freedman** (with consultation requested as needed)
Biofire FilmArray	**$29,000** (in-kind for device, training, service, kits)
TOTAL	**$24,997**

We have been working with bioMérieux Canada, the distributor of the **Biofire FilmArray** on approaches to integrate rapid diagnostics to improve the care of children with STEC infection. For the current study proposal they have agreed to provide an in-kind device ($6,000/year), service ($5,000/year), and 100 test kits ($18,000) for total in-kind support of $29,000.

8 Publication Plan

We will interpret our findings in the context of value added. We will compare the outcomes in children randomized to testing with the Biofire FilmArray and those randomized to standard of care. We will evaluate the role the Biofire FilmArray might play in rapidly identifying the etiology of the hematochezia compared with standard testing. We will explore the role the Biofire FilmArray might play in selectively identifying children who require blood tests, intravascular volume expansion and close monitoring.

If this study yields findings of clinical relevance, we would seek subsequent funding to conduct an economic evaluation to determine if the cost of care provided to individuals randomized to testing with the BioFire FilmArray is less than that provided to children in the standard care group. We will employ data collected regarding utilization of testing (BioFire FilmArray, blood, urine, stool), diagnostic imaging, ED care (i.e. visit cost), physician billing, and medication administration to evaluate the relative cost of the two approaches and we will determine the cost per case of STEC infection identified.

Funding will be sought from a variety of sources to support the hiring of graduate students. Potential sources include philanthropic (IPH, ACHRI, U of C, AIHS, CIHR), industry (bioMerieux), or stakeholders (CLS, ProvLab, AHS, MNCY, kidney or emergency SCN). If safe and effective, we will subsequently work with CLS to integrate this technology into standard of care. We will also use the data obtained to justify the use of this technology in a CIHR RCT proposal that is currently under review that proposes to use rapid diagnostic approaches to enroll STEC-infected children in a volume expansion trial. We will also be submitting an NIH over-the-cap R01 multinational proposal that will include this technology (to be submitted in 2019; NIH R34 in May 2017).

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10 Attachments

Appendix 1: Quantified time lag to diagnosis in Alberta's children.