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TITLE: Intravesicle Lactobacillus to Reduce Urinary Symptoms After Spinal Cord Injury

PRINCIPAL INVESTIGATOR: Suzanne Groah, MD, MSPH

CONTRACTING ORGANIZATION: MedStar Health Research Institute

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6. AUTHOR(S)

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

MedStar National Rehabilitation Hospital
102 Irving St, NW
Washington, DC 20010

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14. ABSTRACT: Urinary tract infection (UTI) is the most common outpatient infection world-wide, and for people with spinal cord injury (SCI) with neurogenic bladder (NB) it is not only the most common infection, but also the most common secondary condition, cause for emergency room visits, and infectious cause of hospitalization. Despite its prevalence, attempts to ameliorate UTI among people with SCI are stymied by long-standing diagnostic challenges due to the facts that "gold standard" diagnostic tests (urinalysis and urine culture) have lower sensitivity and specificity for UTI in this population. With our prior work we have advanced research in this domain and prepared ourselves to uniquely propose and pursue the stated aims. Specifically, we have laid the groundwork for this project by: 1) advancing patient-centered urinary symptom measurement and interpretation through development and validation of Urinary Symptom Questionnaires for people with Neurogenic Bladder (USQNB); 2) transforming clinical dogma around healthy urine by demonstrating that healthy urine is not sterile; 3) identifying Lactobacillus as a component lacking in the urine ecosystem of people with NB; 4) obtaining regulatory approvals for first-in-human safety testing of selfinstilled intravesical Lactobacillus RhamnosusGG文 (LGG文); 5) demonstrating the safety and tolerability of instilled intravesical LGG文; and 6) demonstrating utility of a novel biomarker, urine NGAL, to discriminate between levels of inflammation indicative of UTI versus those of urinary tract colonization in children with NB. Hypothesis or Objective: This proposal specifically focuses on the population of people with SCI and NB who manage their bladders with intermittent catheterization (IC). The objectives of this proposed study are: 1) to define clinically meaningful change (i.e. differentiating states of health and illness) with respect to urinary symptoms, urine inflammation, and the urine ecosystem in this population; 2) to determine the optimal intravesical LGG文 dose to be used to reduce urinary symptoms in a future clinical trial; and 3) advance diagnosis, self-management, and clinical research for urinary symptoms in SCI by developing and validating a research model that integrates quantitative and qualitative clinical data to reliably detect clinically meaningful and interpretable: i) symptom clusters (across person); and ii) change from baseline (within person).

15. SUBJECT TERMS NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The long-term purposes of this research are to advance urinary symptom and urinary tract infection (UTI) evidence and antibiotic sparing therapeutics for urinary symptoms and UTI among the population of people with neurogenic lower urinary tract dysfunction due to spinal cord injury. The study population includes individuals with neurogenic bladder due to Spinal Cord Injury (SCI) over the age of 18 who utilize *intermittent catheterization for bladder management.* The objectives of the research among this population are: 1) to define clinically meaningful change (i.e. differentiating states of health and illness) with respect to urinary symptoms, urine inflammation, cultivable bacteria, and the urine ecosystem; and 2) to determine the optimal intravesical *Lactobacillus RhamnosusGG*® (LGG®) dose to be used to reduce urinary symptoms in a future clinical trial.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Spinal cord injury, SCI, neurogenic bladder, neurogenic lower urinary tract dysfunction, NLUTD, urinary symptoms, bladder health, *Lactobacillus*, probiotics, paraplegia, tetraplegia

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

In May, 2022 we hosted the pre-conference at American Spinal Injury Association (ASIA) annual meeting titled "State of the Art Advances and Discoveries in Neurogenic Lower Urinary Tract Dysfunction (NLUTD)" We had 62 registered participants participating virtual and in-person. Nineteen national leaders presented on a variety of bladder related topics.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Sites: MNRN= MedStar National Rehabilitation Hospital; GU= Georgetown University; CNH= Children's National Hospital; UP= University of Pittsburgh

	Timeline	Complete	Date	Site
Major Task 1: Create & prepare documentation for SA 1, and 2	Months			
Obtain FDA Amendment approval of current IND	Pre-award	100%	1/7/2020	MNRN
Refine eligibility criteria, exclusion criteria, screening protocol	1	100%	7/23/2019	MNRN, GU
Finalize consent form, protocol, high dose training manual	1	100%	7/23/2019	MNRN
Obtain IRB approval from MedStar IRB and CNH IRB	2-3	100%	12/20/2019	MNRN, CNH
Update Reliance Agreement between MedStar IRB and GU as needed		100%	Ongoing	MNRN, GU
Obtain Military 2nd level IRB review for all three sites (ORP/HRPO)	3-6	100%	5/19/2020	MNRN, CNH, GU
Submit amendments, adverse events and protocol deviations as needed	As Needed	N/a	N/a	MNRN
Coordinate with sites for annual IRB report for continuing review	Annually	100%	Ongoing	MNRN
Maintain FDA IND active throughout study (Approved on: 07/10/2015)	1-36	100%	Ongoing	MNRN
Major Task 2: Coordinate Study Staff for Pilot Clinical Trials				
Subtask: Preparation for Pilot Clinical Trial				
Build and test REDCap Database	3-5	100%	5/1/202	CNH

	Timeline	Complete	Date	Site
Major Task 3: Participant Recruitment, Participant Evaluation (SA 1)				
Subject Screening and Enrollment	7-30	N/a	In progress	MNRN
Recruit 120 SCI participants from Washington, DC area	7-30	60%	In progress	MNRN
Collect first non-symptomatic urine specimens from each participant	7-30	91%	In progress	MNRN
Collect second non-symptomatic urine specimen from each participant	7-30	77.8%	In progress	MNRN
Prepare urine collections for assessment for urine NGAL, white blood cells, nitrite, cultivable bacteria, and the urinary microbiome	7-30	N/a	In progress	MNRN, CNH, UP
Major Task 4: Participant Recruitment, Participant Evaluation (SA 2)				
Subject screening, enrollment, randomization, participant training	7-29	N/a	In progress	MNRN, GU
Recruit 182 SCI participants	7-30	73.1%	In progress	MNRN, GU
Randomize participants into low or high dosing arms	7-30	73.1%	In progress	GU
Send out study package to all participants including gloves, saline solution, lube, Lactobacillus GG capsules, and instillation guidelines	7-30	73.1%	In progress	MNRN
Of the 182, recruit n=68 local participants for urine pilot trial	7-30	77.9%	In progress	MNRN
Collect USQNB from participants weekly	7-30	N/a	In progress	MNRN
Collect before instillation urine samples from local sample (n=68) including 40% attrition rate	7-30	13.1%	In progress	MNRN
Collect post instillation urine samples from local sample (n=68) including 40% attrition rate	7-30	13.1%	In progress	MNRN
Prepare urine collection for and carry out UA, UC, and microbiome analyses	7-30	N/a	In progress	MNRN, CNH, UP
Collect any unused Lactobacillus GG capsules/ subjects used all Lactobacillus GG capsules	8-31	29.1%	In progress	MNRN
Major Task 5: SA3 modeling activities				
Subtask 1: Model formation				
Obtain data from SA1 and SA2; data necessary for the modeling developed and validated in SA3 will be obtained in SA1 and SA2,or simulated based on these data and our preliminary data.	15	10%	In progress	GU
Analyze data from SA1 and SA2, integrating methods from data science and bioinformatics, using statistical model fitting to determine model utility.	15-36	10%	In progress	GU
Build and test a Bayesian Network using the combination of data science, bioinformatics, statistical model fitting, and clinical considerations, all applied to the data from SA1 and SA2, and/or simulated data based on the SA1 and SA2 results.		10%	In progress	GU

Generate probability estimates from a Bayesian Network that quantifies the likelihood that any given individual with the observed characteristics falls into each of the possible outcome categories.	2-36	10%	In progress	GU
Major Task 5: Dissemination of Study Results				
Prepare presentations for national and international dissemination	10-36	0%	Not yet started	MNRN, GU, CNH UP

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major Task 1: All documentation has been created and finalized for SA 1 and 2. Exempt IRB approval was received at Children's National Hospital (CNH) and the 2022 annual continuation at MedStar IRB was completed on September 14, 2022. Our current approval is through September 5, 2023. The annual ORP/HRPO submission was completed on October 22, 2021. We continue to maintain our FDA IND #16306. All subtasks under Major Task 1 are either ongoing tasks or completed.

Major Task 2: All study related data is managed by REDCap at CNH with weekly reports sent to study staff. Except for continuous training with Consumer Experts, all subtasks under Major Task 2 are completed.

Major Task 3: Enrollment of SA1 was initially delayed due to the COVID-19 pandemic. Protocols to minimize interaction with patients were developed and put in place. In addition, we developed a new drop off protocol for transferring samples to Children's National Hospital (CNH). CNH has developed procedures for the use of lab space to minimize interaction for CNH staff in the lab space. We have enrolled subjects for Aim 1 since August 2020. As of August 30, 2022 we have enrolled 72/120 subjects.

Major Task 4: Enrollment for SA2 began nationwide end of May 2020. Local enrollment begun in August 2020. As of August 30, 2022, 133 participants (56 of them local) have enrolled in the study to date (randomized into 73 high dose, and 60 low dose). All participants are sent supplies and receive training with the consumer expert prior to starting the study. 53 participants have completed the study so far.

Major Task 5:

Currently we are assembling the existing data this center/team has obtained over the past 10 years to inform the model that we proposed originally. This requires checking the concordance of earlier methods and libraries (from which microbiome organisms are identified) with more recent ones. All samples were obtained from "asymptomatic" individuals, but there is no information about whether these participants in prior data collecting enterprises were "pre-symptomatic" rather than

asymptomatic for 72 hours after the sample. This modeling work will establish the methods and order of applications of methods, to be utilized when the current set of data become available. Because this project features descriptions of the asymptomatic ("normal") microbiome, we designed the project to assure that data contributors are asymptomatic for 72 hours post urine sample. Many, but not all, participants meet this criterion on their first sample; some require up to four samples before reaching the criterion. These few participants will represent our "pre-symptomatic" results, and will be contributing to analyses relating to symptom clusters. Qualitative analysis and descriptions of these individuals will be an important validation check on the modeling we do for those who are asymptomatic (for 72 hours after the sample). Thus, the entire process represents a mixed-methods approach to understanding the urobiome and "change from baseline".

What was completed in the last reporting year

This subtask (developing and validating an integrative model) requires ongoing background research, including literature and data considerations, which have been ongoing. New literature reviews have identified over 200 additional microbes in the urinary microbiome (urobiome) but also identified either a very small subset of "known uropathogens" or a small set of "urotypes". These developments (in 2022) are complicating the modeling approach, but our focus remains on the variety of descriptions (urotypes) that all apply to individuals in the asymptomatic state. This quarter SA3 effort has focused on both reviewing the clinical literature and understanding methodological innovations and their relevance to either the entire urobiome, just pathogens or protective species, or possibly to "urotypes". The latter are problematic because they are based solely on the patterns of genomes in urine samples and are not associated with any symptoms. However, recent publications (in 2021-2) have begun to recognize the need for a description of "normal" urobiomes in order to define "abnormal" or unhealthy urobiomes. Thus, the potential impact of this work is increasingly being recognized by independent laboratories around the world. Tree-based ensemble modeling, which accommodates collinearity (as well as very large data sets), will achieve the same predictive outcome as the Bayesian Network we originally proposed, but may be more interpretable and yield additional testable hypotheses. However, with 200 new microbes only recently discovered in the urobiome, a full-genomic analysis that uses our currently existing data will be missing 200 species because the analyses were done years ago and reflect the more limited libraries of that time. The increase in species count also brings an increase in the zero inflation problem because some of the new species are recognized when they occur only in one or a few samples.

We now recognize that the learning algorithm(s) to be developed will need to identify urotypes of the asymptomatic state. These will be identified by modeling a data set from 2012 for healthy controls (n=25) without NLUTD and asymptomatic individuals with NLUTD (n=21 -two known pre-symptomatic samples will be removed). We will then test these urotypes against a second data set from 2016 (n=50). With the results of asymptomatic urotype identification across these two prior data sets, we will be able to compare these findings with recently published asymptomatic urotypes defined based on novel urine culture methods as well as on 16S sequencing – neither of which have been applied to individuals with NLUTD. We will be able to contextualize the NLUTD asymptomatic urotypes with other research on the urobiome to confirm our learning algorithm generates a valid and reliable prediction rule. Once we have 16S data for our 72-hour asymptomatic samples, we can then test the reproducibility of these urotypes (for SA3).

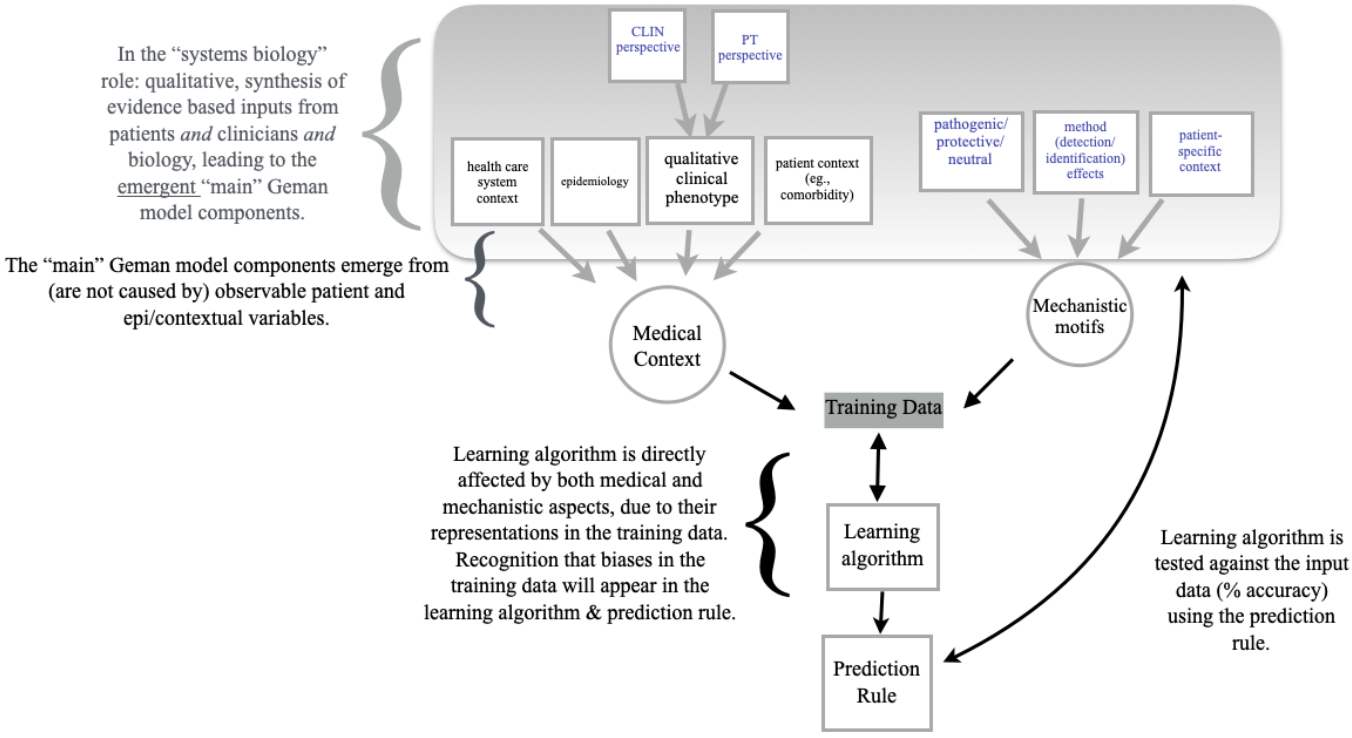

Figure: Revised model to be tested.

All of the input (square boxes in grey "systems biology", in the figure above) has been specified; although we are no longer simulating data sets, we utilize the evidence-informed binning (for changing any continuous variables into categorical data). This approach is typically left to automation, and represents part of the qualitative contribution to the methods.

The new (2022) publications primarily affect the "mechanistic motifs" side of the model. With urotypes, or a focus on known pathogen/protective species, that side of the model will be greatly simplified and a Bayesian Network is much simpler to utilize for the asymptomatic samples. The individuals who are pre-symptomatic will be qualitatively assessed for the variety and range of USQNB symptoms they express within 72 hours of their urine sample. We will test the prediction rules and asymptomatic urotypes to see if we can detect meaningful presymptomatic urotypes.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

During our NCE year of the grant, we hope to complete enrollment of participants for SA1 and SA2 within the restrictions of our COVID-19 protocols. Protocols could be modified during the fall and winter should COVID-19+ cases increase in the Metropolitan Washington D.C area warranting changes in institutional policies and procedures involving research and/or face-to-face interactions. We are currently working on interim data analysis will be completed, and abstracts will be submitted to nationwide conferences.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to Report

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Expenditures during Year 3 of the grant are close to budgeted expenditure rate in consideration to where we are with the study. Overall, we are still at a lower than anticipated expenditure rate due to not receiving study approval until May 2020, and the COVID-19 pandemic which caused major limitations to our enrollment for over a year, and to some extent is still limiting our enrollment efforts.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use of biohazards and/or select agents

N/a

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

  Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. Use an asterisk (*) if presentation produced a manuscript.*

At the ASIA pre-conference in May, our team presented on several topics related to the bladder Is UTI complicated? (Suzanne Groah) Lactobacillus as an antibiotic sparing therapeutic (Suzanne Groah) Animal models of UTI and urinary symptoms (Katie Forster) Bladder Check App: A consumer friendly app created from patient-centered, patient reported outcomes on urinary symptoms (Amanda Rounds)

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Based on our bladder health research, Dr. Rounds received a PVA grant to develop a Bladder Health App.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

No new materials to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name	Project Role	Research ID	Person month worked	Contribution to project
Suzanne Groah	Project PI	0000-0003-1213-1959	3.0	As the PD, Dr. Groah leads the review of all study related tasks completed under Major Tasks 1-4
Inger Ljungberg	Project Manager	N/a	0.6	Ms. Ljungberg is managing all work with DOD, HRPO and FDA in addition to budget expenditures and subcontracts
Amanda Rounds	Research Coordinator	0000-0003-0238-4629	2.5	Dr. Rounds is the coordinator of this study and completed the majority of screening, consenting, sending out supplies to consented participants, and schedules training sessions between participants and consumer expert
Kathaleen Brady	Research Coordinator	N/a	0.5	Ms. Brady assists with screening and consenting of study subjects for both Aims.
Emily Leonard	Research Coordinator	N/a	0.1	Dr. Leonard assists with screening and consenting of study subjects for both Aims.
Christopher Riegner	Research Coordinator	N/a	0.1	Mr. Riegner assists with screening and consenting of study subjects for both Aims.

Ayanna Brown	Research Coordinator	N/a	0.2	Ms. Brown assisted with screening and consenting of study subjects for both Aims.
Allison Maxwell	Research Coordinator	N/a	1.3	Ms. Brady assisted with screening and consenting of study subjects for both Aims.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
<u>Organization Name:</u>
<u>Location of Organization: (if foreign location list country)</u>
<u>Partner's contribution to the project</u> (identify one or more)

- *Financial support;*

- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization Name: Georgetown University (Academic Institution)
Location of Organization: Washington, DC
Partner's contribution to the project: **Financial support; Collaboration**
Dr. Tractenberg is the Co-PI of the study. Her prime responsibilities completing the analysis of each aim. Dr. Tractenberg also designed, and will carry out, the modeling proposed for SA3.

Organization Name: University of Pittsburgh (Academic)
Location of Organization: Pittsburgh, PA
Partner's contribution to the project **Financial support; Collaboration**
Dr. Forster oversees all urine specimen study-related protocols including sample processing, freezing performed at Children's National Medical Center (CNMC). In addition. Dr. Forster will oversee uNGAL testing and preparation of microbiome libraries at University of Pittsburgh.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

This is reported in the SOW at the beginning of the document.

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

See separate attachment

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

- Quad Chart