PI: **Ambroggio, Lilliam**	Title: Metabolomics Evaluation of the Etiology of Pneumonia	
Received: 07/08/2016	FOA: PA16-190	Council: 01/2017
Competition ID: FORMS-D	FOA Title: MENTORED RESEARCH SCIENTIST DEVELOPMENT AWARD (PARENT K01)	
1 K01 AI125413-01A1	Dual:	Accession Number: 3955629
IPF: 615001	Organization: CINCINNATI CHILDRENS HOSP MED CTR	
Former Number:	Department: Pediatrics	
IRG/SRG: MID-B	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: Year 2: Year 3: Year 4: Year 5:	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N

Senior/Key Personnel:	*Organization:*	*Role Category:*
Lilliam Ambroggio	Cincinnati Childrens Hospital Medical Center	PD/PI
Samir Shah	Cincinnati Children's Hospital Medical Center	Other Professional-Mentor
Maurizio Macaluso	Cincinnati Children's Hospital Medical Center	Other Professional-Co-Mentor
Richard Ruddy	Cincinnati Children's Hospital Medical Center	Other Professional-Co-Mentor
Kathleen Stringer	University of Michigan	Other Professional-Co-Mentor
Heidi Sucharew	Cincinnati Children's Hospital Medical Center	Other Professional-Co-Mentor
Lindsey Romick-Rosendale	Cincinnati Children's Hospital Medical Center	Other (Specify)-Collaborator
Assem Ziady	Cincinnati Children's Hospital Medical Center	Other (Specify)-Collaborator

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier**

1. TYPE OF SUBMISSION*

❍ Pre-application ❍ Application ● Changed/Corrected Application

4.a. Federal Identifier [redacted]

b. Agency Routing Number

2. DATE SUBMITTED	**Application Identifier**	**c. Previous Grants.gov Tracking Number**
	FP00011450	GRANT12210373

5. APPLICANT INFORMATION **Organizational DUNS*:** 071284913

Legal Name*: Cincinnati Childrens Hospital Medical Center
Department:
Division: Hospital Medicine
Street1*: [redacted]
Street2:
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: First Name*: Kathy Middle Name: Last Name*: Goodin Suffix:
Position/Title: DIRECTOR-SPO
Street1*: [redacted]
Street2:
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email: [redacted]

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** [redacted]

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*	**10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER**
National Institutes of Health	TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Metabolomics Evaluation of the Etiology of Pneumonia

12. PROPOSED PROJECT		**13. CONGRESSIONAL DISTRICTS OF APPLICANT**
Start Date*	Ending Date*	OH-001
04/01/2017	03/31/2022	

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Lilliam Middle Name: Last Name*: Ambroggio Suffix:
Position/Title: ASSISTANT PROFESSOR
Organization Name*: Cincinnati Childrens Hospital Medical Center
Department: Pediatrics
Division: Hospital Medicine
Street1*: [redacted]
Street2:
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email*: [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$[redacted]
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$[redacted]
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Kathy Middle Name: Last Name*: Goodin Suffix:
Position/Title*: DIRECTOR-SPO
Organization Name*: Cincinnati Childrens Hospital Medical Center
Department:
Division: Sponsored Programs
Street1*: [redacted]
Street2:
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email*: [redacted]

Signature of Authorized Representative*
Kathy.Goodin

Date Signed*
07/08/2016

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:Cover_Letter_Ambroggio_July_2016.pdf

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Cincinnati Childrens Hospital Medical Center
Duns Number: [redacted]
Street1*: [redacted]
Street2:
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*: [redacted]
Project/Performance Site Congressional District*: OH-001

File Name

Additional Location(s)

Funding Opportunity Number: PA-16-190. Received Date: 2016-07-08T13:23:03.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ○ **Yes** ● **No**

IRB Approval Date: 04-15-2016

Human Subject Assurance Number 00002988

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Project_Summary_Ambroggio_K01.pdf
8. Project Narrative*	Project_Narrative_Ambroggio_July_2016.pdf
9. Bibliography & References Cited	References.pdf
10.Facilities & Other Resources	FACILITIES_AND_OTHER_RESOURCES_Ambroggio_K01_2.pdf
11.Equipment	

Funding Opportunity Number: PA-16-190. Received Date: 2016-07-08T13:23:03.000-04:00

Project Summary
Lilliam Ambroggio, PhD, MPH is an infectious diseases epidemiologist whose overarching career goal is to improve outcomes for children with common, serious infections by developing methods to improve diagnostic accuracy and implementing these methods into clinical practice. The research she proposes entitled *Metabolomic Evaluation in the Etiology of Pneumonia (MEEP)* combines advanced statistical techniques with ^{1}H-Nuclear Magnetic Resonance (NMR) metabolomics methodology to identify metabolites, which will facilitate etiologic diagnosis of community-acquired pneumonia (CAP) in children. Such pathogen identification will result in timely and accurate diagnosis that will permit targeted and effective management of this disease.
Candidate: Dr. Ambroggio is an Assistant Professor of Pediatrics with a joint appointment in the Divisions of Hospital Medicine and Biostatistics and Epidemiology at Cincinnati Children's Hospital Medical Center (CCHMC). She completed a Master's in Public Health and a Ph.D. in Epidemiology at Drexel University prior to beginning a post-doctoral fellowship at CCHMC. Her previous work in the clinical management of CAP focusing on antibiotic prescribing and diagnostic tools to detect pneumonia in combination with her previous training in molecular and cellular biology have prepared her to conduct the proposed research. The proposed career development plan will build upon her previous training with four training goals to enhance her trajectory toward becoming an independent investigator: 1) Experiential and didactic learning in study design and execution of quantitative ^{1}H-NMR metabolomics; 2) Acquire and apply advanced statistical analyses; 3) Interpret metabolomics data and its biological context and 4) Develop leadership and professional skills to execute multicenter studies. Dr. Ambroggio proposes training activities that include didactic and experiential learning to enable her to gain the necessary skills for metabolomic research.
Mentors/Environment: Dr. Ambroggio and her primary mentor, Samir S. Shah, MD, MSCE, have assembled a strong team of co-mentors and advisors to guide Dr. Ambroggio through the proposed training and research activities. The proposed career development plan utilizes the intellectual and metabolomics resources available through the University of Cincinnati and CCHMC, as well as resources available at the University of Michigan through Dr. Ambroggio's external mentor, Kathleen Stringer, PharmD. In addition Dr. Ambroggio will attend national seminars and workshops when optimal training is not available locally. As an institution CCHMC is committed to supporting junior faculty members through internal grants, administrative support and structured opportunities for faculty networking and education. Dr. Ambroggio will be obtaining biological specimens for this proposal from a fully operational, externally-funded prospective cohort study, CARPE DIEM. Both the ED and inpatient services at CCHMC provide an established research infrastructure and a large ambulatory and hospitalized patient population to conduct the proposed research. In addition all mentors have agreed to participate on Dr. Ambroggio's scholarly oversight committee which has been meeting quarterly since 2013.
Research: There is currently no accurate method to identify the etiology of CAP in children. This results in overtreatment with antibiotics or delays in appropriate treatment in children who are at risk for CAP-related morbidity. This proposal is the first step in developing a specific, fast and noninvasive approach for pathogen identification in children diagnosed with CAP. Aim 1 characterizes the sources (e.g. age and sex) of variation that exist in a healthy child's metabolome over three points. Aim 2 compares metabolite profiles from children who had a positive PCR test from either the nasopharynx or the blood for a virus, bacterial infection such as *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* with children who have no known infections. The purpose of this aim is to identify unique metabolite profiles using quantitative ^{1}H-NMR for each pathogen identified. Aim 3 will use urine samples from patients with CAP and compare them with samples from healthy contorls over three time points to determine the impact of antibiotic treatment on metabolite profiles. The completion of these aims will generate a metabolite profile database of common pathogens associated with childhood CAP and drive a systems biology approach to CAP diagnosis and treatment.
Summary: The innovation of the proposed research is the integration of robust clinical phenotype data from an ambulatory population with quantitative NMR metabolomics using novel statistical methods to address the clinically challenging problem of pediatric CAP diagnostics. The strong collaborations between the Divisions of Hospital Medicine, Biostatistics and Epidemiology, and Emergency Medicine at CCHMC and with the metabolomics core at the University of Michigan ensure the success of the proposed research. This award will provide Dr. Ambroggio with the training and research needed to be successful in a future, multi-center study to validate the metabolite profiles of pathogens causing CAP in children. Furthermore, this career development award will facilitate Dr. Ambroggio's development into a nationally-recognized independent investigator and leader conducting research that improves diagnostic tools for children with infectious diseases, specifically CAP.

Project Narrative

Community-acquired pneumonia (CAP) causes substantial morbidity in children. It is the fifth most common cause of pediatric hospitalization and, cumulatively, the most costly among infants and children. Currently there is no single test available that can distinguish between the >10 pathogens that cause CAP. The objective of this prospective cohort study is to determine distinct metabolite profile for major classes of pathogens that cause CAP in children (e.g. virus, typical and atypical bacteria). Urine and blood samples will be collected from children diagnosed with CAP in the Emergency Department or who are hospitalized at Cincinnati Children's Hospital Medical Center. Urine from children whose PCR tests are positive for a virus, typical bacteria or atypical bacteria will be sex and aged-matched to control samples. All urine samples will then be evaluated using quantitative ^{1}H-nuclear magnetic resonance. Advanced statistical methods will be applied to the identified metabolite dataset to determine unique metabolite profiles. These profiles will be used as the foundation for future studies in the diagnostic capabilities of ^{1}H-NMR for pathogen identification in children diagnosed with CAP. In addition, the concepts learned through this grant, as well as the career development pursued by the investigator, will be readily applicable to diagnostic testing for multiple infectious diseases.

REFERENCES

1. Carraro S, Giordano G, Reniero F, Perilongo G, Baraldi E. Metabolomics: a new frontier for research in pediatrics. J Pediatr 2009;154:638-44.
2. Ambroggio L, Lorch SA, Mohamad Z, Mossey J, Shah SS. Congenital anomalies and resource utilization in neonates infected with herpes simplex virus. Sexually transmitted diseases 2009;36:680-5.
3. Ambroggio L, Taylor JA, Tabb LP, Newschaffer CJ, Evans AA, Shah SS. Comparative effectiveness of empiric beta-lactam monotherapy and beta-lactam-macrolide combination therapy in children hospitalized with community-acquired pneumonia. J Pediatr 2012;161:1097-103.
4. Ambroggio L, Tabb LP, O'Meara T, Sheffler-Collins S, McGowan KL, Shah SS. Influence of antibiotic susceptibility patterns on empiric antibiotic prescribing for children hospitalized with community-acquired pneumonia. Pediatr Infect Dis J 2012;31:331-6.
5. Ambroggio L, Thomson J, Murtagh Kurowski E, et al. Quality improvement methods increase appropriate antibiotic prescribing for childhood pneumonia. Pediatrics 2013;131:e1623-31.

[redacted]

7. Atzei A, Atzori L, Moretti C, et al. Metabolomics in paediatric respiratory diseases and bronchiolitis. J Matern Fetal Neonatal Med 2011;24 Suppl 2:59-62.
8. Mickiewicz B, Vogel HJ, Wong HR, Winston BW. Metabolomics as a novel approach for early diagnosis of pediatric septic shock and its mortality. American journal of respiratory and critical care medicine 2013;187:967-76.
9. Lau SK, Lee KC, Curreem SO, et al. Metabolomic Profiling of Plasma from Patients with Tuberculosis Using Untargeted Mass Spectrometry Reveals Novel Biomarkers for Diagnosis. J Clin Microbiol 2015.
10. Tzoulaki I, Ebbels TM, Valdes A, Elliott P, Ioannidis JP. Design and analysis of metabolomics studies in epidemiologic research: a primer on -omic technologies. Am J Epidemiol 2014;180:129-39.
11. Katsnelson A. Momentum grows to make 'personalized' medicine more 'precise'. Nature medicine 2013;19:249.
12. Lacy P, McKay RT, Finkel M, et al. Signal intensities derived from different NMR probes and parameters contribute to variations in quantification of metabolites. PLoS One 2014;9:e85732.
13. Ramilo O, Allman W, Chung W, et al. Gene expression patterns in blood leukocytes discriminate patients with acute infections. Blood 2007;109:2066-77.
14. Wardlaw T, Johansson EW, Hodge M. Pneumonia: The forgotten killer of children. The United Nations Children's Fund/World Health Organization; 2006.
15. Keren R, Luan X, Localio R, et al. Prioritization of comparative effectiveness research topics in hospital pediatrics. Arch Pediatr Adolesc Med 2012;166:1155-64.
16. Michelow IC, Olsen K, Lozano J, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 2004;113:701-7.
17. Guo X, Gao L, Liao Q, et al. Long non-coding RNAs function annotation: a global prediction method based on bi-colored networks. Nucleic acids research 2013;41:e35.
18. Vuori-Holopainen E, Peltola H. Reappraisal of lung tap: review of an old method for better etiologic diagnosis of childhood pneumonia. Clin Infect Dis 2001;32:715-26.
19. Mendoza-Paredes A, Bastos J, Leber M, Erickson E, Waseem M. Utility of blood culture in uncomplicated pneumonia in children. Clin Med Insights Pediatr 2013;7:1-5.
20. Toikka P, Irjala K, Juven T, et al. Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. Pediatr Infect Dis J 2000;19:598-602.
21. Paschke AA, Zaoutis T, Conway PH, Xie D, Keren R. Previous antimicrobial exposure is associated with drug-resistant urinary tract infections in children. Pediatrics 2010;125:664-72.
22. Blaschke AJ. Interpreting assays for the detection of Streptococcus pneumoniae. Clin Infect Dis 2011;52 Suppl 4:S331-7.
23. Serkova NJ, Standiford TJ, Stringer KA. The emerging field of quantitative blood metabolomics for biomarker discovery in critical illnesses. Am J Respir Crit Care Med 2011;184:647-55.
24. Serkova NJ, Brown MS. Quantitative analysis in magnetic resonance spectroscopy: from metabolic profiling to in vivo biomarkers. Bioanalysis 2012;4:321-41.

25. Slupsky CM, Rankin KN, Fu H, et al. Pneumococcal pneumonia: potential for diagnosis through a urinary metabolic profile. J Proteome Res 2009;8:5550-8.
26. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015;372:835-45.
27. Rudan I, O'Brien KL, Nair H, et al. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. Journal of global health 2013;3:10401.
28. Zhou F, Kyaw MH, Shefer A, Winston CA, Nuorti JP. Health care utilization for pneumonia in young children after routine pneumococcal conjugate vaccine use in the United States. Arch Pediatr Adolesc Med 2007;161:1162-8.
29. Florin TA, French B, Zorc JJ, Alpern ER, Shah SS. Variation in emergency department diagnostic testing and disposition outcomes in pneumonia. Pediatrics 2013;132:237-44.
30. Cruikshank DP, Dalton JB, Dalle Ore CM, et al. Surface composition of Hyperion. Nature 2007;448:54-6.
31. Schutzle H, Forster J, Superti-Furga A, Berner R. Is serum procalcitonin a reliable diagnostic marker in children with acute respiratory tract infections? A retrospective analysis. Eur J Pediatr 2009;168:1117-24.
32. Lynch T, Bialy L, Kellner JD, et al. A systematic review on the diagnosis of pediatric bacterial pneumonia: when gold is bronze. PLoS One 2010;5:e11989.
33. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53:e25-76.
34. Kronman MP, Hersh AL, Feng R, Huang YS, Lee GE, Shah SS. Ambulatory visit rates and antibiotic prescribing for children with pneumonia, 1994-2007. Pediatrics 2011;127:411-8.
35. Peng K, Xu W, Zheng J, et al. The Disease and Gene Annotations (DGA): an annotation resource for human disease. Nucleic acids research 2013;41:D553-60.
36. Beckonert O, Keun HC, Ebbels TM, et al. Metabolic profiling, metabolomic and metabonomic procedures for NMR spectroscopy of urine, plasma, serum and tissue extracts. Nature protocols 2007;2:2692-703.
37. Beckonert O, Keun HC, Ebbels TM, et al. Metabolic profiling, metabolomic and metabonomic procedures for NMR spectroscopy of urine, plasma, serum and tissue extracts. Nature protocols 2007;2:2692-703.
38. da Gloria Carvalho M, Pimenta FC, Jackson D, et al. Revisiting pneumococcal carriage by use of broth enrichment and PCR techniques for enhanced detection of carriage and serotypes. J Clin Microbiol 2010;48:1611-8.
39. Bernini P, Bertini I, Luchinat C, Nincheri P, Staderini S, Turano P. Standard operating procedures for pre-analytical handling of blood and urine for metabolomic studies and biobanks. J Biomol NMR 2011;49:231-43.
40. Slupsky CM, Rankin KN, Wagner J, et al. Investigations of the effects of [redacted] diurnal variation, and age in human urinary metabolomic profiles. Anal Chem 2007;79:6995-7004.
41. Slupsky CM, Cheypesh A, Chao DV, et al. Streptococcus pneumoniae and Staphylococcus aureus pneumonia induce distinct metabolic responses. J Proteome Res 2009;8:3029-36.
42. Wishart DS. Quantitative metabolomics using NMR. Trends Analyt Chem 2008;27:228-37.
43. Stringer KA, Serkova NJ, Karnovsky A, Guire K, Paine R, Standiford TJ. Metabolic consequences of sepsis-induced acute lung injury revealed by plasma (1)H-Nuclear magnetic Resonance quantitative metabolomics and computational analysis. Am J Physiol Lung Cell Mol Physiol 2011;2011:L4-L11.
44. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.
45. Kochhar S, Jacobs DM, Ramadan Z, Berruex F, Fuerholz A, Fay LB. Probing [redacted]-specific metabolism differences in humans by nuclear magnetic resonance-based metabonomics. Analytical biochemistry 2006;352:274-81.
46. Walsh MC, Brennan L, Malthouse JP, Roche HM, Gibney MJ. Effect of acute dietary standardization on the urinary, plasma, and salivary metabolomic profiles of healthy humans. Am J Clin Nutr 2006;84:531-9.
47. Assfalg M, Bertini I, Colangiuli D, et al. Evidence of different metabolic phenotypes in humans. Proceedings of the National Academy of Sciences of the United States of America 2008;105:1420-4.
48. Chiu CY, Yeh KW, Lin G, et al. Metabolomics Reveals Dynamic Metabolic Changes Associated with Age in Early Childhood. PLoS One 2016;11:e0149823.

49. Payne DC, Currier RL, Staat MA, et al. Epidemiologic Association Between FUT2 Secretor Status and Severe Rotavirus Gastroenteritis in Children in the United States. JAMA pediatrics 2015:1-6.
50. Centers for Disease Control and Prevention C. National Health and Nutrition Examination Survey Home Urine Collection. Atlanta: Centers for Disease Control and Prevention, CDC; 2013.
51. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38:963-74.
52. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. 2nd ed. Hoboken, N.J.: John Wiley & Sons; 2004.
53. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med 1991;10:585-98.
54. Basagana X, Barrera-Gomez J, Benet M, Anto JM, Garcia-Aymerich J. A framework for multiple imputation in cluster analysis. Am J Epidemiol 2013;177:718-25.
55. Laing R, Slater W, Coles C, et al. Community-acquired pneumonia in Christchurch and Waikato 1999-2000: microbiology and epidemiology. N Z Med J 2001;114:488-92.
56. Millar EV, Watt JP, Bronsdon MA, et al. Indirect effect of 7-valent pneumococcal conjugate vaccine on pneumococcal colonization among unvaccinated household members. Clin Infect Dis 2008;47:989-96.
57. Abdullahi O, Nyiro J, Lewa P, Slack M, Scott JA. The descriptive epidemiology of Streptococcus pneumoniae and Haemophilus influenzae nasopharyngeal carriage in children and adults in Kilifi district, Kenya. Pediatr Infect Dis J 2008;27:59-64.
58. Laiakis EC, Morris GA, Fornace AJ, Howie SR. Metabolomic analysis in severe childhood pneumonia in the Gambia, West Africa: findings from a pilot study. PLoS One 2010;5.
59. Galetto-Lacour A, Alcoba G, Posfay-Barbe KM, et al. Elevated inflammatory markers combined with positive pneumococcal urinary antigen are a good predictor of pneumococcal community-acquired pneumonia in children. Pediatr Infect Dis J 2013;32:1175-9.
60. Song JY, Eun BW, Nahm MH. Diagnosis of Pneumococcal Pneumonia: Current Pitfalls and the Way Forward. Infect Chemother 2013;45:351-66.
61. Carvalho Mda G, Tondella ML, McCaustland K, et al. Evaluation and improvement of real-time PCR assays targeting lytA, ply, and psaA genes for detection of pneumococcal DNA. J Clin Microbiol 2007;45:2460-6.
62. Butler JC, Bosshardt SC, Phelan M, et al. Classical and latent class analysis evaluation of sputum polymerase chain reaction and urine antigen testing for diagnosis of pneumococcal pneumonia in adults. J Infect Dis 2003;187:1416-23.
63. Michelow IC, Lozano J, Olsen K, et al. Diagnosis of Streptococcus pneumoniae lower respiratory infection in hospitalized children by culture, polymerase chain reaction, serological testing, and urinary antigen detection. Clin Infect Dis 2002;34:E1-11.
64. Stralin K, Tornqvist E, Kaltoft MS, Olcen P, Holmberg H. Etiologic diagnosis of adult bacterial pneumonia by culture and PCR applied to respiratory tract samples. J Clin Microbiol 2006;44:643-5.
65. Abdeldaim G, Herrmann B, Molling P, et al. Usefulness of real-time PCR for lytA, ply, and Spn9802 on plasma samples for the diagnosis of pneumococcal pneumonia. Clin Microbiol Infect 2010;16:1135-41.
66. Azzari C, Cortimiglia M, Moriondo M, et al. Pneumococcal DNA is not detectable in the blood of healthy carrier children by real-time PCR targeting the lytA gene. Journal of medical microbiology 2011;60:710-4.
67. Harris KA, Hartley JC. Development of broad-range 16S rDNA PCR for use in the routine diagnostic clinical microbiology service. Journal of medical microbiology 2003;52:685-91.
68. Harris KA, Turner P, Green EA, Hartley JC. Duplex real-time PCR assay for detection of Streptococcus pneumoniae in clinical samples and determination of penicillin susceptibility. J Clin Microbiol 2008;46:2751-8.
69. Gollomp K, Rankin SC, White C, et al. Broad-range bacterial polymerase chain reaction in the microbiologic diagnosis of complicated pneumonia. J Hosp Med 2012;7:8-13.
70. Ren S, Hinzman AA, Kang EL, Szczesniak RD, Lu LJ. Computational and statistical analysis of metabolomics data. Metabolomics 2015:1-22.
71. Benjamin Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Mulitple Testing. Journal of the Royal Statistical Society Series B (Methodological) 1994;57:289-300.
72. Bouatra S, Aziat F, Mandal R, et al. The human urine metabolome. PLoS One 2013;8:e73076.

73. Jokinen J, Scott JA. Estimating the proportion of pneumonia attributable to pneumococcus in Kenyan adults: latent class analysis. Epidemiology 2010;21:719-25.

74. Florin TA, Ambroggio L. Biomarkers for community-acquired pneumonia in the emergency department. Current infectious disease reports 2014;16:451.

75. Swann JR, Tuohy KM, Lindfors P, et al. Variation in antibiotic-induced microbial recolonization impacts on the host metabolic phenotypes of rats. J Proteome Res 2011;10:3590-603.

FACILITIES AND OTHER RESOURCES

The research infrastructure at Cincinnati Children's Hospital Medical Center (CCHMC) (Section 1) and at the University of Michigan (Section 2) including facilities, personnel, faculty, students, and equipment is among the best in the nation and provides the ideal environment for carrying out the proposed research.

Section 1: Cincinnati Children's Hospital Medical Center

Clinical and Research Resources: *Cincinnati Children's Hospital Medical Center* (CCHMC) is a not-for-profit hospital and research center pioneering breakthrough treatments, providing outstanding family-centered patient care and training healthcare professionals for the future. CCHMC was founded in 1883 and relocated in 1926 to its present site across the street from the *University of Cincinnati College of Medicine (UC)*. William Cooper Procter, a benefactor of the hospital, funded a building devoted to research in children's diseases that opened in 1931, and included a $2.7 million endowment, currently valued at $1.6 billion in 2012. He established that income from the endowment would support research and development, a principle that continues to form the core philosophical approach to the relationship of the endowment and research today. Today, CCHMC is a free-standing children's hospital with 629 beds and over 30,000 annual admissions that houses the *Department of Pediatrics* for UC. CCHMC is the primary provider of inpatient, subspecialty and emergency care in Greater Cincinnati and the surrounding counties serving over 2 million people. CCHMC has an extensive clinical and research community and is committed to promoting and expanding pediatric research and quality improvement. CCHMC has a long and rich history of research focused on diseases of children and young adults. Research breakthroughs have included the Sabin oral polio vaccine, rotavirus vaccine (Rotarix®), the first practical heart-lung machine, and the first successful bone marrow transplant for sickle cell disease. CCHMC again received Magnet status by the American Nurses Credentialing Center in 2014. In the U.S. News and World Report's 2014-2015 Best Children's Hospitals Honor Roll, CCHCM was ranked third among Departments of Pediatrics. CCHMC ranks second nationally among pediatric medical centers in NIH-funded research ($129 million in overall sponsored program awards in 2013-2014). Furthermore, toward our goal of discovery, institutional support for research in fiscal year 2012 totaled $84 million. CCHMC is the largest pediatric research institution in the nation, with nearly 1.5 million square feet of research space.

Cincinnati Children's Hospital Medical Center Research Foundation (CCRF) is the administrative and organizational entity for pediatric research missions. It includes all 41 divisions – six of which are basic research divisions – within the Department of Pediatrics. Total CCRF funding has doubled to over $450 million since 2003. Research administration and regulatory oversight groups oversee a total research budget of $275 million. National Institutes of Health funding of $129 million represents the second largest in the US among all Children's Hospitals or Pediatric Departments. Furthermore, the research endowment of ~$2 billion supports scientific training, infrastructure, and core services for basic research development and CCHMC. CCRF has 724 faculty members engaged in basic, clinical and translational research and is one of the largest pediatric research institutions in the country. They are committed to promoting the advancement of science and medicine as well as career advancement of young investigators while being a leader in improving pediatric quality of care and safety. In FY2015, the faculty collectively published more than 2,000 peer reviewed manuscripts. CCRF has dedicated research space encompassing almost 1.5 million square feet, making it the largest pediatric research institution in the nation.

The ***Division of Hospital Medicine***, directed by Dr. Ambroggio's primary mentor, Samir S. Shah, MD, MSCE, includes 45 academic faculty members, 7 fellows, and 15 support staff. The division includes 3 clinical services: Burnet Campus inpatient units (A6N and A6S, 24 beds each), Liberty Campus inpatient unit (12 beds), and the Hospital Medicine Surgical Service (A3N, 24 beds), the latter of which partners with the CCHMC surgical subspecialists to provide medical co-management for medically-complex patients who require surgical procedures. The division cares for more than 25,000 encounters each year; this patient volume represents one-fourth of all patients hospitalized at CCHMC. The Division of Hospital Medicine, in which Dr. Ambroggio has a primary appointment, cares for the majority of virtually all children hospitalized with community-acquired pneumonia. Dr. Ambroggio has access to a Clinical Research Manager, 6 Clinical Research Coordinators (CRCs), a Regulatory Coordinator, and a Grants Specialist. The six clinical research

coordinators will aid in sample collection from patients who consented to be included in the project when they originally presented in the Emergency Department. In 2015, division members published 122 peer-reviewed publications and received ~$1 million in grant support.

CCHMC received accreditation from the Association for the Accreditation of Human Research Protection Programs (AAHRPP) in 2007. The Office for Research Compliance and Regulatory Affairs (ORCRA) and the Office of Sponsored Programs offer a number of educational opportunities, including sessions addressing informed consent, writing clinical study protocols, grant budgetary management, and IRB issues. Furthermore, research in the Division of Hospital Medicine is further supported by having a dedicated institutional review board liaison ("research compliance specialist") who assists with efficiently developing and modifying protocols to facilitate research while maintaining strict protection of human subjects.

Computer/AV Equipment: Dr. Ambroggio has an HP desktop and laptop computer that with a secure connection to the CCHMC server allows her to transport work easily between CCHMC and University of Michigan as needed. The computers are equipped with standard word processing, bibliographic and data management software. Additionally, Dr. Ambroggio has the software needed for analysis and presentation of quantitative data (i.e. SAS version 9.3.2). Dr. Ambroggio has access to a photocopier, a fax machine, and a digital scanner that are available within the suite where her office is located. Dr. Ambroggio has sufficient space (50 gigabytes and more available if needed) on the CCHMC server, which is backed up nightly, to store all data collected for the grant. As part of Dr. Ambroggio's joint appointment with the Division of Biostatistics and Epidemiology, she will be able to run large datasets that require large amounts of memory by using a server based version of SAS stored on a HP ProLiant DL585 G2 system, containing four Opteron 8218 2.6 GHz dual core processors. The server offers 32 GB of RAM, and each user can initially obtain 500 GB of dedicated storage. In addition, there is 400 GB available for SAS temporary files. The operating system is SUSE Linux Enterprise Server 10.3 (x86_64). The server has redundant power supplies, is located in a secure data center and is backed up daily.

Office: The Division of Hospital Medicine is housed in a contemporary office space on the 5th and 6th floor of the Old Research Building on the CCHMC main campus. This 10,200 square foot office space includes 31 private offices, 3 conference rooms, 2 huddle offices, and 37 work stations for administrative support and research staff. This space also includes a fax machine, copier, and several laser printers, including a high-quality color laser printer. Within that space, Dr. Ambroggio has her own office, located directly across the hall from the office of her primary mentor, Dr. Samir Shah. Her co-mentor, Dr. Maurizio Macaluso, is located in an adjacent building. Her office can be locked and has multiple locking file cabinets, as well as shelving, to store both research-related materials and references. Dr. Ambroggio has access to an administrative assistant with a desk outside her office, and clinical research coordinators in the same suite. All of Dr. Ambroggio's local mentors and advisors have their individual offices in either the same building as her office or in a building nearby.

The ***Division of Emergency Medicine***, directed by Dr. Stephen Porter and until June 2015, Dr. Ambroggio's advisory committee member, Richard Ruddy, MD, is responsible for managing two large emergency departments (ED) and four urgent care facilities together with annual visits of over 163,000 pediatric and adolescent patients with 42 faculty. This research will take place in the primary emergency department (Avondale) which is a Level 1 Trauma Center that had over 92,000 visits in 2014. Faculty research aims to improve healthcare delivery among the ED population, with research interests including infectious diseases, traumatic brain injury/concussion, asthma, resuscitation/airway management, patient-family experience of care, simulation, and mental health. Divisional faculty received >$1.67 million in direct annual grant support in 2014.

The Division has a sophisticated infrastructure of research personnel who assist emergency medicine investigators and collaborators with all aspects of their research. The *Research Team* consists of a Clinical Research Manager, a Clinical Research Supervisor, a Financial Analysist and ten Clinical Research Coordinators (CRCs), a Regulatory Coordinator, a Quality Assurance Specialist, and a Grants Specialist. The Research Manager assists with formulating and maintaining research budgets, initial study design and

determining the feasibility of the study. The Grant Specialist aids with the development of grants as well as post-grant management. The Regulatory Coordinator ensures that the study follows all internal IRB requirements, federal, state and internal regulations. The CRCs work directly with the investigators to develop a manual of operations for each study, enroll patients, and maintain documentation and research forms in compliance with Federal HIPAA and human subjects' regulations. Research enrollment will occur in the Emergency Department, which sees >1100 cases of community-acquired pneumonia annually, by the ED CRCs, who will then coordinate subsequent sample collection with the CRCs in the Division of Hospital Medicine.

The ***Pediatric Emergency Care Applied Research Network (PECARN)*** is the first federally funded pediatric emergency medicine research network in the United States and consists of 18 pediatric emergency departments (www.pecarn.org). PECARN consists of six research nodal centers. Dr. Ruddy, the Emergency Medicine Division Director at CCHMC is the nodal principal investigator of the Hospitals of the Midwest Emergency Research Node (HOMERUN) of PECARN. PECARN works to conduct high-priority, multi-institutional research on the prevention and management of acute illnesses and injuries in children and adolescents and could also be a home for multi-center pneumonia projects.

The ***Division of Biostatistics and Epidemiology (DBE****),* where Dr. Ambroggio holds a joint faculty appointment and is directed by Maurizio Macaluso, DrPH, MD, offers a depth and expertise across a broad range of biostatistical and epidemiologic methods. This breadth of expertise allows all faculty and staff within the division easy access to peer consultation and technical review. The DBE conducts both independent and collaborative research and has a total of 21 primary, 14 jointly-appointed faculty members, 58 professional staff members and 5 support staff members. In FY 2016, DBE faculty received $11.69M in grant funding support and had a total of 138 peer-reviewed publications. DBE also enjoys strong ties to the University of Cincinnati (Department of Mathematics, and Department of Environmental Health, Division of Epidemiology and Biostatistics). The Division includes a ***Data Management Center (DMC)*** that supported 90 studies in 2015 by assisting with grant application and protocol review, budgeting and resourcing for data management, case report form design, database development, data entry and documentation, discrepancy management, data cleaning and preparation for analysis. Dr. Ambroggio's data manager, Judd Jacobs, and data programmer, Jessi Poteet, are members of the DMC and take primary responsibility for managing the master study database used in parent study CARPE DIEM. Mr. Jacobs and Ms. Poteet merge all clinical, specimen and laboratory data into one large database for CARPE DIEM, which can then be used for final analysis. The DMC also maintains the REDCap database containing all clinical data from CARPE DIEM and performs quality checks throughout the study to ensure proper data entry from all systems, including data entered by the clinical research coordinators, biomedical informatics, Biomaterial Tracking and Management software, and the clinical laboratory. These data checks are extremely important in maintaining the highest quality of data and staying in compliance with our regulatory policies.

The CCHMC ***Division of Biomedical Informatics (BMI)*** supports researchers with resources such as data storage systems, database servers, collaboration tools, and an inventory of research software applications. They provide consultations to support these applications and to help determine the best option to meet a researcher's data management and storage needs. BMI extracts and maintains clinical data from our electronic medical records into our secure REDCap database as part of the parent study, CARPE DIEM.

Laboratory: The ***Clinical Laboratory*** at CCHMC is part of the Division of Pathology and Laboratory Medicine, and directed by Paul Steele, MD. This laboratory is the main clinical laboratory for CCHMC and consists of 5 core clinical laboratories: phlebotomy/processing, chemistry, hematology, coagulation and microbiology. The laboratory has extensive experience performing a host of clinical testing for patients at CCHMC, in addition to collaborating with researchers. The laboratory is CLIA-certified and College of American Pathologists-accredited. Standard operating procedures are in place to ensure reliable and reproducible test results. The Clinical Laboratories perform conventional biomarker testing for the parent study *Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine (CARPE DIEM)*, including complete blood counts with differential, C-reactive protein and blood cultures.

The ***Laboratory for Specialized Clinical Studies (LSCS),*** directed by Monica Malone McNeal and housed within the CCHMC Division of Infectious Diseases, has a 20-year history of providing support for clinical and vaccine trials. The LSCS provides testing capabilities targeted to support clinical research. The laboratory specializes in the development and validation of customized assays and includes integration of customized statistical software. The laboratory employs experienced staff trained to conduct numerous specialized bio-analytical procedures. The 7000 square foot laboratory is CAP- and CLIA-accredited. All assays are conducted following GLP guidelines. Extensive documentation is maintained in compliance with GLP and all testing is fully auditable. A laboratory quality assurance officer and an independent regulatory affairs department support laboratory services. Laboratory space and equipment includes two separate tissue culture areas, a walk-in freezer, a walk-in warm room, extensive ultracold freezer storage, automated liquid nitrogen storage, biosafety cabinets and incubators, fume hoods, sterilizers, and glassware prep area. A state-of-the-art Rees Centron system monitors all controlled temperature units 24/7 and alerts personnel in case of equipment or power failure. The laboratory is approved for Biosafety Level 2 (BL2) containment. Laboratory personal have specific training for blood, urine, and nasopharyngeal samples. Access to the laboratory is limited when work is being conducted. Laboratory personal have personal protective equipment (PPE) for handling chemicals, human samples and Class II pathogens according to the Safety Guidelines in Policy #108 of the CCHMC Environment of Care Manual. Technicians must adhere to the practice of Standard Precautions as stated in Infection Control and Prevention Program Policy IC-1.2. The LSCS will perform quantitative real-time polymerase chain reaction (PCR) that is used to measure the pneumococcal bacterial load, respiratory viral polymerase chain reaction (PCR) and *M. pneumoniae* PCR

The ***Cincinnati Biobank Core Facility (CBCF)*** occupies space in the research building dedicated to processing and storing samples (e.g., tissues, DNA, serum, plasma). The Biobank is the site of all specimen storage for the biorepository developed for CARPE DIEM, and leveraged in this K01 proposal. The Biobank Facility has 1,000 square feet within its on-site facility at CCHMC, with five workstations and multiple freezer units. The Biobank Facility also has an off-site facility located approximately 10 miles away from campus that has four workstations and 42 freezer units. The Biobank Facility has ten full-time employees, including a PhD-level director, three regulatory research assistants, five laboratory research assistants and a database manager. An AutoGenFlex STAR automated DNA extraction instrument (DNA from up to 5 mL of whole blood, saliva, or tissue), a Promega Maxwell 16 (DNA or RNA from up to 350 ul of whole blood, saliva, or PAXgene tubes), a Fluidigm EP1 HX (tests 96 SNPs on 96 samples using microfluidics) and a Trinean DropSense 96 multichannel spectrophotometer are available. Three -80°C and two -20°C upright freezers, a 4°C refrigerator, a custom portable freezer pan (-20°C cold table), a Hereaus Megafuge 16R centrifuge, and desk space with networked computer work stations for 5 technicians are available. Additional -80°C freezers, a liquid nitrogen freezer, and -20°C freezer are available 2 floors above in the main Department of Pathology space. A monitored alarm system and emergency generators are maintained by CCHMC for all freezers. Each freezer operates on a unique circuit, and all equipment is included on the facility's emergency generator system. The CBCF uses specimen tracking software, Biomaterial Tracking and Management, to electronically record the location and availability of every aliquot of every specimen collected from each patient. Dr. Ambroggio has access to this software and is able to easily track the specimens and their individual aliquots collected as part of this proposal.

NMR-based Metabolomics Core Facility*:* The NMR-based Metabolomics Core (NBMC) provides state-of-the-art technology in a centralized location accessible to research investigators and clinicians, serving CCHMC and UC COM communities. The NMR-based Metabolomics Core facilitates broad spectrum and targeted metabolomics analysis of polar components, as well as methods for targeted analysis of metabolites, with experience in the analysis of cells, organ tissue (e.g. liver, muscle, intestines, tongue, and tumor), biological fluids (e.g. urine, serum, plasma, amniotic fluid and saliva), and exhaled breath collected from human subjects or animal models. The NBMC Facility measures concentrations of small molecules in biological samples. We use Bruker Biospin licensed TopSpin and Amix softwares in conjunction with Chenomx NMR Suite for analysis of unbiased metabolomics data. In short, proton (^{1}H) NMR spectra of all study groups are compared and analyzed using automated methodologies employing both univariate and multivariate statistical tools such as analysis of variance (ANOVA), significant difference spectra (SDS), principal component analysis (PCA) and partial least squares (PLS)(1). Processed ^{1}H NMR spectra will be binned to small regions (0.01-0.005ppm) and

analyzed using AMIX (Bruker Biospin, Inc., Billerica, MA), for PCA analysis. The binned data prepared during the PCA analysis will also be analyzed using a univariate approach, based on bin-by-bin differences between groups of spectra from different sites. In order to identify the NMR peaks that are significantly different between the study populations, ^{1}H significant difference spectra (SDS) will be generated using the same peak intensities in each bin. To avoid significant false discovery rates, the Student's t-test between groups was subjected to False Discovery Rate (FDR) control at the 0.05 level.

The NBMC facility, located within the Division of Pathology at CCHMC, utilizes a Bruker IVDr 600MHz NMR system that is fully-automated, designed specifically for metabolomics based studies of biological fluids, housed in the Medical Science Building (MSB) at University of Cincinnati College of Medicine (UC COM). The primary spectrometer utilized by the NBMC provides a high field multi-nuclear NMR capability to CCHMC, UCCOM and external academic and industry collaborators. The Bruker IVDr, a top-of-the-line spectrometer, is capable of running most contemporary homonuclear, heteronuclear one and two-dimensional pulse sequences, using pre-designed software, and is equipped with a 96-well SampleJet auto-sampler unit that renders the NMR system fully-automated. The Bruker spectrometer is equipped with a 5mm triple resonance conventional probe, which allows for routine acquisition of 1D and 2D ^{1}H-^{1}H correlations as well as 1D ^{13}C and 2D ^{1}H-^{13}C correlations used to confirm small metabolite identities. If higher field spectra are required, CCHMC researchers have access to a state-of-the-art Varian 800MHz NMR instrument also located with the UC COM NMR Facility. The usual array of peripheral analytical equipment is available including an electronic balance, pH meters, distillation equipment, bench-top centrifuges, rotary evaporators, a dual SpeedVac concentrator and lyophilizer system, and a cryogenic homogenizer. Dr. Ambroggio has access and permission from the director, Dr. Rosendale-Romick, to use the dedicated space and equipment for her experiments under the supervision of the director.

The NBMC operates under Biosafety Level 2 (BL2) regulations and follows all NIH guidelines for ensuring the use of proper microbiological practices and laboratory techniques. Laboratory personal have specific training for blood, urine, and nasopharyngeal samples. Access to the laboratory is limited when work is being conducted. All residual specimen and specimen containers are disposed of in the appropriate biohazard container within the lab. All samples are transported to the core lab in biohazard bags to minimize risk of exposure. All samples that are not being immediately analyzed are stored in our 80 freezer located inside our locked core lab space. All lab staff are outfitted in proper lab attire including lab coats and appropriate personal protective equipment (PPE) at all times.

Ziady LC/MS^{2} Laboratory: Dr. Ziady's laboratory occupies approximately 800 sq. ft. with an additional 144 sq. ft. room, which houses a Tandem Liquid Chromatography-Mass Spectrometer. The imaging and analysis systems are located primarily within the R building, occupying 1,500 square feet (in the same building containing the CF research laboratories of Drs. Ziady and also Dr. Ambroggio's office). Access to the imaging suite is controlled by keycard and user login and will be accessible to Dr. Ambroggio during her training period in the 4th year of the award. Dr. Ziady's laboratory operates under Biosafety Level 2 (BL2) regulations and follows all NIH guidelines for ensuring the use of proper microbiological practices and laboratory techniques

Animal: n/a

Other*:*
Center for Clinical and Translational Research (CCTST): Research across UC and the Academic Health Center (AHC) is supported by the Center for Clinical and Translational Science and Training (CCTST), funded in part by our Institutional Clinical and Translational Science Award (CTSA). Access to the CCTST is available to every investigator via Research Central, a physical and virtual portal staffed by research methods experts. The CCTST coordinates a wide range of services, including biostatistics, biomedical informatics, data management, training grant application assistance, inpatient and outpatient clinical research services for both adult and child studies, support for community engagement activities, and regulatory knowledge (the AHC's regulatory and management infrastructure includes 4 Institutional Review Boards, 2 Institutional Animal Care and Use Committees, 2 Institutional Biosafety Committees, 2 Radiation Safety Committees, and 2 clinical trials offices). The CCTST also coordinates a number of institutional programs, including pilot grant programs, the MS in Clinical and Translational Research and Certificate in Clinical and Translational Research training

programs, the KL2 and 2 K12 programs, and novel technologies and affiliated cores. Additional details are available at http://cctst.uc.edu.

Faculty Development: CCHMC has an *Office for Faculty Development* led by Dr. Jessica Kahn, who also serves as the Assistant Chair of Academic Affairs and Faculty Development. This office sponsors numerous seminars on topics such as developing effective collaborations, setting career goals, scientific writing, and negotiation strategies. All of the Faculty Development seminars are recorded and archived to increase accessibility to this important resource. An organized peer group (the "K club") of CCHMC and UC faculty who are applying for or have received NIH career development awards meet twice a month. This group provides mentorship, as well as career development and networking opportunities, with the primary goal of ensuring successful completion of K awards and transition to R01 funding.

Library resources: The CCHMC *Pratt Library* is located in a connected building adjacent to Dr. Ambroggio's office and is a primary resource for both books and journals, including >350 print journal subscriptions and nearly 400 additional journal titles available via electronic access. The library employs three full-time librarians to assist with literature searches and locating needed electronic and print media resources. Also, the *Health Sciences Library of the University of Cincinnati College of Medicine* is located across the street from the CCHMC main campus and offers online access to more than 4000 journals. Both libraries offer training and educational opportunities as well as assistance with literature searches and locating references.

Environment: Contribution to Success*:* The scientific environments at CCHMC and UC provide an ideal setting for Dr. Ambroggio to establish herself as an expert in pediatric infectious diseases and, with the support of a career development award, achieve research independence. The resources of CCHMC and the CCTST, combined with experienced mentors and a large patient population, ensure the success of the proposed research and career development. Specifically, the proposed research and career development plan utilize the intellectual resources available through CCHMC, including research support from the CCTST and relevant CCHMC offices. Additionally, the Divisions of Hospital Medicine, Biostatistics and Epidemiology and Emergency Medicine have an extensive track record of successful collaboration and the large patient populations necessary for the successful completion of this proposal. Additionally, as an institution, CCHMC is committed to institutional support of early investigators through internal grants, administrative support, and structured opportunities for faculty networking and education.

Section 2: University of Michigan

I have an established collaboration with the state-of-the-art facilities at the University of Michigan, College of Pharmacy (CoP) and the Biochemical Nuclear Magnetic Resonance (NMR) core, and as necessary, the Michigan Regional Comprehensive Metabolomics Research Core (MRC) to successfully accomplish our proposed aims.

Stringer Laboratory: Dr. Kathleen Stringer, external metabolomics mentor on this proposal, has a fully equipped laboratory (~500 sq. ft) on the 3rd floor of the College of Pharmacy (CoP) building on the central University of Michigan (Ann Arbor) campus. Her lab is fully equipped to process urine samples and conduct the proposed metabolomics experiments. In addition, her lab houses lyophilizers and speedvac for serum/plasma/blood sample extractions that are necessary for conducting metabolomics assays in these biofluids. Her laboratory is also equipped with a fume hood, refrigerators, and -20°C and -80°C freezers. Dr. Stringer's laboratory is approximately ¼ mile from the $(MRC)^2$ in Brehm Tower which can be easily reached on foot or by utilizing the University of Michigan's bus system. The Stringer Laboratory provided analysis for the samples used for pilot data for this proposal and will do so for the samples generated by this study.

Computers and Software: Dr. Stringer and her laboratory personnel including Dr. Larisa Yeomans and Ms. Cora McHugh, have their own personal computers for secure data entry and analysis. All computers are internet and email capable and are equipped with the necessary software for word processing, data entry and statistical analysis. In addition, a computer in Dr. Stringer's laboratory is equipped with Chenomx software

(chenomx.com) that will be used to identify and quantify metabolites from the NMR spectra generated under the two proposed aims.

Biochemical Nuclear Magnetic Resonance (NMR) Core (CoP): The acquisition of NMR spectra for untargeted metabolomics will be conducted in the CoP's Biochemical NMR core laboratory. The CoP facility houses a state-of-the-art Varian 500 NMR spectrometer which has pulsed field gradients, auto tune, auto shim, a 3mm ONE probe and a twelve slot sample changer robot. It is a "research grade" instrument capable of performing all of the solution NMR techniques commonly reported in the literature. It is computer operated via the VNMRJ 3.2 software package. Commonly performed experiments include simple spectra, T1 and T2 relaxation experiments, solvent suppression, selective decoupling and nOe experiments, as well as one (1D) and two-dimensional (2D) COSY, NOESY, HSQC and HMBC. In addition to the needed NMR equipment, the core also houses several computers equipped with spectral analysis software including Chenomx NMR suite 7.6 (chenomx.com).

Michigan Regional Comprehensive Metabolomics Research Core ($(MRC)^2$), Ann Arbor, MI (http://mrc2.umich.edu/): The $(MRC)^2$ is a fully integrated program that provides researchers nation-wide with the expertise and infrastructure to determine the levels of known and unknown metabolites in cells, tissues and biological fluids. In addition, the $(MRC)^2$ provides opportunities for training in the technology of metabolomic analysis, statistical analysis and bioinformatic evaluation of metabolite data as well as approaches to incorporation of metabolomics into basic, preclinical, translational and clinical research.

The $(MRC)^2$ is one of six NIH-funded regional metabolomics facilities (http://www.metabolomicsworkbench.org) that also supplies expertise and method development for both untargeted and targeted metabolomic analysis. The untargeted analysis platform uses high mass resolution and accuracy LC/MS-TOF and GC/MS to assess the relative levels of nearly >5000 molecular features (metabolites) which are reproducibly found in plasma, other biological fluids, and tissues. Assigning the molecular structural identity of specific features is aided by a library of over 1,000 authentic chemical compounds. A network of statisticians (e.g., Dr. George Michailidis) and bioinformatics faculty (e.g., Dr. Alla Karnovsky) and staff can help with interpretation of large untargeted datasets containing many observations. Directed assays are performed using traditional multiple reaction monitoring (MRM) methods, including internal standards, typically resulting in COV values of 15%-20% for analytes such as amino acids, acyl-carnitines, glycolytic and TCA cycle intermediates, steroids, and other biochemical compound classes as outlined on the website (http://www.med.umich.edu/mmoc/cores/molecular.html).

For metabolomics assays conducted in $(MRC)^2$, all solvents are similarly purchased in bulk from a single manufacturer's lot in sufficient quantity to complete planned experiments. All samples are bar-coded by the $(MRC)^2$ laboratory information management system (LIMS) and all chromatographic runs are LIMS-scheduled tasks. Raw data files are tracked and processed by their LIMS identifiers and archived to a DVD at regular intervals. The $(MRC)^2$ uses the LIMS system which is specifically designed to store the results of the LC/MS experiments. It provides a web-based user-friendly interface that provides secure access to the data. $(MRC)^2$ has developed an infrastructure to support data processing and analysis.

The $(MRC)^2$ comprises 2200 ft^2 of laboratory space in Brehm Tower and has the full range of expertise to successfully complete sample measurements and analyses, currently processing ~800 samples per month. The Core is well equipped with standard laboratory equipment and includes the following suite of mass spectrometers:

1) Two Agilent 6890 gas chromatograph (GC) equipped with HP5973 mass detector GC/MS system with electron impact ionization (EI) and GC/ECNI/MS and positive/negative ion capabilities. The instruments are equipped with an autosampler and an on-column injector. The GC/MS systems will be used to measure derivatized amino acids, low molecular polar and non-polar metabolites, nucleic acids and lipid metabolites. In addition, this versatile instrument is capable of analysis of complex lipoproteins, glycolipids, sphingolipids and other small molecule analytes quantitatively.

2) Two Agilent Triple Quadrupole mass spectrometers (6410 and 6490) coupled with Agilent 1290 UHPLC. These instruments offer exceptional sensitivity for directed metabolomics in the MRM mode for lipids, amino acids and products of intermediary metabolism. They have the ability to perform both ESI and atmospheric pressure chemical Ionization (APCI) and can be utilized both for directed and undirected metabolomic analysis.

3) An Agilent LC/MSD Time of flight mass spectrometer. This instrument has high mass accuracy and is ideal for directed and undirected metabolomic profiling of small molecules for accurate mass determination. It can also be utilized to perform both ESI and APCI.

4) Three Quadrupole TOF instrument (Q-TOF) instruments coupled Agilent Rapid Resolution HPLC or UPLC which provide high sensitivity, high mass accuracy, high mass range, and rapid throughput ideal for metabolomic profiling. This instrument has high mass accuracy and capability to perform tandem MS analysis making it ideal for both directed and undirected metabolomic studies. This can provide extremely valuable structural information and may simplify, for example, in determining complex metabolite structures. Additionally, these instruments can be utilized for untargeted metabolomics.

5) The Core also has an Agilent 6890 GC and a Jasco HPLC system equipped with variable UV detector, fluorescence detector, electrochemical detector and diode array detector. Both instruments have an autosampler. These instruments are capable of analyzing a wide variety of small molecules, preparing internal standards for GC/MS and LC/MS analysis and purifying the samples prior to injection into the mass spectrometer.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | First Name*: Lilliam | Middle Name | Last Name*: Ambroggio | Suffix:

Position/Title*: ASSISTANT PROFESSOR
Organization Name*: Cincinnati Childrens Hospital Medical Center
Department: Pediatrics
Division: Hospital Medicine
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*:
Zip / Postal Code*:

Phone Number*: [redacted] | Fax Number: | E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI | Other Project Role Category:

Degree Type: MPH, PHD | Degree Year: 2008, 2011

	File Name
Attach Biographical Sketch*:	Ambroggio_NIH_Biosketch_2016_06_27.pdf
Attach Current & Pending Support:	

Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

PROFILE - Senior/Key Person

Prefix: First Name*: Samir Middle Name Last Name*: Shah Suffix:

Position/Title*: Professor of Pediatrics
Organization Name*: Cincinnati Children's Hospital Medical Center
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Other Professional Other Project Role Category: Mentor

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	Shah_NIH_Biosketch_6_30_16.pdf
Attach Current & Pending Support:	SamirShah_Other_Support.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Maurizio Middle Name Last Name*: Macaluso Suffix:

Position/Title*: Professor and Director
Organization Name*: Cincinnati Children's Hospital Medical Center
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Other Professional Other Project Role Category: Co-Mentor

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	Macaluso_NIH_Biosketch_5_12_2016.pdf
Attach Current & Pending Support:	Other_Support_Macaluso_5_26_16.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Richard Middle Name Last Name*: Ruddy Suffix:

Position/Title*: Professor of Pediatrics
Organization Name*: Cincinnati Children's Hospital Medical Center
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*:
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Other Professional Other Project Role Category: Co-Mentor

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	Ruddy_NIH_Biosketch_5_28_2016_Reviewed.pdf
Attach Current & Pending Support:	Ruddy_Other_Support_6_20_2016.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Kathleen Middle Name Last Name*: Stringer Suffix:

Position/Title*: Professor
Organization Name*: University of Michigan
Department:
Division:
Street1*: [redacted]
Street2:
City*:
County:
State*:
Province:
Country*:
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Other Professional Other Project Role Category: Co-Mentor

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	Stringer_NIH_Biosketch_5_12_2016_Reviewed.pdf
Attach Current & Pending Support:	Stringer_OtherSupport_Jun2016_FINAL.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Heidi Middle Name Last Name*: Sucharew Suffix:

Position/Title*: Assistant Professor
Organization Name*: Cincinnati Children's Hospital Medical Center
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Other Professional Other Project Role Category: Co-Mentor

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	Sucharew_biosketch_05_23_16_Reviewed.pdf
Attach Current & Pending Support:	Other_Support_Heidi_6_17_16.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Lindsey Middle Name Last Name*: Romick-Rosendale Suffix:

Position/Title*: Assistant Professor
Organization Name*: Cincinnati Children's Hospital Medical Center
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Other (Specify) Other Project Role Category: Collaborator

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	Romick_Rosendale_NIH_Biosketch_5_12_2016_Revie.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: First Name*: Assem Middle Name Last Name*: Ziady Suffix:

Position/Title*: Associate Professor
Organization Name*: Cincinnati Children's Hospital Medical Center
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Other (Specify) Other Project Role Category: Collaborator

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	Ziady_NIH_biosketch_5_12_2016_Reviewed.pdf
Attach Current & Pending Support:	

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Ambroggio, Lilliam

eRA COMMONS USER NAME (agency login): [redacted]

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Washington	BS	06/2003	Molecular and Cellular Biology
Drexel University	MPH	06/2008	Epidemiology
Drexel University	PHD	06/2011	Epidemiology
Cincinnati Children's Hospital	Fellow	08/2011	Post-Doctoral Fellowship in Clinical Research

A. PERSONAL STATEMENT

My long-term research goal is to improve outcomes for children with common, serious infections by developing methods to improve diagnostic accuracy and implementing these methods into clinical practice. The objective of the proposed research is to combine advanced statistical and NMR metabolomics methodologies to inform pathogen-detection in childhood pneumonia. This research proposes the use of novel methods to identify pathogens causing CAP in an ambulatory and inpatient population of children with different levels of disease severity. My previous work has focused on antibiotic resistance, empiric antibiotic choice, and imaging modality in managing CAP in children. I am uniquely positioned to accomplish the aims stated in this proposal as I have a strong foundation in molecular and cellular biology and epidemiological methodology and have outlined a strong training plan to gain expertise in NMR metabolomics and advanced statistical methodology. In addition, the CARPE DIEM study infrastructure including recruitment and sample collection for children with CAP that is being leveraged as part of this proposal is fully funded by the Gerber Foundation and the Ohio Governor's Fund. I am currently a full-time Assistant Professor in the Divisions of Hospital Medicine and Biostatistics and Epidemiology. I plan to continue to conduct research in infectious diseases in children, focusing on developing and improving diagnostic tools for children diagnosed with common infectious diseases, such as pneumonia, globally. A K01 award would provide me with the resources to conduct novel research in the area of etiology identification for pediatric pneumonia.

B. Research and/or Professional Experience:

Positions and Employment

2003 - 2006 Research Technician, Division of Clinical Research and Human Biology, Clurman Laboratory, Fred Hutchinson Cancer Research Center, Seattle, WA

2006 - 2007 Practicum, Project Dulce, Esperanza Health Center, Philadelphia, PA

2007 - 2007 Research Intern, Latino Adolescent Sexual Health Preference Study, Concern for Health Options: Information, Care and Education, Philadelphia, PR

2007 - 2008 Research Intern, Public Health Governance in Ethiopia, International Clinical Epidemiology Network Inc., Philadelphia, PA

2007 - 2011 Teaching Assistant, Department of Epidemiology and Biostatistics, Drexel University, Philadelphia, PA

2011 - 2013 Research Fellow, Division of General & Community Pediatrics Research, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH

2013 - Assistant Professor, Assistant Professor, Divisions of Hospital Medicine and Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine , Cincinnati, OH

Other Experience and Professional Memberships

2006 - 2010 Member, American Public Health Association
2009 - Member, Society of Epidemiologic Research
2011 - Member, Academic Pediatric Association
2011 - Member, Infectious Diseases Society of America
2012 - Member, American College of Epidemiology
2013 - Member, European Society of Pediatric Infectious Diseases

Honors

2008 Member, Hygeia Academic Honor Society, School of Public Health, Drexel University
2008 Excellence in Communication Award, School of Public Health, Drexel University
2011 Graduate Student Travel Award, College of Graduate Studies, Drexel University
2012 Infectious Disease Week Conference Trainee Travel Award, Infectious Disease Society of America
2012 Principal Investigator, Early Career Award, Thrasher Research Fund
2012 Outstanding Promise Doctoral Award in Physical and Life Sciences, Drexel University
2013 Principal Investigator, Trustee Award, Cincinnati Children's Hospital Medical Center
2013 Principal Investigator, Young Investigator Award, Academic Pediatric Association
2013 #10 on "The Drexel 40 Under 40", Drexel Magazine, Drexel University
2014 Academic-Community Research Partnership Award for the project "Reduced Variability in the Management of CAP", Center for Clinical and Translational Science and Training, University of Cincinnati
2014 Award for Excellence in Teamwork in Quality Improvement, Series of projects entitled "Improving adherence to evidence-based recommendations for common serious childhood infections", Team Leader on Appropriate Antibiotic Prescribing for Childhood Community-Acquired Pneumonia, Society of Hospital Medicine

C. Contributions to Science

1. **Pediatric Pneumonia Diagnosis and Management.** Healthcare utilization and clinical management among children who are hospitalized with common infectious diseases has been shown to vary across institutions. The following publications demonstrate clinical outcomes associated with these variations and my methodological expertise in conducting healthcare service research including comparative effectiveness studies and in using administrative databases such as the "Pediatric Health Information System" (PHIS) in studying these questions. In the first study a high-risk subgroup of HSV-infected infants, those with cardiac congenital anomalies, warranted additional clinical interventions to improve outcomes. We determined the comparative effectiveness of β- lactam monotherapy and β-lactam and macrolide combination therapy on clinical outcomes in the treatment of children hospitalized with community-acquired pneumonia (CAP). The findings from this study suggested macrolide antibiotics do not have a role in the treatment of young children with CAP. In contrast, older children hospitalized with CAP may benefit from use of macrolide antibiotics, likely due to the effect of macrolides on atypical bacteria such as Mycoplasma pneumoniae. In addition, we wanted to determine the influence of hospital-level penicillin non-susceptible Streptococcus pneumoniae patterns on individual-level antibiotic prescription. This cross-sectional study used a multi-level analysis combining hospital-level microbiologic data obtained by survey with patient-level billing data. Hospitals reporting higher levels of penicillin-resistance among pneumococcal bacteria disproportionately prescribed broad-spectrum antibiotics. This study lends support to the hypothesis that physician prescribing habits can be meaningfully altered by strategies that focus on microbiologic reporting rather than direct physician education.

a. Ambroggio L, Lorch SA, Mohamad Z, Mossey J, Shah SS. Congenital anomalies and resource utilization in neonates infected with herpes simplex virus. Sex Transm Dis. 2009 Nov;36(11):680-5. PubMed PMID: 19617865; PubMed Central PMCID: PMC2783783.

b. Ambroggio L, Tabb LP, O'Meara T, Sheffler-Collins S, McGowan KL, et al. Influence of antibiotic susceptibility patterns on empiric antibiotic prescribing for children hospitalized with community-acquired pneumonia. Pediatr Infect Dis J. 2012 Apr;31(4):331-6. PubMed PMID: 22228236.

c. Ambroggio L, Taylor JA, Tabb LP, Newschaffer CJ, Evans AA, et al. Comparative effectiveness of empiric β-lactam monotherapy and β-lactam-macrolide combination therapy in children hospitalized with community-acquired pneumonia. J Pediatr. 2012 Dec;161(6):1097-103. PubMed PMID: 22901738.

d. Ambroggio L, Test M, Metlay JP, Graff TR, Blosky MA, et al. Adjunct Systemic Corticosteroid Therapy in Children with Community-Acquired Pneumonia in the Outpatient Setting. Journal of the Pediatric Infectious Diseases Society. 2014 March 27; 4(1):21-27.

2. **Implementation and Standardization of Care for Pediatric Pneumonia.** The Institute of Medicine reported that it can take almost 14 years to incorporate evidence into practice. Quality improvement science has been used to implement processes at a systems level rather than relying on individuals. Therefore we used quality improvement methods to implement the PIDS/IDSA childhood pneumonia guideline at our institution. We first implemented the antibiotic recommendations, supportive of narrow-spectrum antibiotics as first-line therapy, in our emergency department and inpatient service. We increased guideline-recommended prescribing from <40% to 100% over a 6 month period. In addition we found that there were no negative consequences of increasing narrow spectrum antibiotic prescribing. We also performed another QI study to increase the number of blood cultures ordered for children hospitalized with pneumonia. Similarly we found no negative consequences related to this increase.

   a. Ambroggio L, Thomson J, Murtagh Kurowski E, Courter J, Statile A, et al. Quality improvement methods increase appropriate antibiotic prescribing for childhood pneumonia. Pediatrics. 2013 May;131(5):e1623-31. PubMed PMID: 23589819; PubMed Central PMCID: PMC3639461.

   b. Thomson J, Ambroggio L, Murtagh Kurowski E, Statile A, Graham C, et al. Hospital outcomes associated with guideline-recommended antibiotic therapy for pediatric pneumonia. J Hosp Med. 2015 Jan;10(1):13-8. PubMed PMID: 25263758; PubMed Central PMCID: PMC4322863.

   c. Murtagh Kurowski E, Shah SS, Thomson J, Statile A, Sheehan B, et al. Improvement Methodology Increases Guideline Recommended Blood Cultures in Children With Pneumonia. Pediatrics . 2015 March 16;

3. **Methodological Content Expertise.** The following reviews and commentaries demonstrate specific areas of content and methodological interest.

   a. [redacted]

   b. Ambroggio LV, Shah SS. Administrative data: expanding the infrastructure for pediatric research. J Pediatr. 2013 Apr;162(4):681-4. PubMed PMID: 23196133.

   c. Shah SS, Ambroggio L, Florin TA. Invited Editorial: Biomarkers for Predicting Illness Severity in Children with Acute Lower Respiratory Tract Infections. Journal of the Pediatric Infectious Diseases Society. 2014;

   d. Florin TA, Ambroggio L. Biomarkers for community-acquired pneumonia in the emergency department. Curr Infect Dis Rep. 2014 Dec;16(12):451. PubMed PMID: 25348745.

Complete List of Published Work in My Bibliography: http://www.ncbi.nlm.nih.gov/myncbi/1-9npwz8rCo5V/bibliograpahy/47384868/public/?sort=date&direction=ascending

D. RESEARCH SUPPORT

Ongoing Research Support

2016/07/01-2017/06/30

Stephen Waggoner (PI)
Human natural killer cell responses in cytomegalovirus infection and vaccination
Overall Goal: A vaccine to prevent diseases associated with cytomegalovirus is desperately needed. Protection against cytomegalovirus requires virus-specific antibodies and T cells, the stimulation of which we have discovered is inhibited by natural killer (NK) cells in mice. These studies will reveal the role of NK cells and guide innovative strategies to modulate these cells in prevention of cytomegalovirus infection.
Role: Statistician

2016/01/15-2018/12/31
Academic Research Committee Award, Cincinnati Children's Hospital Medical Center
Lilliam Ambroggio (PI)
Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine (CARPE DIEM) Extension
Overall Goal: The objective of this study is to identify distinct metabolite profiles for the major classes of pathogens that cause CAP in children (e.g. virus, typical and atypical bacteria). Urine, blood samples, and nasopharyngeal swabs will be collected from children diagnosed with CAP in the Emergency Department or who are hospitalized at Cincinnati Children's Hospital Medical Center. All urine samples will then be evaluated using quantitative ^{1}H-nuclear magnetic resonance. Advanced statistical methods such as partial least squares-discriminant analysis will be applied to the identified metabolite dataset to determine unique metabolite profiles.
Role: PI

2015/01/10-2017/09/30
Governor's Office, State of Ohio
Octavio Ramilo (PI)
Children's Hospitals Research Initiative in Pneumonia (CHIRP)
Overall Goal: The objectives of this study are: to improve etiologic diagnosis of pediatric CAP using a combination of molecular diagnostic assays and host gene expression profiles (RNA biosignatures) and to evaluate the utility of a Molecular Distance to Health genomic score to triage patients based on severity and clinical outcomes.
Role: Site Co-Investigator

2013/08/01-2016/07/30
Research Initiation Funds, Cincinnati Children's Hospital Medical Center
Lilliam Ambroggio (PI)
Overall Goal: This grant has been used to set up the PI's research program during her first three years as faculty at CCHMC. These funds also support the infrastructure for Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine (CARPE DIEM).
Role: PI

Completed Research Support

2013/07/01-2015/06/30

132925, Place Outcomes Research Award
Shah, Samir (PI)
Reduced Variability in the Management of CAP
Role: Co-PI

[redacted]

2011/09/12-2013/07/01
NRSA T32HP10027, Ruth L. Kirschestein National Research Service Award
Copeland, Kristen (PI)
General and Community Pediatric Research
The objective of this fellowship is to improve the health of children by developing future independent investigators in primary care research.
Role: Fellow

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Shah, Samir S.

eRA COMMONS USER NAME (agency login): [redacted]

POSITION TITLE: James M. Ewell Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA	BA	05/1993	Biology
Yale University School of Medicine, New Haven, CT	MD	05/1998	Medicine
University of Pennsylvania School of Medicine, Philadelphia, PA	MSCE	05/2007	Epidemiology
Children's Hospital of Philadelphia, Philadelphia, PA	N/A	06/2001	Pediatrics Internship/Residency
Children's Hospital of Philadelphia, Philadelphia, PA	N/A	06/2005	Pediatric Infectious Diseases Fellowship
Children's Hospital of Philadelphia, Philadelphia, PA	N/A	06/2005	Academic General Pediatrics Fellowship

A. PERSONAL STATEMENT

I have content and methodological expertise in studies examining approaches to improve the diagnosis and treatment of childhood pneumonia. I am a Pediatric Infectious Diseases and Pediatric Hospital Medicine physician with formal training in research methodology and extensive experience in patient-oriented clinical research. I am an expert in childhood pneumonia as recognized by my role as Associate Chair of the National Childhood Pneumonia Diagnosis and Management Guidelines Committee, jointly sponsored by the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society. This clinical practice guideline, recently published with me as co-first author, informs Dr. Ambroggio's proposed project. There is a pressing need for the development of accurate diagnostic testing to guide empirical treatment and predict outcomes in children with community-acquired pneumonia. Dr. Ambroggio's focus on children with pneumonia aligns with the intent of the national guideline emphasis on identification of biomarkers relevant to childhood pneumonia. I have demonstrated a successful track record of multi-center collaboration and leadership in my role as Vice Chair of the Pediatric Health Information Systems (PHIS) Research Group, which includes 35 physicians from 18 hospitals. I am also an Executive Council Member of the Pediatric Research in Inpatient Settings Network, an organization sponsored by leading academic societies with >100 hospital members to create research infrastructure to facilitate the conduct of multi-center patient-oriented research. The network has received >$18 million in grant support over the past five years. I will aide in Dr. Ambroggio's collaboration with this network for subsequent grants.

B. POSITIONS AND HONORS

Positions and Employment

2005 - 2011 Assistant Professor of Pediatrics at the Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA

2005 - 2011 Attending Physician in Infectious Diseases and General Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA

2006 - 2011 Senior Scholar, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA

2011 - 2011 Associate Professor of Pediatrics and Epidemiology at the Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA

2011 - Attending Physician in Infectious Diseases and Hospital Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

2011 - 2012 Associate Professor of Pediatrics at Cincinnati Children's Hospital Medical Center, University of

Cincinnati College of Medicine, Cincinnati, OH

2012 - Professor of Pediatrics at Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH

2012 - Director, Division of Hospital Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

2012 - James M. Ewell Endowed Chair, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Other Experience and Professional Memberships

- Member (elected), American Pediatric Society

2005 - Fellow, American Academy of Pediatrics

2006 - Member, Clinical Affairs Committee, Pediatric Infectious Diseases Society

2007 - Member, Editorial Board, JAMA Pediatrics

2007 - Chair, Pediatric Health Information Systems Research Group

2008 - Infectious Diseases Society of America

- Associate Chair, National Childhood Pneumonia Guidelines Writing Committee (published in 2011)
- Member, National Bone/Joint Infections Guideline Writing Committee (2014-Present)

2008 - 2012 Editorial Advisory Board, Infection Control and Hospital Epidemiology

2009 - Executive Leadership Council, Pediatric Research in Inpatient Settings Network

- Vice Chair (2015-Present)

2009 - 2010 Assistant Editor, Journal of Hospital Medicine

2011 - Founding Associate Editor, Journal of the Pediatric Infectious Diseases Society

2011 - 2012 Associate Editor, Journal of Hospital Medicine

2012 - Deputy Editor, Journal of Hospital Medicine

2013 American Pediatric Society (elected member)

Honors

2007 Faculty Teaching Honor Roll, The Children's Hospital of Philadelphia

2008 Jean A. Cortner Division Teaching Award (Infectious Diseases), The Children's Hospital of Philadelphia Pediatric Residency Program

2009 Excellence in Research Award, Society of Hospital Medicine

2011 Young Investigator Award, Pediatric Infectious Diseases Society

2013 Division Teaching Award (Hospital Medicine), Cincinnati Children's Hospital Medical Center Residency Program

2014 Excellence in Teamwork in Quality Improvement Award, Society of Hospital Medicine

2014 Academic-Community Research Partnership Award, Center for Clinical and Translational Science and Training

2015 Miller-Sarkin Mentoring Award, Academic Pediatric Association

2015 Pediatric Hospital Medicine Award for Research Excellence, jointly awarded by the American Academy of Pediatrics, the Academic Pediatric Association, and the Society of Hospital Medicine (inaugural award; awarded for substantial research contributions to improve the care of hospitalized children)

C. CONTRIBUTIONS TO SCIENCE (articles selected from >200 peer-reviewed publications)

1. Variation in care contributes to health care delivery inefficiency and increased costs. My work highlighting care variation has spurred development of national guidelines for the diagnosis and management of childhood pneumonia, which I co-authored. Additional accomplishments include demonstrating the association between process measures and clinical outcomes in common respiratory conditions, including pneumonia and bronchiolitis.

   a. Bradley JS, Byington CL, **Shah SS*** and Alverson B, Carter ER, Harrison C, Kaplan SL, Mace SE, McCracken GH Jr., Moore MR, St. Peter SD, Stockwell JA, Swanson JT. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America.

Clin Infect Dis 2011 Oct;53(7):e25-e76. PubMed PMID: 21880587 (*denotes that Bradley, Byington, and Shah are co-listed as first authors)

b. Florin TA, Byczkowski T, Ruddy R, Zorc JJ, Test M, **Shah SS**. Variation in management of bronchiolitis persists after the 2006 AAP bronchiolitis guidelines. J Pediatr 2014

c. Florin TA, French B, Zorc JJ, Alpern ER, **Shah SS**. Variation in emergency department diagnostic testing and disposition outcomes in children with community-acquired pneumonia. Pediatrics 2013 Aug;132(2):237-244. PubMed PMID: 23878049

d. Morse RB, Hall M, Fieldston ES, McGwire G, Anspacher M, Sills MR, Williams K, Oyemwense N, Mann KJ, Simon HK, **Shah SS**. Hospital-level compliance with asthma care quality measures at children's hospitals and subsequent asthma-related outcomes. JAMA. 2011 Oct 5;306(13):1454-60. PubMed PMID: 21972307.

2. Implementing evidence is essential to improving hospital-based care. I have led or been a part of work in this area, focusing on understanding barriers and challenges to implementing evidence-based guidelines, specifically around bronchiolitis and pneumonia, identify approaches to overcome such barriers.

a. Neuman MI, Hall M, Hersh AL, Brogan TV, Parikh K, Newland JG, Blaschke AJ, Williams DJ, Grijalva CG, Tyler A, **Shah SS**. Influence of hospital guidelines on management of children hospitalized with pneumonia. Pediatrics. 2012 Nov;130(5):e823-30. PubMed PMID: 23090342.

b. Mittal V, Hall M, Morse R, Wilson KM, Mussman G, Hain P, Montalbano A, Parikh K, Mahant S, **Shah SS**. Impact of institutional bronchiolitis clinical practice guideline implementation on tests and treatments. J Pediatr 2014 Sep;165(3):570-576. PubMed PMID: 24961787

c. Parikh K, Hall M, Mittal V, Montalbano A, Mussman GM, Morse RB, Hain P, Wilson KM, **Shah SS**. Establishing benchmarks for the hospitalized care of children with asthma, bronchiolitis, and pneumonia. Pediatrics. 2014 Sep;134(3):555-62. PubMed PMID: 25136044.

d. Ambroggio LV, Thomson J, Kurowski EM, Courter J, Statile A, Graham C, Sheehan B, Iyer S, **Shah SS**, White CM. Quality improvement methods to increase appropriate antibiotic prescribing for childhood pneumonia. Pediatrics 2013 May;131(5):e1623-e1631. PubMed PMID: 23589819

3. As Vice Chair of the Pediatric Research in Inpatient Settings (PRIS) Network, I have extensive experience with conducting large multi-center studies that combine data from multiple sources, including the Pediatric Health Information System. My work has demonstrated that early conversion from intravenous to oral antibiotic therapy for bone infections is associated with fewer complications and no difference in treatment failure compared with prolonged intravenous therapy. We also established new data sources for comparative effectiveness research, including the Society of Thoracic Surgeons-Pediatric Health Information System joint database and PHIS+, a database that combines administrative data from PHIS with clinical data from 6 children's hospitals.

a. Keren R, **Shah SS**, Srivastava R, Rangel S, Bendel-Stenzel M, Harik N, Hartley J, Lopez M, Seguias L, Tieder J, Bryan M, Gong W, Hall M, Localio R, Luan X, deBerardinis R, Parker A. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. JAMA Pediatr. 2015 Feb;169(2):120-8. PubMed PMID: 25506733.

b. Pasquali SK, Jacobs JP, Shook GJ, O'Brien SM, Hall M, Jacobs ML, Welke KF, Gaynor JW, Peterson ED, **Shah SS**, Li JS. Linking clinical registry data with administrative data using indirect identifiers: implementation and validation in the congenital heart surgery population. Am Heart J 2010 Dec;160(6):1099-1104. PubMed PMID: 21146664; PubMed Central PMCID: PMC3011979.

c. Gouripeddi R, Warner PB, Mo P, Levin JE, Srivastava R, **Shah SS**, de Regt D, Kirkendall E, Bickel J, Korgenski EK, Precourt M, Stepanek RL, Mitchell JA, Narus SP, Keren R. Federating clinical data from six pediatric hospitals: process and initial results for microbiology from the PHIS+ consortium. AMIA Annu Symp Proc 2012 Nov;2012:281-290. PubMed PMID: 23304298; PubMed Central PMCID: PMC3540481.

d. Steenhoff AP, Josephs JS, Rutstein RM, Gebo KA, Siberry GK, GaurAH, Warford R, Korthuis PT, Spector SA, **Shah SS**. Incidence of and risk factors for community-acquired pneumonia in US HIV-infected children, 2000-2005. AIDS 2011 Mar;25(5):717-720. PubMed PMID: 21252630; PubMed Central PMCID: PMC3576877.

4. Much of my work has focused in defining comparative effectiveness of treatments for childhood pneumonia. This work has demonstrated that narrow-spectrum antibiotic therapy is effective and that different pleural fluid drainage approaches for pleural empyema result in comparable outcomes.

a. **Shah SS**, Hall M, Newland JG, Brogan TV, Farris RW, Williams DJ, Larsen G, Fine BR, Levin JE, Wagener JS, Conway PH, Myers AL. Comparative effectiveness of pleural drainage procedures for the treatment of complicated pneumonia in childhood. J Hosp Med. 2011 May;6(5):256-63. PubMed PMID: 21374798; PubMed Central PMCID: PMC3112472.
b. Thomson J, Ambroggio L, Murtagh Kurowski E, Statile A, Graham C, Courter JD, Sheehan B, Iyer S, White CM, **Shah SS**. Hospital outcomes associated with guideline-recommended antibiotic therapy for pediatric pneumonia. J Hosp Med 2015 Jan;10(1):13-18. PubMed PMID: 25263758; PubMed Central PMCID: PMC4322863.
c. Ambroggio L, Taylor JA, Tabb LP, Newschaffer CJ, Evans AA, **Shah SS**. Comparative effectiveness of empiric β-lactam monotherapy and β-lactam-macrolide combination therapy in children hospitalized with community-acquired pneumonia. J Pediatr. 2012 Dec;161(6):1097-103. PubMed PMID: 22901738.
d. Queen MA, Myers AL, Hall M, **Shah SS**, Williams DJ, Auger KA, Jerardi KE, Statile AM, Tieder JS. Comparative effectiveness of empiric antibiotics for community-acquired pneumonia. Pediatrics. 2014 Jan;133(1):e23-9. PubMed PMID: 24324001.

D. RESEARCH SUPPORT

Ongoing Research Support

2015/10/01-2017/9/30
Governor's Office of the State of Ohio
Ramilo, O. (PI)
Children's Hospitals Research Initiative in Pneumonia (CHIRP)
This project establishes a multicenter network of Ohio children's hospitals to focus on developing novel methods to identify etiology and predict illness severity in children with pneumonia. The main areas of focus include transcriptional profiles, procalcitonin, and metabolomics.
Role: Site PI

2014/04/01-2019/03/31
R01 HL122261, National Heart Lung and Blood Institute
Pasquali, Sara K. (PI)
Understanding quality and costs in congential heart surgery
This project applies advanced Bayesian methods to empirically combine information across multiple quality domains to develop a composite quality metric in congenital heart surgery. The metric will be evaluated against current quality indicators, as well as measures of resource utilization.
Role: Co-I

2014/05/01-2017/04/31
IHS-1306-00811, Patient-Centered Outcomes Research Institute
Shah, Samir S. (PI)
Improving post-discharge outcomes by facilitating family-centered transitions from hospital to home
The goal is to improve the outcomes of inpatient to outpatient transitions for hospitalized children and their families. The study uses qualitative methods to identify barriers to the transition home, implementation methods to ensure that a nurse home visit addresses those barriers, and a randomized controlled trial to determine the efficacy of nurse home visits in improving patient transitions.
Role: PI

2011/10/01-2016/09/30
U19 HS021114, Agency for Healthcare Research and Quality
Lannon, Carole (PI)
Center for Education on Research and Therapeutics (CERTs) Research Center

The Centers for Education and Research on Therapeutics (CERTs) program is a national initiative to increase awareness of the benefits and harms of new, existing, or combined uses of therapeutics (drugs, medical devices, and biological products) through education and research.
Role: Co-I

Recently Completed Research Support

2013/01/02-2016/01/01
Cycle 2, Patient-Centered Outcomes Research Institute
Keren, Ron (PI)
Comparative effectiveness of home intravenous vs. oral antibiotic therapy for serious bacterial infections.
Role: Site PI

2015/03/11-2015/09/12
Hirschfeld, S. (PI)
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Medical Science and Computing Consulting Agreement: Pediatric Terminology Harmonization Initiative-Pediatric Infectious Diseases
The goal of this contract was to create a rigorously defined group of “controlled” or “harmonized” terminologies to facilitate communication of research efforts. This particular project focused on ~600 terms used in pediatric infectious diseases.
Role: Working Group Co-Lead

2013/07/01-2015/06/30
N/A, Place Outcomes Research Award
Shah, Samir S. (PI)
Reducing variability in the management of children with community-acquired pneumonia
This multicenter study includes 10 pediatric office practices with a goal of implementing the national childhood pneumonia guideline outpatient recommendations and measuring the association between adherence and patient outcomes.
Role: PI

2013/07/01-2015/06/30
N/A, Place Outcomes Research Award
Schaffzin, Joshua K. (PI)
Surgical site infection prevention continuum development
This study implements pre- and post-operative standardize approaches to pre- and post-operative infection prevention and systematic information transfer across the continuum of surgical care spanning the pre-, intra-, and post-operative periods with a goal of decreasing surgical site infections.
Role: Co-PI

2010/09/01-2015/01/31
R01 HS019862, Agency for Healthcare Research and Quality
Keren, Ron (PI)
PHIS+: Augmenting the Pediatric Health Information System with clinical data
This project created an infrastructure for comparative effectiveness research by merging administrative data from the Pediatric Health Information System with clinical, laboratory, microbiology, and radiology data from 6 of the largest children's hospitals in the U.S. The database includes information on more 1 million hospitalized children.
Role: Site PI

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Maurizio Macaluso

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Professor and Director, Division of Biostatics and Epidemiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Palermo, Italy	M.D.	1979	Medicine and Surgery
University of Palermo, Italy	Residency	1982	Hygiene and Preventive Medicine
University of Alabama at Birmingham	Dr. P.H.	1991	Epidemiology

A. Personal Statement

As the Director of the Division of Biostatistics and Epidemiology of Cincinnati Children Hospital Medical Center (CCHMC) and the co-director of the Biostatistics, Epidemiology and Research Design Core of the Center for Clinical and Translational Research and Training I have been able to and will continue to contribute methodological expertise to Dr. Ambroggio's training plan and current research proposal. I have over 30 years' worth of content and methodological expertise in biomedical, public health and epidemiological research. My work has touched immunology, epidemiologic research methods, and infectious disease epidemiology. I have acted as a mentor for basic bench scientists and behavioral and social scientists, including masters' and doctoral-level students, post-doctoral fellows and junior scientists. I have done so in academic institutions, in government agencies and in four continents. Dr. Ambroggio's proposal is well aligned with our Division's vision of "Big Data for Little Children," bringing high-dimensional data from areas such as –omics research from the bench to the bedside to the community, in what is the ideal trajectory of translational science applied to child health.

B. Positions and Honors

2011-Present: Professor (tenured), Department of Pediatrics, University of Cincinnati College of Medicine; Director, Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

2000-2011: Chief, Women's Health and Fertility Branch, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA (CDC)

2000-2003 Professor (tenured), Department of Epidemiology and International Health, School of Public Health, University of Alabama at Birmingham, Birmingham, AL (UAB) (Leave of absence 3/14/01-3/13/03)

1994-2000 Associate Professor (tenured), Department of Epidemiology and International Health, School of Public Health, UAB

1991-1994 Assistant Professor, Department of Epidemiology, School of Public Health, UAB

Secondary Appointments

2012-Present Professor, Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, OH

2011-Present Director, Biostatistics, Epidemiology and Research Design Core, Center for Clinical and Translational Science and Training, University of Cincinnati, Cincinnati, OH

1998 - 2001 Co-Director, UAB Center for Contraceptive Development and Technology Transfer
1994 - 2001 Scientist, UAB Comprehensive Cancer Center
1991 - 1994 Associate Scientist, UAB Comprehensive Cancer Center
1997 - 2001 Scientist, UAB Center for AIDS Research
1997 - 2001 Scientist, UAB Center for Health Promotion
1996 - 2001 Scholar, John J. Sparkman Center for International Public Health Education
1995 - 2001 Associate Professor, Division of Geographic Medicine, Department of Medicine, School of Medicine

Adjunct Appointments

2007-2012 Visiting Professor, Department of Hygiene and Preventive Medicine, University of Palermo, Palermo, Italy
2003-2012 Adjunct Professor, Department of Epidemiology, Rollins School of Public Health. Emory University, Atlanta, GA
2003-Present Adjunct Professor, Department of Epidemiology, School of Public Health, UAB
2000-2011 Senior Fellow, WHO/CDC Collaborative Center on Reproductive Health
2000 Guest Professor, School of Public Health, Shandong University, Jinan, Shandong Province, People's Republic of China

Honors and Awards

1979 Summa Cum Laude Graduation in Medicine and Surgery
1979 Fellow, American College of Epidemiology
1997, 1998 UAB President's Award for Excellence in Teaching: Nominated
2006 33rd Annual Federal Employee of the Year– Outstanding Team Award (with the National Assisted Reproductive Technology Surveillance System Team) – Nominated
2006 Charles C. Shepard Science Award for Assessment and Epidemiology
2009 CDC/ATSDR Award for Employee Motivation and Development – Nominated
2009 American Fertility Association Illuminations Award

C. Contribution to Science

1. I began my career in cancer epidemiology at the National Tumor Institute in Milan, Italy, where I gained experience in cancer registration and became interested in occupational carcinogenesis and in the etiology of neoplasms of the reproductive organs. With investigators in Italy and Canada, I worked on refining "job-exposure matrices." I also worked on breast cancer with clinical oncologists, and documented a relation between parity and younger age at diagnosis in a large case series.

a) **Macaluso M**, Tamburini M, Massara G, Bertario L, Di Pietro S. Parity and breast cancer: confirmed evidence of an effect on age at diagnosis. Breast Cancer Res Treat. 1982; 2(3):257-60.
b) **Macaluso M**, Vineis P, Continenza D, Ferrario F, Pisani P, Audisio R. Job/exposure matrices: experience in Italy. In Acheson ED (Ed.): Job exposure matrices. Conference Report. M.R.C. Environmental Epidemiology Unit Scientific Report No 2, Southampton 1983, 22-29.
c) Pisani P, Berrino F, **Macaluso M**, Pastorino U, Crosignani P, Baldasseroni A. Carrots, green vegetables and lung cancer: a case-control study. Int J Epidemiol. 1986 Dec;15(4):463-8.
d) Berrino F, Vigano' C, Gatta G, Crosignani P, Pisani P, **Macaluso M**. Italy, Lombardy Region, Varese Province. In Muir C, Waterhouse J, Mack T, Powell J, Whelan S, (Eds.): Cancer Incidence in Five Continents Vol. V. IARC Sci. publ. 88. International Agency for Research on Cancer, Lyon 1987, 560-565.

2. At the University of Alabama at Birmingham (UAB) I worked in a series of cohort studies of the mortality of workers in chemical, petrochemical, and automobile manufacturing plants in the USA. These studies showed that workplace exposure to carcinogens makes subgroups of workers prone to developing malignant neoplasms. I developed methods for retrospective exposure assessment that were used in a study of workers employed in synthetic rubber manufacturing, potentially exposed to 1,2-butadiene and styrene. This research documented a dose-dependent association between exposure to butadiene and mortality from leukemia, providing the evidence base for lowering of the permissible exposure limit in the USA to 1 ppm.

a) Delzell E, **Macaluso M**, Cole P. A follow-up study of workers at a dye and resin manufacturing plant. J Occup Med. 1989 Mar;31(3):273-8.

b) **Macaluso M,** Delzell E, Cole P, Wongsrichanalai C, Cowles S. Validity of a mortality study based on a corporate health surveillance system. J Occup Med. 1991 Nov;33(11):1180-6.

c) **Macaluso M,** Delzell E, Rose V, Perkins J. Use of organic solvents and potential worker exposure in the motor vehicle manufacturing industry. Am J Ind Med. 1993 Mar;23(3):449-60.

d) **Macaluso M,** Larson R, Delzell E, Sathiakumar N, Hovinga M, Julian J, Muir D, Cole P. Leukemia and cumulative exposure to butadiene, styrene and benzene among workers in the synthetic rubber industry. Toxicology. 1996 Oct 28;113(1-3):190-202.

e) **Macaluso M**, Larson R, Lynch J, Lipton S, Delzell E. Historical estimation of exposure to 1,3-butadiene, styrene, and dimethyldithiocarbamate among synthetic rubber workers. J Occup Environ Hyg. 2004 Jun;1(6):371-90.

3. At UAB I also worked on collaborative research on the role of folic acid deficiency in the development of preneoplastic lesions of the uterine cervix. Human papillomavirus (HPV) was just beginning to be recognized as a cause of cervical cancer. In a case-control study published in JAMA in 1992 we documented that low red blood cell folate levels greatly enhanced the ability of HPV-16 to produce cervical dysplasia. In the following two decades I collaborated with Dr. Piyathilake in a number of studies. In the aggregate, this research has produced evidence that methyl-donor micronutrients are associated with reduced risk of HPV infection, faster clearance, and reduced severity/progression of HPV-related cervical lesions.

a) Butterworth CE Jr, Hatch KD, **Macaluso M**, Cole P, Sauberlich HE, Soong SJ, Borst M, Baker VV. Folate deficiency and cervical dysplasia. JAMA. 1992 Jan 22-29; 267:528-33.

b) Piyathilake CJ, Henao O, Frost AR, **Macaluso M**, Bell WC, Johanning GL, Heimburger DC, Niveleau A, Grizzle WE. Race- and age-dependent alterations in global methylation of DNA in squamous cell carcinoma of the lung (United States). Cancer Causes Control. 2003 Feb; 14:37-42

c) Piyathilake CJ, Henao OL, **Macaluso M**, Cornwell PE, Meleth S, Heimburger DC, Partridge EE. Folate is associated with the natural history of high-risk human papillomaviruses. Cancer Res. 2004 Dec 1;64:8788-93.

d) Piyathilake CJ, **Macaluso M,** Alvarez RD, Chen M, Badiga S, Edberg JC, Partridge EE, Johanning GL: A higher degree of methylation of the HPV 16 E6 gene is associated with a lower likelihood of being diagnosed with cervical intraepithelial neoplasia. Cancer, 2011 Mar 1; 117(5):957-63.

4. While at UAB, I took the scientific lead on a prospective study of barrier contraception for the prevention of sexually transmitted diseases funded by NICHD. As the HIV pandemic was rapidly growing, the development of effective barrier methods and of interventions to promote their use was very important for public health. I led a research program that encompassed the development and evaluation of behavioral interventions, the development of new methods to address the methodological limitations that plague condom effectiveness research, and studies of the acceptability, safety and efficacy of barrier methods. Some of the research funding came from the Division of Reproductive Health at CDC, which later selected me for the position of Chief, Women's Health and Fertility Branch. At UAB and at the CDC, I pioneered the development of new objective biomarkers of sexual activity and condom failure, which today are increasingly recognized for their importance in evaluating new barrier methods by standard setting organizations like the International Standards Organization (ISO).

a) **Macaluso M**, Lawson L, Akers R, Valappil T, Hammond K, Blackwell R, Hortin G. Prostate-specific antigen in vaginal fluid as a biologic marker of condom failure. Contraception. 1999 Mar; 59(3):195-201

b) **Macaluso M**, Kelaghan J, Artz L, Austin H, Fleenor M, Hook EW 3rd, Valappil T. Mechanical failure of the latex condom in a cohort of women at high STD risk. Sex Transm Dis. 1999 Sep; 26(8):450-8

c) **Macaluso M**, Demand MJ, Artz LM, Hook EW 3rd. Partner type and condom use. AIDS. 2000 Mar 31; 14(5):537-46.

d) **Macaluso M**, Blackwell R, Jamieson DJ, Kulczycki A, Chen MP, Akers R, Kim D-j, Duerr A. Efficacy of the male latex condom and of the female polyurethane condom as barriers to semen during intercourse: a randomized clinical trial. Am J Epidemiol, 2007; 166(1):88-96.

5. Children conceived using Assisted Reproductive Technology (ART) comprise 1.5% of U.S. children, but >15% of multiple births. Multiple birth is associated with poor infant and maternal health outcomes; there is evidence of increased risks for ART-conceived singletons. At the CDC, I oversaw the National ART Surveillance System, the publication of the Annual ART Success Rates Report, collaborated with state health departments in evaluating adverse outcomes of ART, and conducted research on ART effectiveness and safety. Infertility likely affects over 7 million U.S. couples, with medical costs likely exceeding $5 billion. I formed and led a CDC-wide working group to improve coordination around reducing the burden of infertility in the US. With the working group I developed a white paper on the need for a national public health strategy for prevention, and diagnosis and management of infertility, coordinated a national symposium held in Atlanta in 2008, and drafted the "Outline of a National Action Plan for the Prevention, Detection and Management of Infertility" which made the basis for the National Action Plan released by the Department of Health and Human Services in 2014.

a) Boulet SL, Schieve LA, Nannini A, Ferre C, Devine O, Cohen B, Zhang Z, Wright V, **Macaluso M**. Perinatal outcomes of twin births conceived using assisted reproduction technology: a population-based study. Hum Reprod 2008; 23:1941-8.

b) **Macaluso M**, Wright-Schnapp TJ, Chandra A, Johnson R, Satterwhite CL, Pulver A, Berman SM, Wang RY, Farr SL, Pollack LA. A public health focus on infertility prevention, detection, and management. Fertil Steril 2010 Jan; 93(1):16.e1-10.

c) Sauber-Schatz EK, Sappenfield W, Grigorescu V, Kulkarni A, Zhang Y, Salihu HM, Rubin LP, Kirby RS, Jamieson DJ, **Macaluso M**. Obesity, assisted reproductive technology, and early preterm birth--Florida, 2004-2006. Am J Epidemiol. 2012 Nov 15; 176(10):886-96.

d) Kulkarni AD, Jamieson DJ, Jones HW, Jr., Kissin DM, Gallo MF, **Macaluso M**, Adashi EY. The Multiple Births Epidemic: Evolving Role of Assisted Reproductive Technology and Ovulation Induction and Ovarian Stimulation. N Engl J Med 2013; 369:2218-25.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Z_FwlwSVl_5-/bibliograpahy/47572367/public/?sort=date&direction=ascending

D. Research Support

ACTIVE

ULRRR026314 (Heubi) 07/01/2015 – 06/30/2020
CCTST/UC
"Clinical and Translational Science Award (BERD)"
This is the national consortium of medical research institutions, funded through Clinical and Translational Science Awards (CTSAs), which is working together to:
- Improve the way biomedical research is conducted across the country
- Reduce the time it takes for laboratory discoveries to become treatments for patients
- Engage communities in clinical research efforts
- Train the next generation of clinical and translational researchers

Role: Director/Co-Director of BioMetrics Core

1R21OH010035-01A1 (Daraiseh) 09/1/2013 – 08/31/2016
CDC NIOSH
Just-In-Time Methods for Understanding Near-Misses, Injuries and Risk Factors
Goal: The study's objectives are to: determine the frequency and type of near-misses and injuries among PHCPs and assess the feasibility of using a real-time data collection method as the basis for active injury surveillance in healthcare organizations. A secondary objective is to assess the relationship of individual and work factors with these events.
Role: Co-Investigator

(Kim, Macaluso, Liu, Zou) 01/01/2015 – 12/31/2018
PCORI
Propensity Score-based Methods for CER Using Multilevel Data: What Works Best When

Goal: To investigate how to optimally extend the PS methodology and identify what works best when. An additional goal is to develop a novel imputation-based sensitivity analysis approach and to identify valid and most efficient PS methods for two existing CER studies.
Role: Co-Investigator

T32DK007695 (Devarajan) 07/01/2014 – 06/30/2019
Research Training in Pediatric Nephrology
Goal: To foster the development of outstanding clinical or basic science physician investigator and leaders who will meet the tremendously underserved academic workforce needs in Pediatric Nephrology.
Role: Mentor

K23 (Reed) 05/01/2014 – 04/30/2018
NIH
Decreasing teen STI prevalence through universal emergency department screening
Goal: The objective of this proposal is to design and test the feasibility and effectiveness of a universal CT/GC screening program in the ED.
Role: Mentor

COMPLETED

Place Outcomes (Daraiseh) 09/01/2013 – 06/30/2014
CCHMC Place Outcomes
Surveillance of Psychiatric Patients to Improve Safety
Goal: We will evaluate patient and staff safety with a novel evidenced-based approach by introducing cameras in psychiatric patient's rooms to monitor potentially harmful behavior.
Role: Co-Investigator

Thrasher Research Fund (Ambroggio) 02/01/2012 – 01/31/2014
CCHMC
Diagnostic Tools for Detecting Pneumonia in Children
Goal: The objective of the proposed study is to determine whether chest ultrasound is a more accurate diagnostic tool in detecting pneumonia in children than chest x-rays.
Role: Co-Investigator

UL1TR000077 (Heubi-Tsevat) 04/03/2009 – 03/31/2015
National Center for Research Resources
"Center for Clinical and Translational Science and Training"
This is the national consortium of medical research institutions, funded through Clinical and Translational Science Awards (CTSAs). This NIH sponsored center supports clinical research on campus.

- Improve the way biomedical research is conducted across the country
- Reduce the time it takes for laboratory discoveries to become treatments for patients
- Engage communities in clinical research efforts
- Train the next generation of clinical and translational researchers

Role: Director of Biostatistics, Epidemiology and Research Design Core

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Ruddy, Richard Michael

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Professor of Pediatrics, University of Cincinnati College of Medicine, Medical Director, Cincinnati Children's Hospital – Liberty Campus

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Notre Dame	BS	05/1972	Pre-Professional Studies
Georgetown University School of Medicine	MD	05/1976	MD
Children's Hospital of Philadelphia	Resident Chief Resident	06/1980	Pediatrics

A. Personal Statement

This past decade I have worked within the University of Cincinnati and Cincinnati Children's Hospital Medical Center (CCHMC) to bring together three important interests: (a) leading our institution and Emergency Medicine (EM) in multi-center research through the Pediatric Emergency Care Applied Research Network (PECARN), (b) mentoring junior faculty and fellows and (c) advancing the content area of respiratory illness in infants and children. Within PECARN, my role has progressed from the CCHMC site PI for the first 10 years, to the PI for a three-hospital node comprised of CCHMC, Milwaukee Children's Hospital and St. Louis Children's Hospital, to Chair of the PECARN Steering Committee. The themes critical to our nodal success are our work on knowledge implementation and dissemination, new discovery to advance the health of children, mentoring the next generation of pediatric emergency researchers and partnership with the community in advancing children's health. CCHMC has been one of the most productive sites in subject recruitment for network-wide studies and has made outstanding contributions to over 80 published manuscripts. We have strengthened our divisional improvement science work within CCHMC, and are well known for demonstrating high performance on improving the health care delivery system for children. Within the network we assembled a team of highly qualified clinician-scientists and mentors for junior faculty.

For the past three years I have been one of two senior mentors for Lilliam Ambroggio, PhD, MPH and Todd Florin, MD, MSCE on studies investigating lower respiratory tract infections. This team has been very successful at building a strong infrastructure in the ED and inpatient setting for patient enrollment, prospective clinical data collection and biological specimen collection to answer important questions regarding pneumonia etiology and severity. In addition to our work at CCHMC we are partnering with 6 children's hospitals within Ohio funded by the Governor's Fund of Ohio to expand our current pneumonia study and to propose a multicenter study through PECARN. As one of Dr. Ambroggio's research mentors, I will provide oversight for her research and career development activities. Lastly, I believe that my commitment to partnerships within our academic and local community has helped to generate vital connections that improve the success of clinical research. The Division of EM has long supported work to improve the outcomes for children in our community and throughout the country and therefore we are supportive of Dr. Ambroggio and her proposal.

B. Positions and Honors

1980-81 Lecturer in Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA
1981-85 Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia
1985-89 Assistant Professor of Pediatrics, New York Medical College, Valhalla, NY

1989-91	Associate Professor of Pediatrics, New York Medical College, Valhalla, NY
1991-15	Director, Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
1991-96	Associate Professor of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH
1996-	Professor of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH
2015-	Medical Director, Cincinnati Children's Hospital Medical Center – Liberty Campus

Other Experience and Professional Memberships

1975-	Alpha Omega Alpha Honor Society
1986-92	Board Certification - American Board of Pediatrics; Subspecialty - Pediatric Pulmonology
1992-	Board Certification - Subspecialty - Pediatric Emergency Medicine (Recertification 1998, 2006)
1992-97	Member, Emergency Medical Services Board, Ohio - Trauma Advisory Group Subcommittee.
1993-2004	Member, American Academy of Pediatrics - Executive Committee Section of Emergency Medicine, 1993-1995 and 1997-2000 Chair: 2000-2002, Past Chair: 2002-2004
1993-2003	Member, Academy of Medicine Emergency & Disaster Committee
1996-1997	Physician Leadership Program, Cincinnati Ohio
1997-2013	Medical Advisory Committee - Hamilton County Injury Surveillance System Medical Director: 2002-2012
1998-2002	Chair, Pediatric Emergency Medicine Directors SIG, Ambulatory Pediatric Association
2004-	Grant Reviewer, HRSA/MCHB, EMSC Targeted Issues Grants
2007-2008	Improvement Science Course completion, CCHMC
2007-2010	Member, City of Cincinnati Board of Health, Cincinnati, OH
2009-	Member, American Pediatric Society
2010-	Grant Reviewer – CCHMC Place Outcome Awards
2011-	CCTST Community Grants and Research Committee
2009-2011	Society of Academic Emergency Medicine – Aging and Generational Issues in Academic Emergency Medicine Task Force
2011-2012	Office of Maternal and Infant Health and Infant Mortality Reduction Board
2011-2015	Vice Chair, Steering Committee, Pediatric Emergency Care Applied Research Network
2015-	Chair, Steering Committee, PECARN

Honors

1999, 00, 04, 06, 10, 12, 15	Division Teaching Award Pediatric Resident, CCHMC
2001	Mead Johnson Excellence in Teaching Award
2004	Pediatric Golden Apple Award – Faculty Teaching Award – UC Dept. of Emergency Medicine
2009	Cincinnati Pediatric Society – 2009 Founder's Award Recipient
2010	AAP James Seidel Section of Emergency Medicine Distinguished Service Award
2016	CCHMC Faculty Service Award

C. Contribution to Science

1. **Emergency Department Health Care Improvement** – From 1991 until now, I have had a firm commitment to improve the quality of care provided to children in the ED. At Cincinnati Children's, we strive to become the best pediatric health system at improving outcomes for children. As a Division Director, I sought to ensure that our emergency services could be at the core of that work, in both assessment of quality and variation of care and implementation of evidence-based guidelines. Within the Pediatric Emergency Care Applied Research Network (PECARN), I have been a senior investigator involved in helping to better understand safety in the ED and in the development of quality measures. Our work has led to important system-based improvements to the care provided, in addition to providing me an opportunity to mentor a generation of PEM providers who now are leaders in health care improvement science in pediatric emergency medicine.

Perlstein PH, Lichtenstein P, Cohen MB, **Ruddy RM**, Schoettker PJ, Atheron HD, Kotagal U: Implementing an evidence-based acute gastroenteritis guideline at a children's hospital. Jt Comm J Qual Improv. 2002; 28(1):20-30. PMID: 11787237

Alessandrini E, Varadarajan K, Alpern ER, Gorelick MH, Shaw K, **Ruddy RM**, Chamberlain JM, for the Pediatric Emergency Care Applied Research Network: Emergency Department Quality: An Analysis of Existing Pediatric Measures. Academic Emergency Medicine. 2011; 18(5):519-26. PMID: 21569170

Ruddy RM, Mace SE, Shaw K, Percelay J: Pediatric emergency care in community hospitals with non-pediatric emergency medicine providers. Pediatr Emerg Care. 2008; 24(8):582-5. PMID: 18708908

Timm NL, **Ruddy RM**: Demographics of patient visits during high daily census in a pediatric ED. Am J Emerg Med. 2010; 28(1):56-60. PMID: 20006202

2. **Pediatric Respiratory Illnesses** – In the early part of my career, my professional activities and interests included both Pediatric Pulmonology and Pediatric Emergency Medicine. This early exposure to both fields led to an academic interest and scholarly output in acute and chronic pediatric respiratory illness. My early experiences with the cystic fibrosis population at The Children's Hospital of Philadelphia formed the basis for much of my subsequent work in the ED setting. One of my early clinical trials found nebulized metaproterenol more effective than subcutaneous epinephrine in acute asthma exacerbation, which contributed to the increased use of aerosolized medications for asthma that is now the standard of care. Since that trial, I have collaborated with investigators studying resource utilization and novel diagnostics and therapeutics in asthma, bronchiolitis, croup and pneumonia.

Ruddy RM, Kolski G, Scarpa N, Wilmott R: Aerosolized metaproterenol compared to subcutaneous epinephrine in the emergency treatment of acute childhood asthma. Pediatr Pulmonol. 1986; 2(4):230-6. PMID: 3532010

Luria, JW, Gonzalez del Rey JA, DiGiulio GA, McAneney CM, Olson JJ, **Ruddy RM:** Effectiveness of oral or nebulized dexamethasone for children with mild croup. Arch Pediatr Adol Med. 2001; 155(12):1340-5. PMID: 11732953

Stevenson MD, Heaton PC, Moomaw CJ, Bean JA, **Ruddy RM**. Inhaled corticosteroid use in asthmatic children receiving Ohio Medicaid: trend analysis, 1997-2001. Ann Allergy Asthma Immunol. 2008; 100(6):538-44. PMID: 18592816

Florin TA, Byczkowski T, **Ruddy RM,** Zorc JJ, Test M, Shah SS: Variation in the Management of Infants Hospitalized for Bronchiolitis Persists after the 2006 American Academy of Pediatrics Bronchiolitis Guidelines. J Pediatr. 2014; 165(4):786-92. PMID: 25015578

Florin TA, Byczkowski T, **Ruddy RM**, Zorc JJ, Test M, Shah SS: Utilization of nebulized 3% saline in infants hospitalized with bronchiolitis. J Pediatrics 2015 May; 166(5): 1168-1174.e2 doi:10.1016/j.jpeds.2015.01.045. Epub 2015 Mar 4. PMID: 25747800

3. **Diagnosis of the Febrile Child in the Emergency Department** – Fever is one of the most common reasons for ED visits in infants and young children. Often, it is difficult to determine if a fever is the result of a benign viral infection or due to a potentially devastating bacterial illness, such as meningitis or bacteremia. In the era before the pneumococcal conjugate vaccine, invasive pneumococcal disease (IPD) was prevalent. Some of my early collaborative work in this area focused on diagnostics to detect *S. pneumoniae*. As vaccines were developed and IPD decreased, my focus in this area shifted to focusing testing on those with increased risk of serious infection, thereby decreasing resource use in those who are at low-risk. Some of this work is ongoing through my work in PECARN. I was the site PI of two R01 funded multicenter studies to determine the utility of biomarkers and RNA microarray technology in improving the diagnosis of serious bacterial infection in the febrile neonate. The second study just initiated funding and enrollment.

Mahajan P, Kuppermann N, Suarez N et al and the Febrile Infant Working Group for the Pediatric Emergency Care Applied Research Network (PECARN). RNA transcriptional biosignatures analysis for identifying febrile infants with serious bacterial infections in the emergency department: a feasibility study. Pediatr Emerg Care. 2015; 31(1):1-5. PMID: 25526020

Friedland LR, Menon AG, Reising SF**, Ruddy RM**, Hassett DJ: Development of a polymerase chain reaction assay to detect the presence of *streptococcus pneumoniae* DNA. Diagn Microbiol Infect Dis. 1994; 20(4):187-93. PMID: 7705031

Strait RT, **Ruddy RM**, Friedland LR, Duncan KM, Wilmott RW: A pilot study of the predictive value of plasma tumor necrosis factor α and interleukin 1β for *streptococcus pneumoniae* bacteremia in febrile children. Acad Emerg Med. 1997; 4(1):44-51. PMID: 9110011

Iyer SB, Gerber MA, Pomerantz WJ, Mortensen JE, **Ruddy RM.** Effect of point-of-care influenza testing on management of febrile children. Acad Emerg Med. 2006; 13(12):1259-68. PMID: 17079787

4. **Patient Safety in the Emergency Department** – Both our safety efforts at CCHMC and a PECARN working group began to further focus our local and network efforts on patient safety in emergency services. With infrastructure support locally and the team's efforts we began an important element of safety through ED infrastructure, culture change, crew resource management (through high fidelity simulation) to help us make the ED the safest they can be. This is a true team effort with high reliability organization characteristics and accountability to each other and more reliable systems in our departments.

Ruddy RM, Patterson MD: Medical simulation: a tool for recognition of and response to risk. Pediatr Radiol. 2008; 38(S4):S700-6. PMID: 18810414

Chamberlain JM, Shaw KN, Lillis KA, Mahajan PV, **Ruddy RM**, Lichenstein R, Olsen CS, Dean JM: Creating an Infrastructure for Safety Event Reporting and Analysis in a Multicenter Pediatric Emergency Department Network. Pediatr Emerg Care. 2013 Feb; 29(2):125-30. PMID: 23364372

Shaw KN, Lillis KA, **Ruddy RM**, Mahajan PV, Lichenstein R, Olsen CS, Chamberlain JM, for the Pediatric Emergency Care Applied Research Network (PECARN): Reported Medication Events in a Paediatric Emergency Research Network: Sharing to Improve Patient Safety. Emerg Med J. 2013 Oct: 30 (10):815-9. PMID: 23117714

Shaw KN, **Ruddy RM**, Olsen CS, Lillis KA, Mahajan PV, Dean JM, Chamberlain JM: Pediatric patient safety in emergency departments: unit characteristics and staff perceptions. Pediatrics. 2009; 124(2):485-93.

Ruddy RM, Chamberlain JM, Mahajan PV, Funai T, O'Connell KJ, Blumberg S, R Lichenstein, HL Gramse, KN Shaw, Pediatric Emergency Care Applied Research Network (PECARN): Near Misses & Unsafe Conditions Reported in a Pediatric Emergency Research Network. BMJ Open 2015; 5:e007541. doi:10.1136/bmjopen-2014-007541

5. **Multicenter Pediatric Emergency Research** – As a member of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics I fostered research partnerships across many pediatric emergency medicine programs. An extension of that, in 2001 I was recruited to be the site PI of one of the original 25 sites in PECARN. As the PI for CCHMC, I became heavily focused on building the research infrastructure to produce quality work in the trials, as well as ensuring that junior faculty had sufficient mentoring to succeed in this important work. We were the leading site in the clinical trial evaluating the effectiveness of corticosteroids in bronchiolitis, published in the New England Journal of Medicine. Since 2011, I have been the nodal PI for the Midwest Emergency Node of CCHMC, Children's Hospital of Wisconsin and St. Louis Children's Hospital. Currently I serve as the Chair of the PECARN Steering Committee. The robust infrastructure that we built for clinical research also enabled us to collaborate outside of PECARN in other important studies, including the use of biomarkers helping to predict early appendicitis.

Corneli HM, Zorc JJ, Majahan P, Shaw KN, Holubkov R, Reeves SD, **Ruddy RM**, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. NEJM. 2007; 357(4):331-9. PMID: 17652648

Stanley R, Lillis KA, Zuspan SJ, Lichenstein R, **Ruddy RM**, Gerardi MJ, Dean JM: Development and implementation of a performance measure tool in an academic pediatric research network. Contemp Clin Trials. 2010; 31(5):429-437. PMID: 29478406

Mills AM, Huckins DS, Kwok H, Baumann BM, **Ruddy RM**, Rohman RE, Schrock JW, Lovecchio F, Krief WI, Hexdall A, Caspari R, Cohen B, Lewis RJ: Diagnostic Characteristics of S100A8/A9 in a Multicenter Study of Patients with Acute Right Lower Quadrant Abdominal Pain. Acad Emerg Med. 2012 Jan; 19(1):48-55. PMID: 22221415

Ruddy RM, Chamberlain JM, Mahajan PV, Funai T, O'Connell KJ, Blumberg S, R Lichenstein, HL Gramse, KN Shaw, Pediatric Emergency Care Applied Research Network (PECARN): Near Misses & Unsafe Conditions Reported in a Pediatric Emergency Research Network. BMJ Open 2015;5 (9):e007541. PMID: 26338681.

Glass T, **Ruddy RM**, Alpern E, Gorelick M, Callahan J, Lee L, Gerardi M, Melville K, Miskin M, Holmes J, Kuppermann N, Pediatric Emergency Care Applied Research Network (PECARN): Traumatic Brain Injuries and Computed Tomography Use in Pediatric Sports Participants. American Journ Emerg Med 2015; 33(10):1458-64. PMID: 26256635.

Complete List of Published Work in My Bibliography: http://www.ncbi.nlm.nih.gov/sites/myncbi/1FOK6BiuoIZAK/bibliography/48626594/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1 U03MC22684-01-00 Ruddy, RM (PI)
09/01/15 – 08/31/19
HRSA
EMSC: Network Development Demonstration Project
This funding supports the Pediatric Emergency Care Applied Research (PECARN) Network.
Role: PI

R01HD85233-01 Mahajan P (PI) Ruddy RM (site PI) 8/21/2015-5/30/2020
NICHD
RNA Biosignatures: A Paradigm Change for the Management of Young Febrile Infants
This proposal will assess the impact of viral and bacterial infection on infants less than 60 days and assess the biosignature over time in-hospital.

1R01HD071915-01A1 Schnadower (PI) 12/10/2013-11/30/2018
NICH
Impact of Emergency Department Probiotic Treatment of Pediatric Gastroenteritis
We propose to study the effectiveness and side effects of a probiotic, LGG, in treating children with gastroenteritis. If successful, this therapeutic intervention would be the first treatment that actually changes the disease process and would represent an enormous public health advance both in the US, and potentially, globally.

Completed Research Support:

1 U03MC22684-01-00 Ruddy, RM (PI) 09/01/11 – 08/31/15
HRSA
EMSC: Network Development Demonstration Project
This funding supports the Pediatric Emergency Care Applied Research (PECARN) Network.

[redacted]

1 R01 HD062477 Mahajan, P (PI) 01/01/11 – 05/31/13
RNA Biosignatures in the Emergency Evaluation of Febrile Infants
The goal of this study is to change the paradigm of how young febrile infants are evaluated in the ED, and as a consequence improve their care.
Role: Site PI

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: STRINGER, KATHLEEN A

eRA COMMONS USER NAME (agency login): [redacted]

POSITION TITLE: Professor of Clinical and Translational Pharmacy and Director, NMR Metabolomics Laboratory

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Michigan, Ann Arbor, MI	PharmD	06/1985	Clinical Pharmacy
University of Michigan Hospital, Ann Arbor, MI	Other training	05/1985	Internship
University of Illinois at Chicago, Chicago, IL	Resident	06/1986	Clinical Pharmacy Practice Residency
State University of New York at Buffalo, Buffalo, NY	Postdoctoral Fellow	08/1988	Post-doctoral training in cardiovascular research
University of Colorado Health Sciences Center, Denver, CO	Postdoctoral Fellow	07/1996	American Foundation for Pharmaceutical Education Post-PharmD Fellow in Experimental Pulmonary Research

A. Personal Statement

The goal of the work proposed in this Mentored Research Scientist Development Award (K01) application is to provide Dr. Ambroggio with protected time so that she can have an intensive, supervised career development experience in pediatric infectious diseases epidemiology and metabolomics. In this regard, I will serve as her metabolomics mentor and collaborator. In the preparation of this application, I have assisted and guided Dr. Ambroggio in metabolomics study design including the construction of standard operating procedures for the collection of urine samples for metabolomics assays. In this capacity as her metabolomics mentor, my laboratory personnel and I will teach her the NMR metabolomics workflow “on site” at the University of Michigan’s NMR Metabolomics Laboratory. She will learn sample preparation, NMR spectrum acquisition, spectral processing, metabolite identification and quantification so that she can bring these skills back to her own institution and function as an independent metabolomics investigator. She will also gain, in collaboration with the study’s statisticians, experience in metabolomics data and pathway analysis. I am uniquely qualified to serve in this capacity because I have successfully developed and led a productive metabolomics research program. I have gained considerable experience in quantitative NMR metabolomics, employing both blood and urine samples and have optimized sample collection, processing and analysis techniques. In particular, I have gained expertise in the use of a number of commercially and publically available software platforms including Chenomx (www.chenomx.com) and Metaboanalyst (www.metaboanalyst.ca) and I have forged productive collaborations with a number of of internal and external investigators (Dr. John Younger and Dr. Vicki Ellingrod, University of Michigan; and Dr. Alan Jones, University of Mississippi). In addition to my expertise in metabolomics, I have a strong record of mentorship. I have mentored over 50 PharmD and PhD students and several post-doctoral trainees. In addition, I have had the privilege and opportunity to mentor a number of junior faculty. My capability and effectiveness as a mentor is evidence by my receipt of a Michigan Institute for Clinical and Health Research Distinguished Mentor Award. Collectively, I will utilize my metabolomics and effective mentorship skills to guide and assist in the training of Dr. Lilliam Ambroggio so that she may become a successful independent investigator in epi-metabolomics.

1. Karnovsky A, Weymouth T, Hull T, Tarcea VG, Scardoni G, Laudanna C, Sartor MA, **Stringer KA**, Jagadish HV, Burant C, Athey B, Omenn GS. Metscape 2 bioinformatics tool for the analysis and

visualization of metabolomics and gene expression data. Bioinformatics. 2012 Feb 1;28(3):373-80. PubMed PMID: 22135418; PubMed Central PMCID: PMC3268237.

2. Lacy P, McKay RT, Finkel M, Karnovsky A, Woehler S, Lewis MJ, Chang D, **Stringer KA**. Signal intensities derived from different NMR probes and parameters contribute to variations in quantification of metabolites. PLoS One. 2014;9(1):e85732. PubMed PMID: 24465670; PubMed Central PMCID: PMC3897511.
3. Puskarich MA, Finkel MA, Karnovsky A, Jones AE, Trexel J, Harris BN, **Stringer KA**. Pharmacometabolomics of l-carnitine treatment response phenotypes in patients with septic shock. Ann Am Thorac Soc. 2015 Jan;12(1):46-56. PubMed PMID: 25496487; PubMed Central PMCID: PMC4342803.
4. [redacted]

B. Positions and Honors

Positions and Employment

1982 - 1984	Pharmacy Intern, Sinai Hospital of Detroit, Detroit, MI
1984 - 1984	Research Assistant, Department of Pharmacology, University of Michigan Medical School, Ann Arbor, MI
1988 - 1997	Assistant Professor, School of Pharmacy, University of Colorado Health Sciences Center, Denver, CO
1997 - 2006	Associate Professor of Clinical Pharmacy (with tenure), Department of Clinical Pharmacy, School of Pharmacy, Denver, CO
2003 - 2007	Associate Professor , Graduate Program in Toxicology and Pharmaceutical Sciences, Graduate School, Denver, CO
2006 - 2007	Associate Professor of Clinical Pharmacy (with tenure), Department of Pharmaceutical Sciences, School of Pharmacy, Denver, CO
2007 - 2012	Associate Professor of Clinical Pharmacy (with tenure), Department of Clinical Pharmacy, College of Pharmacy, Ann Arbor, MI
2012 -	Professor of Clinical & Translational Pharmacy, Department of Clinical Pharmacy, College of Pharmacy, Ann Arbor, MI
2014 -	Director, NMR Metabolomics Laboratory, College of Pharmacy, University of Michigan, Ann Arbor, MI
2016 -	Associate Director, Michigan Center for Integrative Research in Critical Care, University of Michigan, Ann Arbor, MI

Other Experience and Professional Memberships

1988 -	Member, American College of Clinical Pharmacy
2003 - 2007	Associate Member, University of Colorado Cancer Center
2007 -	Member, University of Michigan Comprehensive Cancer Center
2007 -	Member, American Thoracic Society
2007 -	Member, The American Physiological Society
2011 -	Affiliate Member, University of Michigan Center for Computational Medicine and Bioinformatics
2014 -	Member, The Metabolomics Society

Honors

1989	Young Investigator's Award, American Association of Colleges of Pharmacy
1994	Gustavus A. Pfeiffer Clinical Pharmacy Post-PharmD Fellowship, American Foundation for Pharmaceutical Education
2014	Distinguished Clinical and Translational Research Mentor, Michigan Institute for Clinical and

Health Research

C. Contribution to Science

1. **Metabolomics**: I have been involved in conducting metabolomics studies for nearly 8 years. I directed and published some of the first metabolomics studies in sepsis and acute respiratory distress syndrome. I continue to pioneer the development and application of NMR metabolomics approaches to further knowledge of disease mechanism, the identification of drug target opportunities and to metabolically phenotype drug response.

    a. Serkova NJ, Van Rheen Z, Tobias M, Pitzer JE, Wilkinson JE, **Stringer KA**. Utility of magnetic resonance imaging and nuclear magnetic resonance-based metabolomics for quantification of inflammatory lung injury. Am J Physiol Lung Cell Mol Physiol. 2008 Jul;295(1):L152-61. PubMed PMID: 18441091; PubMed Central PMCID: PMC2494785.

    b. **Stringer KA**, Serkova NJ, Karnovsky A, Guire K, Paine R 3rd, Standiford TJ. Metabolic consequences of sepsis-induced acute lung injury revealed by plasma ^{1}H-nuclear magnetic resonance quantitative metabolomics and computational analysis. Am J Physiol Lung Cell Mol Physiol. 2011 Jan;300(1):L4-L11. PubMed PMID: 20889676; PubMed Central PMCID: PMC3023293.

    c. Evans CR, Karnovsky A, Kovach MA, Standiford TJ, Burant CF, **Stringer KA**. Untargeted LC-MS metabolomics of bronchoalveolar lavage fluid differentiates acute respiratory distress syndrome from health. J Proteome Res. 2014 Feb 7;13(2):640-9. PubMed PMID: 24289193; PubMed Central PMCID: PMC4068805.

    d. **Stringer KA**, Younger JG, McHugh C, Yeomans L, Finkel MA, Puskarich MA, Jones AE, Trexel J, Karnovsky A. Whole Blood Reveals More Metabolic Detail of the Human Metabolome than Serum as Measured by 1H-NMR Spectroscopy: Implications for Sepsis Metabolomics. Shock. 2015 Sep;44(3):200-8. PubMed PMID: 26009817; PubMed Central PMCID: PMC4537695.

2. **Drug development**: I have directed the development and tested the feasibility of tissue plasminogen activator (tPA) for inhalation. This effort has advanced knowledge of the safety and efficacy of tPA for the treatment of pediatric plastic bronchitis. In addition, it resulted in FDA approval of its orphan drug status and the investigational new drug (IND) application for the use of inhaled tPA for the treatment of pediatric plastic bronchitis. Collectively, this work serves as the basis for a planned phase II clinical trial which will permit its translation into the clinic.

    a. Dunn JS, Nayar R, Campos J, Hybertson BM, Zhou Y, Manning MC, Repine JE, **Stringer KA**. Feasibility of tissue plasminogen activator formulated for pulmonary delivery. Pharm Res. 2005 Oct;22(10):1700-7. PubMed PMID: 16180128; PubMed Central PMCID: PMC2040297.

    b. **Stringer KA**, Tobias M, Dunn JS, Campos J, Van Rheen Z, Mosharraf M, Nayar R. Accelerated dosing frequency of a pulmonary formulation of tissue plasminogen activator is well-tolerated in mice. Clin Exp Pharmacol Physiol. 2008 Dec;35(12):1454-60. PubMed PMID: 18671720; PubMed Central PMCID: PMC2779770.

    c. Lackowski NP, Pitzer JE, Tobias M, Van Rheen Z, Nayar R, Mosharaff M, **Stringer KA**. Safety of prolonged, repeated administration of a pulmonary formulation of tissue plasminogen activator in mice. Pulm Pharmacol Ther. 2010 Apr;23(2):107-14. PubMed PMID: 19879371; PubMed Central PMCID: PMC2821999.

    d. Heath L, Ling S, Racz J, Mane G, Schmidt L, Myers JL, Tsai WC, Caruthers RL, Hirsch JC, **Stringer KA**. Prospective, longitudinal study of plastic bronchitis cast pathology and responsiveness to tissue plasminogen activator. Pediatr Cardiol. 2011 Dec;32(8):1182-9. PubMed PMID: 21786171; PubMed Central PMCID: PMC3207025.

3. **Drug discovery, drug action and transport**: I have directed, led, and intellectually contributed to studies that identified new drug actions, mechanisms of drug transport and identified potential new drug candidates. This includes work with the drug clofazimine and tissue plasminogen activator.

a. **Stringer KA**, Dunn JS, Gustafson DL. Administration of exogenous tissue plasminogen activator reduces oedema in mice lacking the tissue plasminogen activator gene. Clin Exp Pharmacol Physiol. 2004 May-Jun;31(5-6):327-30. PubMed PMID: 15191406.

b. Min KA, Talattof A, Tsume Y, **Stringer KA**, Yu JY, Lim DH, Rosania GR. The extracellular microenvironment explains variations in passive drug transport across different airway epithelial cell types. Pharm Res. 2013 Aug;30(8):2118-32. PubMed PMID: 23708857; PubMed Central PMCID: PMC3706189.

[redacted]

d. [redacted]

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/kathleen.stringer.1/bibliography/40956426/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

2016/04/01-2020/01/31
R01GM111400, NIH
Stringer (PI)
L-Carnitine Pharmacometabolomics in Sepsis (CaPS)
The goal of this project is to determine to what extent L-carnitine utilization is directly linked to metabolic adaptiveness and mortality in patients with severe sepsis.
Role: Principal Investigator

2012/07/12-2016/06/30
R01GM078200, NIH
Rosania (PI)
Chemical Address Tags: A chemoinformatics & image data management and analysis plan
The goal of this project is to develop machine vision and image analysis tools to identify chemical address tags by relating the chemical structure of small molecules to their subcellular localization as apparent in image data.
Role: Co-Investigator

2015/07/01-2016/06/30
R01GM103799-S1, NIH
Jones (PI)
L-carnitine Treatment for Vasopressor Dependent Septic Shock
This is a phase II randomized clinical trial of carnitine efficacy and safety in septic shock. The supplement will fund the metabolomics assay of serum samples collected as part of the phase I tri-al in order to inform a targeted metabolomics approach for the phase III study.
Role: Co-Investigator

Completed Research Support

2013/06/01-2015/12/31 (no cost extension)

R01GM069438-07S1, NIH
Younger (PI)
Complement C5a in Human Sepsis- Metabolomics Supplement
The goal of this project is to use novel assays of host bactericidal activity and C5a generation and to measure function in a subset of sepsis patients. The supplement funds the metabolomics portion of this study.
Role: Co-Investigator

2010/07/15-2013/06/30
R15 HD065594-01, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Stringer (PI)
Pulmonary Formulation of tPA for Plastic Bronchitis
Role: PI

2014/06/01-2015/05/31
MH082784-07S3, NIH
Ellingrod (PI)
Antipsychotic and folate pharmacogenetics- Sex differences Metabolomics Supplement
The goal of this project is to genetically phenotype patients who respond and do not respond to folate supplementation and to characterize risk of metabolic syndrome. This supplement funds the characterization of sex-differences in the metabolomics data.
Role: Co-Investigator

2014/06/01-2015/05/31
R01MH082784-07S2, NIH
Ellingrod (PI)
Antipsychotic and folate pharmacogenetics- Metabolomics Supplement
The goal of this project is the genetic phenotyping of patients who respond and do not respond to folate supplementation and to characterize risk of metabolic syndrome. This supplement funds the metabolomics component of the work.
Role: Co-Investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Sucharew, Heidi

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
The College of New Jersey, Ewing, NJ	B.A.	05/2000	Statistics
University of Washington, Seattle, WA	M.S.	08/2002	Biostatistics
University of Cincinnati, Cincinnati, OH	Ph.D.	12/2009	Biostatistics

A. Personal Statement

The objective of this study is to improve our understanding of the role of urine metabolites in relation to viral or bacterial community acquired pneumonia and to evaluate the impact of antibiotic treatment on changes in the urine metabolite profile. My academic specialty is in biostatistics with methodology interests in latent variable models and structural equation modeling. My recent areas of application include latent profile analysis of infant neurobehavior and latent class analysis of individual NIH stroke scale scores for mortality prediction. I am an assistant professor in the Division of Biostatistics and Epidemiology at Cincinnati Children's Hospital Medical Center. I currently provide statistical support for researchers and faculty in the Hospital Medicine division within Cincinnati Children's Hospital and the Department of Neurology at the University of Cincinnati. I have an established working collaboration with Dr. Lilliam Ambroggio and am excited to share my expertise with her to accomplish the goals of the research plan. I am also excited about the research/mentoring team, as Lilliam has brought together the expertise from multiple dimensions that will ensure the successful completion of the proposed research work. I have the expertise, leadership, training, and passion necessary to serve as statistician for this application. I'm a biostatistician for the ongoing Epidemiology of Stroke study and have served as associate director for the Biostatistical Core of the Special Program on Translational research in Acute Stroke (SPOTRIAS) grant for Cincinnati and therefore provided statistical support for three NIH-funded, multicenter clinical trials. My methodologic training allows me to apply my skills across a diverse set of research topics. I have a highly productive track record not only in my personal research field, but also on a diverse set of research teams. As a member of this research team, I am committed to the success of this important research work.

a. **Sucharew H**, Khoury JC, Xu Y, Succop P, Yolton K. NICU Network Neurobehavioral Scale profiles predict developmental outcomes in a low-risk sample. Paediatr Perinat Epidemiol. 2012 Jul;26(4):344-52. PMID: 22686386; PMCID: PMC3376022.
b. **Sucharew H**, Khoury J, Moomaw CJ, Alwell K, Kissela BM, Belagaje S, Adeoye O, Khatri P, Woo D, Flaherty ML, Ferioli S, Heitsch L, Broderick JP, Kleindorfer D. Profiles of the National Institutes of Health Stroke Scale items as a predictor of patient outcome. Stroke. 2013, 44(8):2182-7. PMID: 23704102; PMCID: PMC4190834.
c. [redacted]

B. Positions and Honors

Positions and Employment

2000-2001	Teaching Assistant, Department of Biostatistics, University of Washington, Seattle, WA
2001-2002	Research Assistant, Southwest Oncology Group, Seattle, WA
2002-2005	Statistician, CF Therapeutics Development Network Coordinating Center, Seattle, WA
2005-2009	Research Assistant, Department of Environmental Health, University of Cincinnati, Cincinnati, OH
2010-2011	Research Associate, Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
2011-2013	Instructor, Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
2013-present	Assistant Professor, Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Professional Memberships and Honors

2006-2008	Fellow, Molecular Epidemiology in Children's Environmental Health Training Program, National Institute of Environmental Health Sciences
2010-present	American Statistical Association (ASA)
2013-present	American Heart Association
2013-present	Eastern North American Region (ENAR) of the International Biometric Society

C. Contribution to Science

1. Cystic Fibrosis Therapeutic Studies. My early research and publications were focused on improving outcomes for children with cystic fibrosis (CF). Cystic fibrosis is one of the most common inherited fatal diseases in Caucasians. Improving the care of patients with CF requires the continued search for more efficacious treatments that can potentially modify the natural history of the disease and improve symptom control and prognosis. The clinical trial has been a vital tool for expanding our knowledge of disease and response to therapies and is considered the gold standard for assessing the effectiveness of various therapies and interventions. We were the first study to show the correlation between computed tomography (CT) scores and the clinical outcome of respiratory tract exacerbations in CF patients; providing support for CT use as a surrogate outcome in CF therapeutic studies. This finding is important because using outcome surrogates can decrease both study duration and sample size and has particular relevance in the field of adaptive study design. Because subjects with CF frequently have adverse events (AEs) during clinical trials, interpretation of the safety profile of the therapy being tested, especially for small phase 1 and 2 trials, can be very challenging. In clinical trials, it is critical to know background AE rates in the CF clinical trial population in order to have a reference for determining safety. We presented tables of AE rates for both pediatric (5–17 years old) and adult (≥ 18 years old) placebo subjects for short-term and long-term inhaled therapy trials, and described how these tables can be used for interpreting safety data and study planning. These data have improved safety monitoring in CF clinical trials involving novel inhaled drugs.

   a. Brody AS, **Sucharew H**, Campbell JD, Millard SP, Molina PL, Klein JS, Quan J. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med. 2005; 172(9), 1128-32, PMID 16100015.
   b. **Sucharew H**, Goss CH, Millard SP, Ramsey BW; Cystic Fibrosis Therapeutics Development Network. Respiratory adverse event profiles in cystic fibrosis placebo subjects in short- and long-term inhaled therapy trials. Contemp Clin Trials. 2006;27(6):561-70. PMID: 16875884.

2. Environmental Exposures and Child Health. Exposure to air pollution has been consistently associated with poor respiratory outcomes in children including wheezing, bronchitis, and asthma. Few studies, however, have evaluated the etiology for dry night cough despite cough being among the most common symptoms of pediatric asthma presented to family physicians. I was able to combine my research interest in structural equation modelling techniques and environmental exposures to simultaneously evaluate family, home, health, and environmental factors for association with recurrent dry night cough during early childhood. We found that children who were exposed to the highest tertile of traffic exhaust had 45% increased risk of night cough compared with children less exposed, adding to the body of literature on the

respiratory symptoms. Next, we evaluated the potential effect of traffic exposure on the developing brain and found that traffic exhaust exposure during infancy was associated with higher hyperactivity scores at age 7. When defining allergic outcomes in epidemiology studies, results of the skin prick test (SPT) panel are often dichotomized as positive/negative or categorized based on the number of positive responses. In a novel application of Item Response Theory to SPT responses, we showed the benefits of this method over traditional approaches for evaluating atopy. Essential elements play a challenging role in child health and development, as both high and low levels may exert a poor impact. Manganese (Mn) is an example of such and while it plays a vital role in brain growth and development, excessive exposure can result in neurotoxicity. Using penalized splines, we found that both low and high Mn concentrations in blood and hair were negatively associated with child IQ scores.

a. **Sucharew H**, Ryan PH, Bernstein D, Succop P, Khurana Hershey GK, Lockey J, Villareal M, Reponen T, Grinshpun S, LeMasters G. Exposure to traffic exhaust and night cough during early childhood: the CCAAPS birth cohort. Pediatr Allergy Immunol. 2010; 21(2), 253-9, PMID 19824943, PMC
b. Newman NC, Ryan P, Lemasters G, Levin L, Bernstein D, Hershey GK, Lockey JE, Villareal M, Reponen T, Grinshpun S, **Sucharew H**, Dietrich KN. Traffic-related air pollution exposure in the first year of life and behavioral scores at 7 years of age. Environ Health Perspect. 2013;121(6):731-6. PMCID: PMC3672910.
c. **Sucharew H**, Khoury JC, Rao MB, Succop P, Bernstein D, Ryan PH, LeMasters G. Predicting allergic disease at age four using an atopy predisposition score at age two: the application of Item Response Theory. Pediatric Allergy and Immunology. 2012; 23 (2): 195-201. PMID 22192382. [Selected for Editor's Choice March 2012 issue]
d. Haynes EN, **Sucharew H**, Kuhnell P, Alden J, Barnas M, Wright RO, Parsons PJ,Aldous KM, Praamsma ML, Beidler C, Dietrich KN. Manganese Exposure and Neurocognitive Outcomes in Rural School-Age Children: The Communities Actively Researching Exposure Study (Ohio, USA). Environ Health Perspect. 2015 Apr 22. PMID: 25902278.

3. Stroke Research. Initial National Institutes of Health Stroke Scale (NIHSS) score is highly predictive of outcome after ischemic stroke. The total score (range 0 to 42) is comprised of 15 items with individual scores ranging between 0 and 4. We examined whether grouping strokes by presence of individual NIHSS symptoms could provide prognostic information additional or alternative to the NIHSS total score. This study showed that the latent class analysis method of analyzing NIHSS items provides an alternative approach for summarizing prognostic information for forecasting functional outcome and death compared with using the raw NIHSS total score. In particular, two symptom profiles with identical median NIHSS total scores but with widely disparate outcomes were identified. These profiles were recently validated in an acute cohort suggesting a reliable approach to capture the true response patterns that are associated with functional outcome and mortality post stroke. With the recent findings that timely endovascular therapy may improve outcomes in ischemic stroke patients with confirmed large vessel occlusions (LVO), there is now a clinical need for accurate initial triage of patients to hospitals where these therapies are available. To address this need, we derived and validated a new practical neurologic scale, the Cincinnati Prehospital Stroke Severity Scale (CPSSS), in prediction of severe ischemic stroke and LVO.

a. **Sucharew H**, Khoury J, Moomaw CJ, Alwell K, Kissela BM, Belagaje S, Adeoye O, Khatri P, Woo D, Flaherty ML, Ferioli S, Heitsch L, Broderick JP, Kleindorfer D. Profiles of the National Institutes of Health Stroke Scale items as a predictor of patient outcome. Stroke. 2013, 44(8):2182-7. PMCID: PMC4190834.
b. Abdul-Rahim AH, Fulton RL, **Sucharew H**, Kleindorfer D, Khatri P, Broderick JP, Lees KR; VISTA Collaborators. National institutes of health stroke scale item profiles as predictor of patient outcome: external validation on independent trial data. Stroke. 2015;46(2):395-400. PMID: 25503546.
c. Abdul-Rahim AH, Fulton RL, **Sucharew H**, Kleindorfer D, Khatri P, Broderick JP, Lees KR; SITS-MOST Steering Committee. National Institutes of Health Stroke Scale Item Profiles as Predictor of Patient Outcome: External Validation on Safe Implementation of Thrombolysis in Stroke-Monitoring Study Data. *Stroke*. 2015;46(10):2779-85. PMID: 26359360.
d. Katz BS, McMullan JT, **Sucharew H**, Adeoye O, Broderick JP. Design and Validation of a Prehospital Scale to Predict Stroke Severity: Cincinnati Prehospital Stroke Severity Scale. Stroke. 2015. PubMed PMID: 25899242.

Complete List of Published Work in MyBibliography: http://www.ncbi.nlm.nih.gov/sites/myncbi/10mIFUdkMgkA2/bibliography/47756713/public/?sort=date&direction=ascending.

D. Research Support

Active:

PFA-072313 Shah (PI) 07/01/2014 – 06/30/2017
PCORI
Improving post-discharge outcomes by facilitating family-centered transitions from hospital to home
Role: Biostatistician

Shah (PI) 01/04/2016 – 04/28/2017
PCORI - Supplement
Improving post-discharge outcomes by facilitating family-centered transitions from hospital to home
Goal: Our overarching goal is to improve the outcomes of hospital to home transitions for acutely ill hospitalized children and their families. The goal of this supplement is to evaluate a phone call shortly after discharge in improving patient outcomes.
Role: Biostatistician

R34 MH101155-01 Brinkman (PI) 04/01/2014 – 03/31/2017
NIMH
Developing New Technologies to Improve ADHD Mediation Continuity
Role: Biostatistician

R01 (Kleindorfer/Khoury) 04/01/2015 – 03/31/2020
NIH - Resubmission
Comparison of Hemorrhagic & Ischemic Stroke Among Blacks and Whites
Goal: Tracking of population-based stroke incidence in the Greater Cincinnati and Northern Kentucky region, with special emphasis on stroke in the young and stroke recurrence.
Role: Co-I

Place Outcomes Research Award Brady/Heather (PIs) 07/01/2014 – 06/30/2016
Internal Grant
Develop and Evaluate Supplemental Oxygen Data Displays in the Clinical Setting
Role: Biostatistician

Shah (PI) 03/01/2016 – 02/28/2017
APA
Effect of Parental Adverse Childhood Experiences and Resilience on Outcomes After Pediatric Discharge
Goal: The objectives of this proposal are to determine the prevalence of ACEs and levels of resilience among the parents of hospitalized children, their association with a parent's post-discharge coping, and their association with their child's rate of unplanned post discharge utilization.

ARC Lilliam Abroggio (PI) 01/01/2016 – 12/31/2017
Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency medicine (CARPE DIEM)"
Role: Biostatistician

Completed:

P50 NC 44283 Broderick/Khoury (PI/Core B PI) 07/01/2008 – 04/30/2016
NINDS
Recanalization Therapies and Markers of Stroke Outcome

The long-term goal of this program project grant (an application to the SPOTRIAS program – Specialized Program of Translational Research in Acute Stroke) is to improve the early recanalization of occluded arteries in patients with acute ischemic stroke without compromising safety.
Role: Co-I

R21ES021106 Haynes/Sucharew (PI/subsite PI) 07/09/2012 – 06/30/2015
CCHMC/UC
Multiple Risk Factors and Neurodevelopment Deficits in Rural Appalachian Children
Goal: The goal of this study is to assess the impact of Mn exposure on neurocognition in an Appalachian American cohort of school-aged children.
Role: PI of subsite

U19HS021114 Brady (PI) 09/01/2013 – 08/31/2015
Agency for Healthcare Research and Quality
Centers for Education and Research on Therapeutics (CERTs)
Evaluating Huddle Effectiveness
Role: Biostatistician

K23 MH083027 Brinkman (PI) 01/01/2010 – 03/16/2015
NIMH
Medication Continuity in Children Treated for ADHD
The primary goal of this project is to develop expertise for becoming an independent investigator in the study of medication continuity in children with ADHD cared for in primary care settings.
Role: Biostatistician

R01 NS30678 Kissela/Kleindorfer (PIs) / Khoury (Subsite PI) 07/01/2009 – 06/30/2014
NINDS/NIH
Hemorrhagic and Ischemic Stroke Among Blacks and Whites
Some of the major goals of this project are to study temporal trends in the incidence rate, causes, treatment and outcome of stroke in a biracial metropolitan population of 1.3 million of whom 15% are black (2000 Census), and compare these data with those collected using the same methodology during earlier years of the study.
Role: Biostatistician

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Romick-Rosendale, Lindsey

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Assistant Professor, Pathology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Marietta College, Marietta, Ohio	BS	05/2007	Chemistry
Miami University, Oxford, Ohio	PHD	12/2011	Chemistry
Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio	Postdoctoral Fellow	03/2014	Hematology/Oncology
University of Cincinnati, Cincinnati, Ohio	NIH training grant	03/2014	NRSA-T32 NIH Training Grant: Environmental Carcinogenesis

A. Personal Statement

I am the Director of the NMR-Based Metabolomics Core with core responsibilities and research focusing on the use of NMR and MS-based metabolomics as a tool in the study of disease diagnostics and drug surveillance, both in the areas of clinical medicine and basic research. My graduate career focused on the use of NMR-based metabolic profiling to evaluate mouse models of human disease, as well as the effects of various diseases and disorders on metabolic pathways through the analysis of human biological fluids (urine, feces, blood, etc.). My experiences at Miami University under the guidance of Dr. Michael Kennedy, Ohio Eminent Scholar, coupled with my postdoctoral training under Dr. Susanne Wells prepared me to take on a leadership role in the field of metabolomics at Cincinnati Children's Hospital. My close proximity to pediatric hematologists, oncologists and pathologists has allowed me to establish collaborations with them, in which I utilize biological fluids and tissue biopsies from their patients in an effort to identify markers of the diseases and drug treatment regimens that they are studying. My goal is to demonstrate the power of metabolomics as a desirable tool to allow clinicians and basic scientists to better understand the biochemical pathways that are at play during disease onset, disease progression and therapeutic intervention. With this goal in mind, I am excited for the opportunity to collaborate with Dr. Ambroggio on her proposal. As such I will provide guidance and the necessary resources for Dr. Ambroggio to be successful in her application of NMR metabolomics to the field of pediatric pneumonia.

1. Romick-Rosendale LE, Hoskins EE, Privette Vinnedge LM, Foglesong GD, Brusadelli GD, et al. Defects in the fanconi anemia pathway in head and neck cancer cells stimulate tumor cell invasion through DNA-PK and Rac1 signaling. Clin Cancer Res. 2015 Nov 24. PubMed PMID 26603260.

2. Romick-Rosendale LE, Brunner HI, Bennett MR, Mina R, Nelson S, et al. Identification of urinary metabolites that distinguish membranous lupus nephritis from proliferative lupus nephritis and focal segmental glomerulosclerosis. Arthritis Res Ther. 2011; 13(6):R199. PubMed PMID: 22152586; PubMed Central PMCID: PMC3334650.
3. Romick-Rosendale LE, Schibler KR, Kennedy MA. A Potential Biomarker for Acute Kidney Injury in Preterm Infants from Metabolic Profiling. J Mol Biomark Diagn. 2012 Feb; Suppl 3PubMed PMID: 25035813; PubMed Central PMCID: PMC4096988.

4. Romick-Rosendale LE, Lui VW, Grandis JR, Wells SI. The Fanconi anemia pathway: repairing the link between DNA damage and squamous cell carcinoma. Mutat Res. 2013 Mar-Apr; 743-744:78-88. PubMed PMID: 23333482; PubMed Central PMCID: PMC3661751.
5. Romick-Rosendale LE, Legomarcino A, Patel NB, Taft D, Morrow AL, et al. Prolonged antibiotic use induces intestinal injury in mice that is repaired after removing antibiotic pressure: Implications for empiric antibiotic therapy. Metabolomics. 2014 February; 10(1):8-20. PubMed PMID: 26273236; PubMed Central PMCID: PMC4532301

My NCBI Bibliography

B. Positions and Honors

Positions and Employment

2007 - 2011	Graduate Teaching Assistant, Miami University, Oxford, OH
2012 - 2014	Postdoctoral Fellow, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
2014 -	Assistant Professor, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
2014 -	Assistant Professor, University of Cincinnati College of Medicine, Cincinnati, OH

Other Experience and Professional Memberships

2006 -	Member, American Chemical Society
2014 -	Member, National Association of Professional Women
2014 -	Member, Metabolomics Society

Honors

2005	The Ellis L. and Jennie Mae Krause Memorial Scholarship, Marietta College
2006	The LaVallee Award in Chemistry, Marietta College
2007	Miami University Charcher's Summer Research Scholarship, Miami University
2010	Experimental Nuclear Magnetic Resonance Conference Travel Award, Experimental Nuclear Magnetic Resonance Conference
2010	Miami University Research Graduate Assistantship (RGA), Miami University

C. Contribution to Science

1. Metabolomics was first defined as "the quantitative measurements of the multi-parametric metabolic response of a living system to pathophysiological stimuli or genetic modifications". The technique has been minimally utilized thus far in studies of human disease due to the complexity of the organism; however, it has shown to be a potentially useful tool in the area of biomarker identification in a select number of diseases. Metabolomics is the study of an organism's metabolome, which makes this a powerful "omics" technique because the metabolome is downstream of both the genome and proteome and is complementary to other "omic" methods. Metabolomics has been employed in drug surveillance as well as disease diagnosis, identification of changes in metabolites associated with cell apoptosis, cancer cell growth, proliferation rates and metabolic effects related to the Warburg hypothesis of modified energy production. My colleagues and I were able to utilize NMR-based metabolomics to identify potential markers of acute kidney injury (AKI) in preterm infants, which is an otherwise difficult preterm complication to diagnose using conventional methods. Employing the same NMR techniques, we were also able to identify key metabolic changes resulting from the development of lupus nephritis that may lead to improved personalized care in this patient population. Defining changes in the metabolome related to disease onset and progression in any patient population would provide significant information about regulatory pathways in disease in general, and should drive the identification of novel disease biomarkers and therapeutic targets.
   a. Romick-Rosendale LE, Brunner HI, Bennett MR, Mina R, Nelson S, et al. Identification of urinary metabolites that distinguish membranous lupus nephritis from proliferative lupus nephritis and focal segmental glomerulosclerosis. Arthritis Res Ther. 2011; 13(6): R199. PubMed PMID: 22152586; PubMed Central PMCID: PMC3334650.

b. Romick-Rosendale LE, Schibler KR, Kennedy MA. A Potential Biomarker for Acute Kidney Injury in Preterm Infants from Metabolic Profiling. J Mol Biomark Diagn. 2012 Feb; Suppl 3 PubMed PMID: 25035813; PubMed Central PMCID: PMC4096988.

2. Fanconi anemia (FA) is a rare disease characterized by congenital defects, bone marrow failure (BMF), and increased susceptibility to cancers. The two predominant cancers are acute myeloid leukemia (AML) and head and neck squamous cell carcinoma (HNSCC). Although FA as a disease is rare, by utilizing whole-exome sequencing data taken from HNC tumors from patients in the general population I was able to show that a subset of primary, therapy-naïve HNSCCs harbor mutations in important DNA repair pathways including FA. As stated previously, individuals with FA have an astonishing probability of 1 in 3 for developing solid tumors, most commonly HNSCC, by age 48. Unfortunately, a concrete explanation for the high HNSCC susceptibility in this disease population had yet to be uncovered. My colleagues and I were able to determine that perturbation of a number of components of the FA pathway lead to increased cancer cell invasion and migration that was at least in part mediated by a Rac1 and DNA-PK signaling cascade. These findings may allow for therapies directed at these signaling networks to improve not only survival of FA HNSCC patients, but also HNSCC patients in the general population harboring tumors with mutations in FA-related genes.
   a. Romick-Rosendale LE, Lui VW, Grandis JR, Wells SI. The Fanconi anemia pathway: repairing the link between DNA damage and squamous cell carcinoma. Mutat Res. 2013 Mar-Apr; 743-744:78-88. PubMed PMID: 23333482; PubMed Central PMCID: PMC3661751.

   b. Romick-Rosendale LE, Hoskins EE, Privette Vinnedge LM, Foglesong GD, Brusadelli GD, et al. Defects in the fanconi anemia pathway in head and neck cancer cells stimulate tumor cell invasion through DNA-PK and Rac1 signaling. Clin Cancer Res. 2015 Nov 24. PubMed PMID 26603260.

3. The human gastrointestinal tract is home to hundreds of species of bacteria and the balance between beneficial and pathogenic bacteria plays a critical role in human health and disease. The human infant, however, is born with a sterile gut and the complex gastrointestinal host/bacterial ecosystem is only established after birth by rapid bacterial colonization. Imbalance in normal, healthy gut flora contributes to several adult human diseases including inflammatory bowel (ulcerative colitis and Crohn's disease) and Clostridium difficile associated disease, and early childhood diseases such as necrotizing enterocolitis. As a first step towards characterization of the role of gut bacteria in human health and disease, my colleagues and I conducted an 850 MHz 1H nuclear magnetic resonance spectroscopy study to monitor changes in metabolic profiles of urine and fecal extracts of 15 mice following gut sterilization by the broad-spectrum antibiotic enrofloxacin (also known as Baytril). We believe that metabolic profiling of mice sterilized by a broad-spectrum antibiotic offers many possibilities for future studies enabling characterization and monitoring of the metabolic signature of specific pathogenic bacteria as they are reintroduced into the host. Obtaining metabolic profiles that can be attributed to specific bacterial species in host biological fluids and analyzing the changes that occur may lead to a better understanding of how certain inflammatory bowel diseases are initiated.
   a. Romick-Rosendale LE, Goodpaster AM, Hanwright PJ, Patel NB, Wheeler ET, et al. NMR-based metabonomics analysis of mouse urine and fecal extracts following oral treatment with the broad-spectrum antibiotic enrofloxacin (Baytril). Magn Reson Chem. 2009 Dec; 47 Suppl 1: S36-46. PubMed PMID: 19768747.

   b. Romick-Rosendale LE, Legomarcino A, Patel NB, Taft D, Morrow AL, et al. Prolonged antibiotic use induces intestinal injury in mice that is repaired after removing antibiotic pressure: Implications for empiric antibiotic therapy. Metabolomics. 2014 February; 10(1):8-20. PubMed PMID: 26273236; PubMed Central PMCID: PMC4532301

D. Research Support

Current Research Support

2015/05/01-2016/05/01
CCHMC Research Innovations Program (RIP) Funding
Title: Identification of Biomarkers of Fanconi Anemia and Head and Neck Cancer by NMR-Based Metabolomics and MS-Based Lipidomics
Role: PI

Completed Research Support

1988/07/01-2014/03/31
T32 ES007250-24, National Institute of Environmental Health Sciences (NIEHS)
STAMBROOK, PETER J. (PI)
Environmental Carcinogenesis and Mutagenesis
Role: TA

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Ziady, Assem Galal

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Boston College, Boston, MA	B.S.	05/1993	Biochemistry
Physiology & Biophysics, Case Western Reserve University, Cleveland, OH	Ph.D.	01/1999	Cell Physiology
Pediatrics, Case Western Reserve University, Cleveland, OH	Fellow	01/2002	Gene transfer/ delivery
Mass Spectrometry Center, The Cleveland Clinic Foundation, Cleveland, OH	Visiting Fellow	9/2003	Protein Mass Spectrometry

A. Personal Statement

The goal of this application is to provide training for the career development of Dr. Lilliam Ambroggio's into an independent investigator with an expertise in delineating the molecular basis of childhood pneumonia using metabolomics. I am a NIH R01 funded investigator and I recently joined the CCHMC Cystic Fibrosis Center. I am an expert in the use of liquid chromatography mass spectrometry to analyze disease pathways based on protein and metabolite profiles. I have trained a number of researchers and academic clinicians that now serve at the rank of Assistant to Associate professor and have performed similar studies to those proposed in Lilliam's proposal but in the study of cystic fibrosis. Furthermore, I direct the CF biomarker analysis core at CCHMC, and I have previously served as Associate Director of Translational Research for 3 years at Emory University. I have also authored a number of reviews and book chapters on the use of mass spectrometry for the study of lung disease.

B. Positions and Honors

Positions and Employment

10/2003-11/2003 Research Associate, Department of Pediatrics, CWRU, Cleveland, OH
12/2003-10/2011 Assistant Professor, Department of Pediatrics, CWRU, Cleveland, OH
08/2006-10/2011 Assistant Professor, Department of Physiology & Biophysics, CWRU, Cleveland, OH
03/2008-10/2011 Assistant Professor, Department of Biomedical Engineering, CWRU, Cleveland, OH
10/2011-10/2014 Associate Professor, Department of Pediatrics, Emory University, Atlanta, GA
04/2012-10/2014 Associate Professor, Department of Pharmacology, Emory University, Atlanta, GA
06/2012-10/2014 Associate Director of CF Basic & Translational Research, Emory University, Atlanta, GA
11/2012-present Associate Professor, University of Cincinnati School of Medicine, Cincinnati, OH
11/2014-present Associate Professor, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Other Experience and Professional Memberships

1999-present American Society of Gene Therapy
1999-2000 Board member of the March For A Cure in Cleveland, OH (CF Foundation)
1999-2006 Technical and scientific consultant for Copernicus Therapeutics, Inc. (Cleveland, OH)

2004-present American Society of Mass Spectrometry
2007-2011 Member, Institutional Animal Care and Use Committee (IACUC) of CWRU
2006 Member, conference committee for Ohio Collaborative Conference on Bioinformatics
2005-2008 Case Western Reserve University representative to the Ohio Supercomputer Center
2005-2007 Member, Advisory Committee for the CWRU Center of Mass Spectrometry and Proteomics
2010-present Member, Cystic Fibrosis Foundation Biomarker Consortium
2013-present Member, Chemical Gene & Cell Therapy Committee, American Society of Gene & Cell Therapy

Honors and Awards

1993 Scholar of the College, Boston College, Boston, MA
1999 Cystic Fibrosis Foundation fellow award
2000 Cystic Fibrosis Foundation fellow award
2000 American Society of Gene Therapy Merit award
2001 Cystic Fibrosis Foundation fellow award
2002 American Society of Gene Therapy, Research Merit award
2002 American Society of Gene Therapy, Excellence In Research award
2003 Cold Spring Harbor Laboratory merit travel award (Vector targeting meeting)
2012 Best scientific publication of the year Award 2012, Department of Pediatrics, Emory University

Patents

2009 Co-inventor on patent EP Patent 2,025,757
2002 Co-inventor on patent EP Patent 1,200,616
2001 Co-inventor on patent WO 1,997,046,100
2001 Co-inventor on patent US 6,200,801
1999 Co-inventor on patent US 5,972,901

C. Contribution to Science (* Corresponding author)

1. Understanding redox mediated regulation of inflammation in cystic fibrosis. We have played a significant role in the field studying the mechanism of the dysfunction of cellular redox balance in CF, chiefly centered on the behavior of Nrf2, a key transcription factor in the antioxidant response element. My research on the dysfunction of antioxidant responses in CF epithelia was the first to report a dysfunction of the ARE that resulted in elevation of steady state H_2O_2 that contributes to inflammation in CF. Inflammation in CF is the chief cause of mortality and morbidity. Therefore, our findings of a pathway that can be modulated to reduce inflammation were very significant. However, the work was not immediately accepted by the community back in 2008. In the past 2 years the work has become more appreciated as others have shown similar findings. Our more recent work on the mechanism of Nrf2 dysregulation that link it to CFTR dysfunction has been completed at a time when our hypothesis is becoming more widely accepted, and the topic of discussions and presentations at national and international CF meetings. Translationally, our work has increased the interest of the CF foundation and our department to target Nrf2 with activators as an anti-inflammatory approach.

    a. **A.G. Ziady*** and J. Hansen. Redox balance in Cystic Fibrosis. *Int J Biochem Cell Biol*. 2014. 52C:113-123. PMCID: PMC4035434
    b. **A.G. Ziady***, A. Sokolow, S. Shank, D. Corey, R. Myers, S. Plafker, T.J. Kelley. Interaction with CREB binding protein modulates the activities of Nrf2 and NF-κB in Cystic Fibrosis Airway epithelial cells. *Am J Physiol Lung Cell Mol Physiol.* 2012. 302(11):L1221-1231. PMCID: PMC3379036
    c. **A.G. Ziady,*** P.B. Davis. Methods for evaluating inflammation in cystic fibrosis. *Methods Mol Biol*. 2011. 742:51-76.
    d. D.P. Nichols, **A.G. Ziady**, S.L. Shank, J.F. Eastman, P.B. Davis. The triterpenoid CDDO limits inflammation in preclinical models of cystic fibrosis lung disease. *Am J Physiol Lung Cell Mol Physiol*. 2009. 297(5):L828-836. PMCID: PMC2777499

e. J. Chen, M. Kinter, S. Shank, C. Cotton, T.J. Kelley, **A.G. Ziady***. Dysfunction of Nrf-2 in CF epithelia leads to excess intracellular H_2O_2 and inflammatory cytokine production. *PLoS ONE.* 2008. 3(10): e3367 doi:10.1371/journal.pone.0003367. PMCID: PMC2563038

2. Nanoparticle-mediated gene transfer and nucleic acid delivery. We have focused our on developing, optimizing, and examining the biology of nucleic acid nanoparticles. For our DNA nanoparticles have set a paradigm for non-viral gene delivery in vivo, and have played a key role in testing them in the clinic. They are also the subject of 6 patents on which I am inventor. In my lab, we have developed imaging techniques that allow us to examine the activity and distribution of this gene delivery agent in vivo using real-time measurements and have made inroads on translating these experiments to human studies. These studies have allowed us to more efficiently examine the effects of repeated administration over time, as this is needed for a non-viral and non-integrating gene expression system. In recent years we have focused on the biology of the nanoparticles in cells by examining the interactome of the particles. We have defined a number of proteins and cellular pathways responsible for the uptake and nuclear delivery of the particles. This is the first time the biology of the particles has been examined. Our goal is to better understand the determinants of successful gene delivery by the particles and manipulate these pathways to enhance the utility of this vector in humans. The long-term goal for the gene therapy work in our lab is to develop DNA nanoparticles that can target specific cell types, including respiratory airway epithelia, hepatocytes, or neurons.

a. D.M. Yurek, A.M. Fletcher, M. McShane, T.H. Kowalczyk, L. Padegimas, M.R. Weatherspoon, M.D. Kaytor, M.J. Cooper, **A.G. Ziady***. DNA Nanoparticles: Detection of long-term transgene activity in brain using bioluminescence imaging. *Mol Imaging.* 2011. 10(5):327-339. PMCID: PMC3173525
b. X. Chen, S. Shank, P.B. Davis, **A.G. Ziady***. Nucleolin-mediated cellular trafficking of DNA nanoparticle is lipid raft and microtubule dependent and can be modulated by glucocorticoid. *Mol Ther.* 2011. 19(1):93-102. PMCID: PMC3017445
c. **A.G. Ziady***, M. Kotlarchyk, L. Bryant, M. McShane, Z. Lee. Bioluminescent imaging of reporter gene expression in the lungs of wildtype and model mice following the administration of PEG- stabilized DNA nanoparticles. *Microsc Res Tech.* 2010. 73(9):918-928.
d. **A.G. Ziady**, C.R. Gedeon, O. Muhammad, V. Stillwell, S. Oette, T. Fink, W. Quan, T. Kowalczyk, S.L. Hyatt, A. Peischl, J.E. Seng, R. Moen, M.J. Cooper, P.B. Davis. Minimal toxicity of stabilized compacted DNA in the murine lung. *Mol. Ther*. 2003. 8(6): 948-956. PM:14664797
e. **A.G. Ziady***, C.R. Gedeon, T. Miller, W. Quan, J.M. Payne, S.L. Hyatt, T. Fink, O. Muhammad, S. Oette, T. Kowalczyk, M.K. Pasumarthy, R. Moen, M.J. Cooper, P.B. Davis. Transfection of airway epithelium by stable PEGylated Poly-L-lysine DNA nanoparticles in vivo. *Mol. Ther*. 2003. 8(6): 936-947. PM:14664796

3. Understanding the molecular basis of CF and other inflammatory diseases. We have developed a line of work in the lab based on our expertise with proteomics, where we use analyses to examine the proteome of disease severity and progression. In non-bias analyses that are not targeted, we have used high throughput proteomics to discover biomarkers of disease. We have also used targeted approaches to look at changes in protein, for example, the modification of albumin with mold toxins or protein changes that make mycobacterium more virulent. Our chief focus lately is the examination of the proteomic underpinnings of CF disease severity and markers of disease progression.
   a. C. Sinha, A. Ren, K. Arora, C.S. Moon, S. Yarlagadda, K. Woodrooffe, S. Lin, J.D. Schuetz, **A.G. Ziady**, and A.P. Naren. PKA and actin play critical roles as downstream effectors in MRP4- mediated regulation of fibroblast migration. Cell Signal. 2015, 27(7):1345-1355. PMID: 25841995
   b. Q. Li, X. Ding, J.J. Thomas, C.V. Harding, N.D. Pecora, **A.G. Ziady**, S. Shank, W.H. Boom, C.L. Lancioni, R.E. Rojas. Rv2468c, a novel Mycobacterium tuberculosis protein that co-stimulates human CD4+ T cells through VLA-5. *J Leukoc Biol*. 2012. 91(2):311-320. PMCID: PMC3290430

c. C.L. Lancioni, Q. Li, J.J. Thomas, X. Ding, M.G. Drage, N.D. Pecora, **A.G. Ziady**, S. Shank, C.V. Harding, W.H. Boom, R.E. Rojas. Mycobacterium tuberculosis lipoproteins induce human memory CD4+ T cell activation via toll-like receptors 1 and 2. *Infect and Immun 2011*. 79(2):663-673. PMCID: PMC3028837
d. I. Yike, A.M. Distler, **A.G. Ziady**, D.G. Dearborn. Mycotoxin Adducts on Human Serum Albumin: Biomarkers of Exposure to Stachybotrys chartarum. *Environ Health Perspect*. 2006. 114(8):1221-1226. PMCID: PMC1552036

D. Research Support

Ongoing Research Support

CFF CCHMC Research Development Program (Clancy) 07/1/2015-06/30/2019
Cystic Fibrosis Foundation
The Biomarkers Analysis and Assay Development Core of the CCHMC RDP encompasses the assays for the center grant. The Core conducts the examination of CFTR responses to available and future potentiators and correctors, the examination of the links between CFTR and the various pathologies of the disease, and the detailed examination of protein interactions that modulate CFTR localization and function.
Role: Biomarker Analysis and Assay Development Core PI

Gilead Sciences Grant (Nichols, Ziady) 07/1/2015-06/30/2016
Testing the effects of azithromycin exposure on established antibiotic resistance pathways in P. aeruginosa CF clinical isolates. We plan to study the proteome of P. aeruginosa following long term exposure to azithromycin.
Role: Contract PI

1R01HL109362-01 (Ziady) 07/1/11- 04/30/16
NIH/NHLBI
Nrf2 dysfunction in CF epithelia. We plan to examine the mechanisms of the dysregulation of Nrf2 in CF airway epithelial cells using proteomic and biochemical approaches.
Role: PI

1R01HL116226-01 (Clancy, Ziady) 09/26/12-06/30/16
NIH/NHLBI
MR predictors of infection, inflammation, and structural lung damage in CF. We aim to use imaging modalities to study early infection and inflammation in the lungs of CF patients.
Role: Co-PI

For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED

PHS 398 OTHER SUPPORT

Provide active and pending support for all senior/key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

There is no "form page" for other support. Information on other support should be provided in the *format* shown below, using continuation pages as necessary. The sample below is intended to provide guidance regarding the type and extent of information requested.
For instructions and information pertaining to the use of and policy for other support, see Other Support in the Supplemental Instructions, Part III, Policies, Assurances, Definitions, and Other Information.
Effort devoted to projects must be measured using person months. Indicate calendar, academic, and/or summer months associated with each project.

SHAH, Samir S.

Active

R01 HL122261 Sara K. Pasquali (PI) 04/01/2014-03/31/2019 0.6 calendar
National Heart Lung Blood Institute $[redacted]
Understanding quality and costs in congenital heart surgery
Role: Co-Investigator
Goal: The objective is to determine better methods of evaluating quality and cost in children undergoing congenital heart surgery.

Octavio Ramilo (PI) 07/01/2015-6/31/2017 0.2 calendar
Governor's Office, State of Ohio $[redacted]
Children's Hospitals Research Initiative in Pneumonia (CHIRP)
Role: Site Principal Investigator
Goal: To focus on improving the etiologic diagnosis of children with pneumonia.

IHS-1306-00811 Samir S. Shah (PI) 05/01/2014-04/30/2017 2.4 calendar
Patient-Centered Outcomes Research Institute $[redacted]
Improving post-discharge outcomes by facilitating family-centered transitions from hospital to home
Role: Principal Investigator
Goal: The objective is to determine the efficacy of a nurse home visit in improving patient and family outcomes following a child's hospitalization for acute illness.

IHS-1306-00811 Samir S. Shah (PI) 01/04/2016-04/28/2017 0.4 calendar
Patient-Centered Outcomes Research Institute $[redacted]
Supplemental Funding: Improving post-discharge outcomes by facilitating family-centered transitions from hospital to home
Role: Principal Investigator
Goal: The objective is to determine the efficacy of a nurse home visit in improving patient and family outcomes following a child's hospitalization for acute illness.

Pending

David Kimberlin (PI) 07/01/2016-06/30/2018 1.2 calendar
National Institute of Allergy and Infectious Diseases $[redacted]
Burden of neonatal herpes simplex virus infections: disease incidence, adequacy of diagnostic assessment and societal costs
Role: Co-Investigator; disease incidence and diagnostic assessment project lead
Goal: The objective is to determine incidences of neonatal herpes simplex virus (HSV) (KID and MDD), quantifying hospital level variation in evaluation of neonates suspected of having HSV (PHIS), determining

the prevalence of mortality among neonates with HSV (KID), and determining the index hospitalization costs and the post-hospitalization costs, including outpatient and subsequent inpatient utilization costs, for neonates with HSV (MDD).

Karen Wilson (PI) 09/01/2016-06/30/2021 1.2 calendar
National Heart, Lung and Blood Institute $[redacted]
Modifiable risk factors for asthma after bronchiolitis
Role: Site Principal Investigator
Goal: The objective is to understand the modifiable risk factors for asthma after bronchiolitis, and to identify targets for personalized preventive interventions to stop asthma from developing in these patients.

OTHER SUPPORT

Maurizio Macaluso, Ph.D.

ACTIVE

ULRRR026314 (Heubi) 07/1/2015 – 06/30/2020 3.6 cal months
CCTST/UC $[redacted]
Clinical and Translational Science Award (BERD)
This is the national consortium of medical research institutions, funded through Clinical and Translational Science Awards (CTSAs), which is working together to:
- Improve the way biomedical research is conducted across the country
- Reduce the time it takes for laboratory discoveries to become treatments for patients
- Engage communities in clinical research efforts
- Train the next generation of clinical and translational researchers

Role: Director/Co-Director of BioMetrics Core

P30 DK078392 (Bezerra) 08/1/2007 - 05/31/2017 0.54 cal months
NIH/NIDDK $[redacted]
Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease
The major goal is to provide core services to advance digestive disease research at Cincinnati Children's Hospital Medical Center and the University of Cincinnati.
Role: Co-Investigator

T32DK007695 (Devarajan) 07/1/2014 – 06/30/2019 0.6 cal months
Research Training in Pediatric Nephrology $[redacted] No salary support
Goal: To foster the development of outstanding clinical or basic science physician investigator and leaders who will meet the tremendously underserved academic workforce needs in Pediatric Nephrology.
Role: Mentor

K23 (Reed) 05/1/2014 – 04/30/2018 0.6 cal months
NIH $[redacted] No salary support
Decreasing teen STI prevalence through universal emergency department screening
Goal: The objective of this proposal is to design and test the feasibility and effectiveness of a universal CT/GC screening program in the ED.
Role: Co-Investigator

U18HS016957 Lannon (PI) 09/30/2011 – 08/31/2016 0.72 cal months
CERTs (Agcy for Healthcare Research and Quality) $[redacted]
Pursuing Perfection in Pediatric Therapeutics
The CERTs Research Center (RC) will focus on improving outcomes for children by optimizing the use of therapeutics. Additional sub-themes, with expected impact beyond pediatrics, are *pharmacogenomics and personalized medicine, patient safety, and quality improvement methodology*.
Role: Co-Investigator

OPQC Anderson Center 07/01/2015 – 06/30/2016 0.72 cal months
NAS – Federal $[redacted]
On behalf of the Ohio Perinatal Quality Collaborative, the Anderson Center at Cincinnati Children's Hospital Medical Center will provide the project management, QI design and dissemination oversight, and data management and analysis support for the four years of the proposed project.
Role: Co-Investigator

(Kim, Macaluso, Liu, Zou) 01/01/2015 – 12/31/2018 0.36 cal months
PCORI $[redacted]
Propensity Score-based Methods for CER Using Multilevel Data: What Works Best When

Goal: The goal of this project is to investigate how to optimally extend the PS methodology and identify what works best when. An additional goal is to develop a novel imputation-based sensitivity analysis approach and to identify valid and most efficient PS methods for two existing CER studies.
Role: Co-Investigator

1KL2TR001426-01 (Tsevat) 08/14/2015 – 03/31/2019 1.2 cal months
NIH/CCTST $[redacted]
The goal of the Institutional CTSA is to create a research environment that facilitates translating discoveries to clinical application. The KL2 is the mentored career development portion of the CTSA.
Role: Site PI

PENDING

(Piyathilake) 07/1/2016 – 06/30/2021 1.8 cal months
UAB $[redacted]
(PQ 10) Interplay between cervical microbiome and HPV and risk of CIN risk after LEEP
Goal: The goal is to lead the analysis of the microbial 16S and whole metagenome shotgun DNA sequencing data and coordinate all analytic work. Also, to provide expertise in epidemiology, biostatistics and clinical data management in support of this project
Role: PI/CCHMC Sub

K23 (Nehus) 02/12/2016 – 01/31/2021 no salary support
NIH $[redacted]
Early Kidney Injury and Adipokine Dysregulation in Severe Obesity
Goal: The proposed study will investigate the association of adipokine abnormalities with early kidney disease in severely obese adolescents undergoing weight reduction surgery. Improved understanding of obesity-mediated kidney disease will support future studies that identify, treat, and prevent kidney disease in children with severe obesity.
Role: Mentor

U24OD023376-01 (Macaluso/White) 09/1/2016 – 08/31/2023 4.8 cal months
NIH $[redacted]
The ECHO Data Analysis Center at Cincinnati Children's
Goal: The Environmental Influences on Child Health Outcomes (ECHO) program has been established to investigate the longitudinal impact of prenatal, perinatal, and postnatal environmental exposures (physical, chemical, biological, behavioral, social) on pediatric health outcomes with high public health impact in the following four areas: 1) upper and lower airway, 2) obesity, 3) pre-, peri-, and postnatal outcome, and 4) neurodevelopment.
Role: PI

OVERLAP

None

For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED

PHS 398 OTHER SUPPORT

Provide active and pending support for all senior/key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

There is no "form page" for other support. Information on other support should be provided in the *format* shown below, using continuation pages as necessary. The sample below is intended to provide guidance regarding the type and extent of information requested.
For instructions and information pertaining to the use of and policy for other support, see Other Support in the Supplemental Instructions, Part III, Policies, Assurances, Definitions, and Other Information.
Effort devoted to projects must be measured using person months. Indicate calendar, academic, and/or summer months associated with each project.

Ruddy, RM

ACTIVE/PENDING

1 U03MC22684 (Ruddy) 9/01/2011 – 08/31/2019 2.4 Cal
HRSA $[redacted]
EMSC: Network Development Demonstration Project
This funding supports the Pediatric Emergency Care Applied Research (PECARN) Network.
Role: PI

Gerber Pediatric Research Grant 1/2014 – 12/2016 0.3 cal
Gerber Foundation $[redacted]
Clinical prediction model for community-acquired pneumonia
This project will use clinical data and the biomarker procalcitonin to develop a severity score used to predict the development of severe disease and complications in children with community-acquired pneumonia, the most common serious bacterial infection children and leading killer of children worldwide.
Role: Co-I

1R01HD071915-01 (Schnadower) 12/10/2013-11/30/2018 0.2 cal
NIH/NICHD $[redacted]
Impact of Emergency Department Probiotic Treatment of Pediatric Gastroenteritis
We propose to study the effectiveness and side effects of a Probiotic, LGG, in treating children with Gastroenteritis. If successful, this therapeutic intervention would be the first Treatment that actually changes the disease process and would represent an enormous public health advance both in the US, and potentially, globally.
Role: Co-I

R21 (Mahajan) 8/21/2015-4/30/2020 0.6 cal
NIH $[redacted]
RNA Biosignatures: A Paradigm Change for the Management of Young Febrile Infants
This project will study how to: (1) improve the precision and narrow the confidence intervals around the diagnostic accuracy of RNA biosignatures in this population; (2) assure that the discriminatory expression profiles among febrile infants in the studied categories remain stable over time and understand the impact of antipyretics and/or antibiotics on the biosignatures; (3) utilize the technology efficiently at the bedside.
Role: Co-I

1 U03 Admin Supplement (Ruddy) 09/01/15 – 08/31/16 1.8 cal
HRSA $[redacted]
EMSC: Network Development Demonstration Project
This funding supports Dr. Ruddy's role as the CHAIR of the Pediatric Emergency Care Applied Research (PECARN) Network
Role: PI

1 U03 Admin Supplement (Ruddy) 09/01/15 – 08/31/16 0.0 cal
HRSA $[redacted]
EMSC: Network Development Demonstration Project
This funding supports meetings costs for the PECARN network
Role: PI

OVERLAP
None

For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED
For Non-competing Progress Reports (PHS 2590) – Submit only Active Support for Key Personnel

PHS 398/2590 OTHER SUPPORT

Provide active support for all key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

There is no "form page" for other support. Information on other support should be provided in the *format* shown below, using continuation pages as necessary. ***Include the principal investigator's name at the top and number consecutively with the rest of the application.*** The sample below is intended to provide guidance regarding the type and extent of information requested.
For instructions and information pertaining to the use of and policy for other support, see Other Support in the PHS 398 Part III, Policies, Assurances, Definitions, and Other Information.
Note effort devoted to projects must now be measured using person months. Indicate calendar, academic, and/or summer months associated with each project.

Format

NAME OF INDIVIDUAL
ACTIVE/PENDING

Project Number (Principal Investigator) Source Title of Project *(or Subproject)* The major goals of this project are…	Dates of Approved/Proposed Project Annual Direct Costs	Person Months (Cal/Academic/ Summer)

OVERLAP *(summarized for each individual)*

STRINGER, KATHLEEN

ACTIVE

R01 GM078200 (Rosania, PI) 9/1/12-7/31/16 0.6 CM
NIH $[redacted]
Chemical Address Tags: A Cheminformatics & Image Data Management and Analysis Plan
The goal of this project is to develop machine vision and image analysis tools to relate the chemical structure of small molecules to their subcellular localization as apparent in image data.
Role: Co-Investigator

No number (Stringer, PI) 6/30/15-6/30/16 0.0 CM
American Foundation of Pharmaceutical Education $[redacted]
Pulmonary Delivered Tissue Plasminogen Activator (tPA) Drug Action in the Lungs
The goal of this research is to advance understanding of the molecular mechanisms of tPA drug action in the lungs when given for the treatment of the complex pediatric illness, plastic bronchitis (PB).
Role: PI

R01 GM111400 (Stringer, PI) 4/1/16-1/31/20 2.4 CM
NIH $[redacted]
L-Carnitine Pharmacometabolomics in Sepsis (CaPS)
This project will introduce a personalized medicine approach called pharmacometabolomics to sepsis treatment in an effort to determine which patients are more likely to respond to a new therapy.
Role: PI

PENDING

No number (Stringer, PI) 11/1/16-10/31/20 1.8 CM
FDA $[redacted]
IND119678 Phase II Safety & Efficacy of Inhaled Activase for Acute Plastic Bronchitis
The goal of this project is to test the safety and effectiveness of the designated orphan drug, inhaled tPA, for the treatment of acute exacerbations of plastic bronchitis (PB).
Role: PI

R01 (Rosania, PI) 9/1/16-8/31/21 1.2 CM

NIH $[redacted]
Intracellular Drug Inclusions: Unwanted Side Effect or Active Therapeutic Agent?
The goal of this project is to develop strategies for reducing the incidence of systemic off-target side-effects through improved understanding of drug transport properties; this will be of great benefit to patients across all therapeutic areas.
Role: Co-Investigator

R01 GM078200 (Rosania, PI) 9/1/16-8/31/20 (renewal) 1.2 CM
NIH $[redacted]
Chemical Address Tags: A Cheminformatics & Image Data Management and Analysis Plan
The goal of this project is to develop machine vision and image analysis tools to relate the chemical structure of small molecules to their subcellular localization as apparent in image data.
Role: Co-Investigator

No number (Ambroggio, PI) 11/1/16-10/31/19 1.2 CM
Thrasher Research Fund $[redacted]
Using Metabolite Signatures to Distinguish Viral and Bacterial Pneumonia in Children
We hypothesize that pathogen-specific metabolite profiles can be quantified using NMR which will result in the development of a diagnostic test for timely and accurate diagnosis to permit targeted and effective management of pneumonia.
Role: Co-Investigator

OVERLAP
None

Other Support

SUCHAREW, HEIDI

ACTIVE

IHS -1306-00811 (Shah) 07/01/2014 – 06/30/2017 2.4 calendar months
PCORI $[redacted]
Improving post-discharge outcomes by facilitating family-centered transitions from hospital to home
Goal: Our overarching goal is to improve the outcomes of hospital to home transitions for acutely ill hospitalized children and their families.
Role: Co-I

Place Outcomes (Brady) 07/01/2014 – 06/30/2016 0.72 calendar months
CCHMC $[redacted]
Developing and Evaluating User-Designed Data Displays
Goal: Our long term objective is to partner with end-users to develop data visualizations that organize and display data in a way that informs common decisions made on the frontlines of clinical care.
Role: Co-I

R01NS030678 (Kleindorfer/Khoury) 04/01/2015 – 07/31/2018 4.8 calendar months
NIH - Resubmission $[redacted]
Comparison of Hemorrhagic & Ischemic Stroke Among Blacks and Whites
Goal: Tracking of population-based stroke incidence in the Greater Cincinnati and Northern Kentucky region, with special emphasis on stroke in the young and stroke recurrence.
Role: Co-I

R34 MH101155-01 (Brinkman) 04/01/2014 – 03/31/2017 0.6 calendar months
NIMH $[redacted]
Developing New Technologies to Improve ADHD Mediation Continuity
Role: Biostatistician

IHS -1306-00811 (Shah) 01/04/2016 – 04/28/2017 0.48 calendar months
PCORI - Supplement $[redacted]
Improving post-discharge outcomes by facilitating family-centered transitions from hospital to home
Goal: Our overarching goal is to improve the outcomes of hospital to home transitions for acutely ill hospitalized children and their families.
Role: Co-I

Shah, Anita 03/01/2016 – 02/28/2017 0.48 calendar months
APA $[redacted]
Effect of Parental Adverse Childhood Experiences and Resilience on Outcomes After Pediatric Discharge
Goal: The objectives of this proposal are to determine the prevalence of ACEs and levels of resilience among the parents of hospitalized children, their association with a parent's post-discharge coping, and their association with their child's rate of unplanned post discharge utilization.
Role: Biostatistician

Academic Res Committee Funding (Ambroggio) 1/12/2016 – 1/11/2018 1.8 calendar months
CCHMC $[redacted]
Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency medicine (CARPE DIEM)
Goal: The objective of this study is to identify distinct metabolite profiles for the major classes of pathogens that cause CAP in children (e.g. virus, typical and atypical bacteria). Urine, blood samples, and nasopharyngeal swabs will be collected from children diagnosed with CAP in the Emergency Department or who are hospitalized at Cincinnati Children's Hospital Medical Center. All urine samples will then be evaluated using

quantitative 1H-nuclear magnetic resonance. Advanced statistical methods such as partial least squares-discriminant analysis will be applied to the identified metabolite dataset to determine unique metabolite profiles.
Role: Co-I

PENDING

UC CARES (Cecil) 09/01/2016 – 06/30/2021 1.8 calendar months
NIH/UC (sub) $[redacted]
Developmental Effects of Manganese Exposure in Rural Adolescents: The CARES Cohort Comes of Age
Goal: This project will innovatively examine the impact of manganese exposure along with other known neurotoxicants, including lead and tobacco smoke, in a follow-up study of a rural, Appalachian cohort. We will examine the impact of these exposures on neurobehavior, postural balance and gait, brain anatomy and physiology.
Role: Biostatistician

U24OD023376-01 (Macaluso/White) 09/01/2016 – 08/31/2023 1.2 cal months
NIH $[redacted] YRS 3-7 only
The ECHO Data Analysis Center at Cincinnati Children's
Goal: The Environmental Influences on Child Health Outcomes (ECHO) program has been established to investigate the longitudinal impact of prenatal, perinatal, and postnatal environmental exposures (physical, chemical, biological, behavioral, social) on pediatric health outcomes with high public health impact in the following four areas: 1) upper and lower airway, 2) obesity, 3) pre-, peri-, and postnatal outcome, and 4) neurodevelopment.
Role: Co-I

R34 (Brinkman) 04/01/2017 – 03/31/2019 0.72 cal months
NIH $[redacted] YR3 only
Improving Medication Continuity among Adolescents with ADHD
Goal: The overall objective of this application is to develop and test a multi-component intervention that systematically identifies and targets aspects of the UTBC model most
relevant for each adolescent with poor ADHD medication continuity.
Role: Co-I

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Lilliam		Ambroggio		PD/PI	[redacted]	9	0	0	[redacted]	[redacted]	[redacted]

Total Funds Requested for all Senior Key Persons in the attached file **0.00**

Additional Senior Key Persons: File Name: **Total Senior/Key Person** [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	[redacted]

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Federal (MTDC)	8	[redacted]	[redacted]
		Total Indirect Costs	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Arif Karim, 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: BUDGET_JUSTIFICATION_AmbroggioK01_2016_07_08.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12210815 Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Lilliam		Ambroggio		PD/PI	[redacted]	9	0	0	[redacted]	[redacted]	[redacted]

Total Funds Requested for all Senior Key Persons in the attached file **0.00**

Additional Senior Key Persons: File Name: **Total Senior/Key Person** [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	[redacted]

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 2**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12210815 Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Federal (MTDC)	8	118,750.00	[redacted]
		Total Indirect Costs	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Arif Karim, 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: BUDGET_JUSTIFICATION_AmbroggioK01_2016_07_08.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Lilliam		Ambroggio		PD/PI	[redacted]	9	0	0	[redacted]	[redacted]	[redacted]

Total Funds Requested for all Senior Key Persons in the attached file **0.00**

Additional Senior Key Persons: File Name: **Total Senior/Key Person** [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	[redacted]

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 3**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Federal (MTDC)	8	[redacted]	[redacted]
		Total Indirect Costs	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Arif Karim, 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: BUDGET_JUSTIFICATION_AmbroggioK01_2016_07_08.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12210815 Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2020 **End Date*:** 03-31-2021 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Lilliam		Ambroggio		PD/PI	[redacted]	9	0	0	[redacted]	[redacted]	[redacted]

Total Funds Requested for all Senior Key Persons in the attached file **0.00**

Additional Senior Key Persons: File Name: **Total Senior/Key Person** [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	[redacted]

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2020 **End Date*:** 03-31-2021 **Budget Period: 4**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2020 **End Date*:** 03-31-2021 **Budget Period: 4**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Federal (MTDC)	8	118,750.00	[redacted]
		Total Indirect Costs	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Arif Karim, 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: BUDGET_JUSTIFICATION_AmbroggioK01_2016_07_08.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12210815 Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Lilliam		Ambroggio		PD/PI	[redacted]	9	0	0	[redacted]	[redacted]	[redacted]

Total Funds Requested for all Senior Key Persons in the attached file **0.00**

Additional Senior Key Persons: File Name: **Total Senior/Key Person** [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	[redacted]

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Cincinnati Childrens Hospital Medical Center

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Federal (MTDC)	8	118,750.00	[redacted]
		Total Indirect Costs	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Arif Karim, 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: BUDGET_JUSTIFICATION_AmbroggioK01_2016_07_08.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12210815 Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

BUDGET JUSTIFICATION

The proposed budget includes expenses specific to the proposed research and training plan. Patient enrollment, data, and molecular and microbiological testing are collected as part of a parent study, *"Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine"* (CARPE DIEM). CARPE DIEM is led by Dr. Todd Florin as the principal investigator **(see Collaborator Letter)**, Dr. Ambroggio as the co-principal investigator, and Drs. Ruddy and Shah **(see Mentor Letters)** as the two senior mentors**.** Dr. Ambroggio in addition to the other members of the team have received extramural funding through FY17 for the infrastructure involved in recruiting participants, sample collection, molecular and microbiological testing of nasopharyngeal swabs and blood specimens and storage for CARPE DIEM. In order to ensure the success of the proposed K01 the budget described below will cover additional NMR spectral acquisition and analysis, urine collection kits for time points in Aim 1 and Aim 3, enrollment and specimen collection for healthy controls and personnel time distinct from CARPE DIEM. In addition the Division of Hospital Medicine devotes "professional" funds for each of its faculty members each year including Dr. Ambroggio to cover additional expenses regardless of grant funding. These professional funds will be used to cover travel to University of Michigan and travel to two national conferences per year.

Personnel Salary Support

Lilliam Ambroggio, PhD, MPH, Principal Investigator (9.0 calendar months in years 1-5): Dr. Ambroggio is an Assistant Professor of Pediatrics in the Divisions of Hospital Medicine and Biostatistics and Epidemiology at Cincinnati Children's Hospital Medical Center (CCHMC). She will devote 75% of her effort to her research and training for the 5 years of this award. She will be directly involved in every aspect of the study including study design, NMR sample preparation and assay, statistical data analysis, direct supervision of project personnel when applicable and manuscript preparation. She will also be responsible for the fiscal oversight of the proposed work. Benefits are calculated at 25%.

Research Support

Other

Cory Pfefferman, Clinical Research Coordinator (2.4 calendar months in years 2, 4 and 5). Ms. Pfefferman works full-time in the Division of Hospital Medicine. She has worked with Dr. Ambroggio as the CRC for the pilot data for this proposal. She will assist with day-to-day activities of the work proposed here including: IRB processes, recruitment and consent of participants on the inpatient service and in the outpatient clinics for the control group, collection of biological specimens, and general organization of documents and protocols, entering electronic medical record data into REDCap and coordinate CRCs in the Emergency Department on project activities. Her effort in years 1 and 3 are covered by external grants that cover the infrastructure of CARPE DIEM, years 2, 4 and 5 will be covered by the K01. Benefits are calculated at 25%. Total salary and benefits are $9,961 in year 2, $10,568 in year 4 and $10,885 in year 5.

Jessi Poteet and Judd Jacobs, Data Management Team. Ms. Poteet and Mr. Jacobs are part of the Data Management Core and manage the master study database, which contains data from the REDCap database, the electronic medical record, the laboratory computer system, the biobanking tracking system, in addition to results from external laboratories not recorded in the patient's EMR (i.e. laboratory tests not ordered for clinical reasons). They manage all data integrity through regular data checks and are responsible for data cleaning of the clinical data extracted from the EMR. In years 1 and 2 of the proposed K01, their initial support is funded through CARPE DIEM, however the last three years during the analysis phase of this proposal their involvement will be important in producing analytic datasets for the PI to use. Total salary and benefits charged to the Data Management Core for Poteet are $4,907 in year 3, $8,087 in year 4 and $8,330 in year 5. Total salary and benefits charged to the Data Management Core for Jacobs are $5,170 in year 3, $5,325 in year 4 and $5,485 in year 5.

Equipment

No additional equipment will be purchased for this proposal. The study includes the use of NMR spectrometers available through the University of Michigan **(see Dr. Stringer's Letter)** and CCHMC **(see Dr. Romick-Rosendale's Letter)**. In year 1, Dr. Ambroggio will receive ample training in all facets of NMR metabolomics by preparing, assaying and quantifying 50 samples from the study under the overall supervision of Dr. Stringer. In addition, Dr. Yeomans (NMR spectromist) and Ms. McHugh at the University of Michigan will be providing Dr. Ambroggio with the hands on training for the preparation and assaying of the samples. The personnel effort

for Dr. Yeomans and Ms. McHugh is included into the cost of the time on the NMR spectrometer for a total per sample cost of $317 in year 1. At CCHMC, as Dr. Ambroggio is preparing, assaying and quantifying all of the samples required for the study, the only charge is for time on the NMR spectrometer which will be $30 per sample in years 1-3. At CCHMC, 150 samples will be assayed in year 1, 350 in year 2 and 175 in year 3.

Supplies

The laboratory test and supplies needed to support this research are budgeted as follows:

Supply	Samples	Cost	Total Cost	Y1	Y2	Y3	Y4/Y5
Home Urine Collection Kits for 2nd and 3rd time point in Aim 1, and 3rd time point in Aim 3.	150	$20	$3,000	$1,000	$2,000	0	0
16S rRNA to aid in identifying unknown pathogens in Aim 1	50	$35	$1,750	0	0	$1,750	0
Viral and bacterial PCR for NP swabs from control samples	145	$100	$14,500	$5,000	$2,500	$6,000	$1,000

Software

The following statistical software will be necessary to perform the proposed analysis.

1. SAS software version 9.3 from SAS Institute Inc., Cary NC, USA is an advanced statistical software package which will be used to accomplish Aims 1-3 of this proposal. However, SAS software is already provided to Dr. Ambroggio and therefore is not included in the K01 budget.

2. Mplus Base Program and Combination Add-On software (includes Mixture and Multilevel analysis packages) is a statistical software package which will enable Dr. Ambroggio to perform structural equation modeling and latent class analysis. This type of modeling procedures have not been well developed in SAS 9.3 software hence the requirement for additional statistical software. The cost for an academic license for this Mplus software is $895 and has been budgeted into year 3 of this award in preparation for the analysis of Aim 2.

3. MetScape 2 is a plugin for Cytoscape, publicly available bioimformatics software used to visualize and interpret data from metabolomics and expression profiling in the context of human metabolism. Pathways are built using an international database stored on NCIBI that integrates data from Kyoto Encyclopedia of Genes and Genomes (KEGG) and Edinburgh Human Metabolic Network (EHMN). As this software is publicly available, no additional costs have been included in the K01 budget.

4. Chenomx NMR suite is commercially available software that allows for identification and quantification of metabolites in NMR spectra. In addition it accounts for specifications of different NMR equipment. As this software is available to Dr. Ambroggio with the permissions of Dr. Stringer and Dr. Rosendale-Romick at University of Michigan and CCHMC respectively, no additional costs have been included in the K01 budget.

Travel and Education

Education: As a member of the faculty at CCHMC and University of Cincinnati (UC), Dr. Ambroggio has tuition remission at UC. Therefore there is no cost for UC courses listed in the training plan.

Meetings with Dr. Stringer (metabolomics mentor from University of Michigan): A key component of Dr. Ambroggio's career development and mentorship plans involve her working with Dr. Stringer and learning how to run and process samples on the NMR and produce a quantified metabolite database that can be used for the proposed analysis. Travel will be from divisional professional funds to help cover the costs of mileage, meals and accommodations when Dr. Ambroggio visits the University of Michigan (see Dr. Shah letter of support).

National Professional Meetings: Dr. Ambroggio will attend two scientific meetings per year for peer networking and presentation of findings. Additionally these national meetings will be a time for her to meet-in-person with Dr. Stringer in years 1-5. Meetings she will consider attending are: Pediatric Academic Societies, Infectious Disease Week, European Society for Pediatric Infectious Diseases, and International Conference of

the Metabolomics Society. She has budgeted between $300 and $1,000 in years 1-5 of the award to attend these conference with additional cost of attendance funded through divisional “professional” funding which are distributed each year to faculty.

Indirect Costs

CCHMC has agreed to waive its usual indirect cost and has included indirect charges at 8% as specified in the RFA.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)
Section A, Senior/Key Person	[redacted]
Section B, Other Personnel	0.00
Total Number Other Personnel	0
Total Salary, Wages and Fringe Benefits (A+B)	[redacted]
Section C, Equipment	0.00
Section D, Travel	0.00
1. Domestic	0.00
2. Foreign	0.00
Section E, Participant/Trainee Support Costs	0.00
1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other	0.00
6. Number of Participants/Trainees	0
Section F, Other Direct Costs	[redacted]
1. Materials and Supplies	[redacted]
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other 1	0.00
9. Other 2	0.00
10. Other 3	0.00
Section G, Direct Costs (A thru F)	[redacted]
Section H, Indirect Costs	[redacted]
Section I, Total Direct and Indirect Costs (G + H)	[redacted]
Section J, Fee	0.00

Funding Opportunity Number: PA-16-190 . Received Date: 2016-07-08T13:23:03.000-04:00

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 10/31/2018

1. Human Subjects Section

Clinical Trial? ❍ Yes ● No

*Agency-Defined Phase III Clinical Trial? ❍ Yes ❍ No

2. Vertebrate Animals Section

Are vertebrate animals euthanized? ❍ Yes ❍ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

❍ Yes ❍ No

If "No" to AVMA guidelines, describe method and proved scientific justification

3. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

❍ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ❍ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

5. Inventions and Patents Section (RENEWAL)

*Inventions and Patents: ❍ Yes ❍ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ❍ Yes ❍ No

6. Change of Investigator / Change of Institution Section

❑ Change of Project Director / Principal Investigator

Name of former Project Director / Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001
Expiration Date: 10/31/2018

Introduction	
1. Introduction to Application (RESUBMISSION)	1_Introduction.pdf
Candidate Section	
2. Candidate Information and Goals for Career Development	2_Candidate_Information_2016_07_08.pdf
Research Plan Section	
3. Specific Aims	3_Specific_Aims.pdf
4. Research Strategy*	4_Research_Strategy_2016_07_08.pdf
5. Progress Report Publication List (for RENEWAL applications only)	
6. Training in the Responsible Conduct of Research	6_TRAINING_IN_THE_RESPONSIBLE_CONDUCT_OF_RESEA.pdf
Other Candidate Information Section	
7. Candidate's Plan to Provide Mentoring	
Mentor, Co-Mentor, Consultant, Collaborators Section	
8. Plans and Statements of Mentor and Co-Mentor(s)	8_Mentor_Letters_of_Support_2016_07_08.pdf
9. Letters of Support from Collaborators, Contributors, and Consultants	Combined_Letters_of_Support.pdf
Environment and Institutional Commitment to Candidate Section	
10. Description of Institutional Environment	10_Description_of_the_Institutional_Environmen.pdf
11. Institutional Commitment to Candidate's Research Career Development	11_Institutional_Commitment_Letter_2016.pdf
Human Subject Section	
12. Protection of Human Subjects	12__Human_Subjects_Research.pdf
13. Data Safety Monitoring Plan	
14. Inclusion of Women and Minorities	14_Inclusion_of_Women_and_Minorities_Ambroggio.pdf
15. Inclusion of Children	15_Inclusion_of_Children_Ambroggio_K01.pdf
Other Research Plan Section	
16. Vertebrate Animals	16_Vertebrate_Animals.pdf
17. Select Agent Research	17__Select_Agent_Research.pdf
19. Consortium/Contractual Arrangements	
19. Resource Sharing	
20. Authentication of Key Biological and/or Chemical Resources	
Appendix	
21. Appendix	21_Appendix_A_Inclusion_and_Exclusion_Criteria.pdf 21_Appendix_B_home_urine_collection_instructio.pdf

Tracking Number: GRANT12210815
Funding Opportunity Number: PA-16-190. Received Date: 2016-07-08T13:23:03.000-04:00

PHS 398 Career Development Award Supplemental Form

Citizenship*:

U.S. Citizen or Non-Citizen National?* ☑ Yes ❑ No

If no, select most appropriate Non-U.S. Citizen option

- ❑ With a Permanent U.S. Resident Visa
- ❑ With a Temporary U.S. Visa
- ❑ Not Residing in the U.S.

If with a temporary U.S. visa who has applied for permanent resident status and expect to hold a permanent resident visa by the earliest possible start date of the award, also check here: ❑

1. Introduction: I appreciate the reviewers' comments and the opportunity to resubmit this proposal. I am pleased that the reviewers found my proposal to be "outstanding" and that notable strengths were "the candidate's extensive experience, independence, and productivity in epidemiology" and that the "project is of great importance to children's health." Although all weaknesses noted by reviewers were addressed in this resubmission, specific overarching concerns are mentioned below.

Career Development/Career Goals & Objectives:
"Ambitious schedule for training with 3 courses each in Y1-2" Response: I have taken 2 of these courses since the original submission. In this resubmission, I have decreased the course load to 3 courses over 3 years (**Table 1**); I will focus on molecular epidemiology through experiential learning rather than formal coursework.

"it is not clear how she will achieve her goal of learning how to conduct multi-center studies" Response: I am now a site co-I of the Children's Hospital Initiative for Research in Pneumonia, details in **Section 2, Goal 4**.

Research Plan:
"*The panel was quite enthusiastic about the candidate's potential and project itself and encouraged a resubmission with a restructuring of the research plan. Would be wise if stability across days in normal children were an "aim 1" and the current aim 1 change to "aim 2"."* Response: The proposal now includes 3 aims as suggested by the reviewers. Aim 1 examines diurnal variations in the metabolome of healthy children. Aim 2 (previously Aim 1) differentiates bacterial and viral pneumonia from healthy children. Aim 3 (previously Aim 2) compares longitudinal changes in the metabolome of patients with pneumonia with healthy children to assess the patient's response to therapy.

"The data from the CARPE DIEM study should be presented" Response: Please see **Section 4, Table 3 & 5**.

"Prelim data …are compelling, but it would be helpful to know if the different metabolites … had overlapping profiles across all pathogens" Response: Please see **Section 4, Figure 5** for fold-change differences as suggested by pathogen group compared with healthy controls.

"Aim 1 [Sample Size] It would have been better to keep the initial [viral, bacterial, healthy] groupings" Response: The intent of this aim was to distinguish 3 groups: virus, bacteria, and normal, therefore the preliminary data is now better aligned with the original sample size calculation.

"…what type of clinical variables will be collected and what is likely to be missing" Response: According to the clinical variables collected for the 169 patients with pneumonia already enrolled in the study, no clinical data is missing. Data on clinical variables (variables listed in **Section 4, Table 3**) are collected either prospectively or through the EMR. For missing clinical variables, I will conduct a complete case analysis. It is possible that individual metabolites may not be identified in all samples therefore the metabolites that are reported in at least 90% of the samples will be included in the analyses, **Section 4.C.2e.**

"[the question of] pneumococcal colonization vs. disease and given the estimated 60-70% viral etiology, there is likely insufficient numbers to assess this important question. Suggest this be dropped from a resubmission application." Response: **Section 4.C.3a.** has been revised to better illustrate the intent which was to decrease the potential of misclassifying a patient as being infected with *Streptococcus pneumoniae,* but not to directly test the research question of colonization versus infection.

"…should specify that these samples represent pre-antibiotic samples given the hypothesis of Aim 2. This is important because many children have been seen first in clinic within a few days of presenting to an ED and may already be on antibiotics." Response: Of the patients currently enrolled in CARPE DIEM, 23% are receiving antibiotics prior to the ED **(Table 3).** Prior antibiotic use will be taken into account in the multivariable model discussed in Aims 2 and 3. Importantly none of the patients included in the preliminary data in Aim 3 received antibiotics prior to their first urine sample collection **(Figure 6)**.

Mentor. Co-Mentor, Consultants *"**There is an abundance of mentors in this application. However, the concern is offset by the long history that nearly all of them have in formally mentoring the candidate."*** Response: Each of the five mentors has been specifically chosen to complement the proposal according to their expertise therefore it was felt that a multidisciplinary and dedicated group of mentors was the best option to ensure the success of the candidate and the proposal **(Table 1)**.

2. Candidate's Background

My research program focuses on the development and application of novel diagnostic tools to determine the etiology of community-acquired pneumonia (CAP) in children. My overarching goal is to improve outcomes for children with serious infections by developing methods to facilitate accurate diagnosis and implementing these methods into clinical practice. As such I am pursuing a career combining epidemiological methodology with metabolomics, "epi-metabolomics", an emerging field that quantifies small molecules produced from the complex biological interaction between the host and the pathogen.[1] The application of metabolomics to pediatric CAP represents an enormous opportunity to advance knowledge in the field and holds promise for identifying diagnostic and prognostic biomarkers. I am uniquely qualified to conduct this research because I have a strong foundation in molecular and cellular biology with clinical epidemiology expertise and training in improvement science. This award will enable me to advance my knowledge and skills in metabolomics so that I can conduct epi-metabolomics studies that are needed to drive precision medicine in pediatric CAP.

I have 7 years of experience in a laboratory-setting conducting molecular biology research. I previously investigated mechanisms of cell cycle dysregulation that lead to tumorigenesis using both animal and cell culture models. From this I gained a desire to translate knowledge from the bench to the bedside and pursued advanced degrees in Epidemiology. My master's thesis investigated the potential factors that lead to poor outcomes in infants diagnosed with herpes simplex virus.[2] I focused my PhD dissertation first on comparing the effectiveness of β-lactam monotherapy and β-lactam and macrolide combination therapy on clinical outcomes in the treatment of children hospitalized with CAP. The findings suggested that older children hospitalized with CAP may benefit from use of macrolide antibiotics, likely due to the effect of macrolides on atypical bacteria.[3] Secondly, using multi-level analysis, I also investigated the influence of hospital-level penicillin non-susceptible *Streptococcus pneumoniae* patterns on individual-level antibiotic prescription.[4] Hospitals reporting higher levels of penicillin-resistance among pneumococcal bacteria disproportionately prescribed broad-spectrum antibiotics.[2-4]

During my post-doctoral fellowship, I led a multidisciplinary clinical team to implement national evidence-based recommendations for managing CAP in children. This effort provided me greater insight into clinical decision making regarding CAP in the ED and the inpatient service. Using quality improvement science, we were able to increase guideline recommended prescribing to 100% from a median baseline of <40%.[5] In parallel, I received funding from the Thrasher Research Fund and, in collaboration with pediatric radiologists, evaluated the diagnostic accuracy of lung ultrasonography (LUS) compared with chest radiography (CXR) in detecting pneumonia using chest computed tomography (CT) as the gold standard for detection. Our findings suggest that LUS is as accurate as CXR when compared with chest CT for detecting consolidation and pleural effusion in children.[6] Although imagining is useful in the management of CAP, the biggest limitation of any imaging modality is the inability to reliably identify the causative pathogen of CAP.

My exploration of the scientific literature for innovative methods to differentiate bacterial and viral CAP led to recent applications of metabolomics in the field of infectious diseases.[7-9] To gain a better understanding of this new field, I participated in a metabolomics workshop in 2013 at the University of Alabama. It was clear that metabolomics with an epidemiological population health perspective could support the development of a diagnostic test to differentiate viral and bacterial pathogens in CAP. As an Assistant Professor of Pediatrics in the Divisions of Hospital Medicine and Biostatistics and Epidemiology I was awarded two Cincinnati Children's Hospital Medical Center (CCHMC) awards and was a co-investigator on a Gerber Foundation grant. These grants have enabled me to establish and sustain the study infrastructure used in the proposed research and to obtain the preliminary data presented for all aims. These experiences have also uncovered critical areas in training and knowledge that are necessary to enable my independence as an investigator who conducts epi-metabolomics studies for common childhood infectious diseases such as CAP.[10]

Career Goals and Objectives

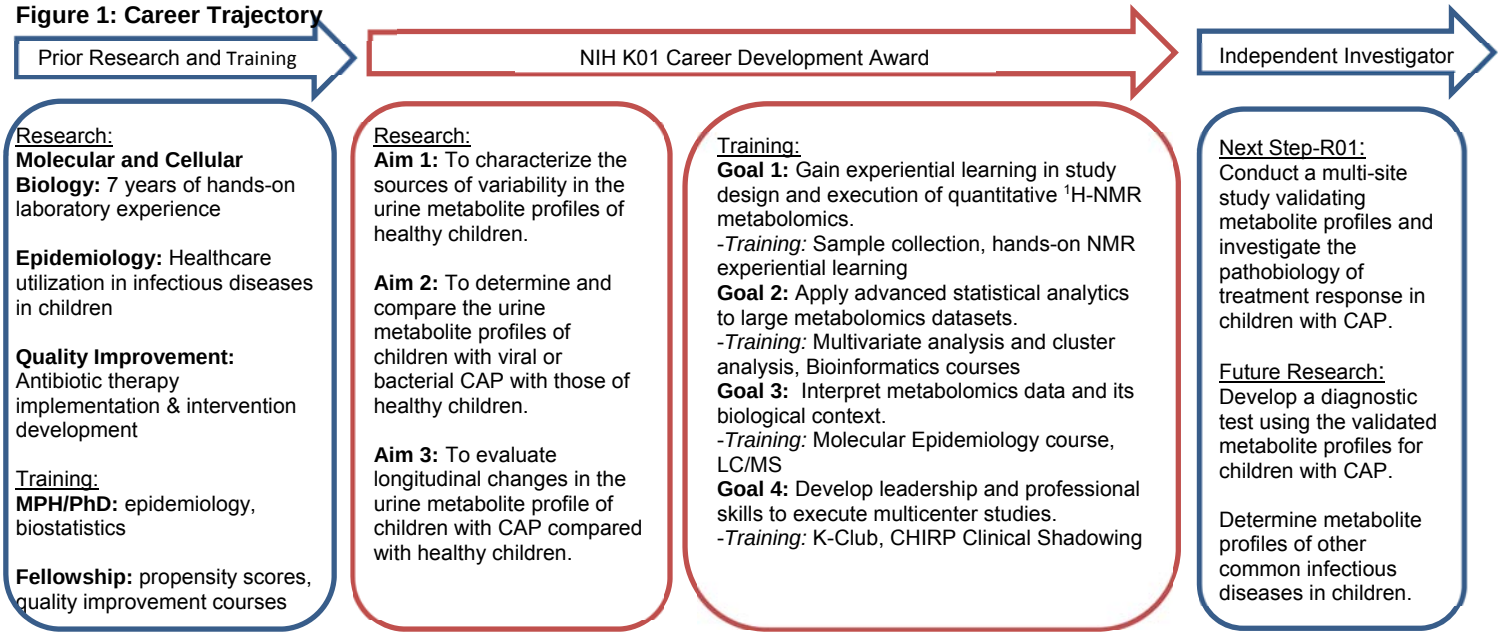
As a field, epidemiology is moving toward systems biology to better identify etiology and underlying disease risk factors.[10] Because there is no fast and reliable diagnostic tool to detect etiology for CAP, new diagnostic tests derived from epi-metabolomics studies may lead to a better predictive model for prescribing effective pharmacotherapy, the goal of precision medicine.[11] My *short-term goal* is to identify candidate metabolites that will ultimately be translated to point-of-care tests for rapid pathogen identification. In direct support of this goal, the overall objective of this application is to combine robust clinical data with metabolomics data using

advanced statistical methodologies to inform pathogen-detection in childhood pneumonia **(Figure 1).** This award will provide me with the time, mentorship, hands-on laboratory-based research experience to conduct ^{1}H-NMR and liquid chromatography-mass spectrometry (LC/MS) quantitative metabolomics experiments and gain expertise in cluster analysis and interpretation.

Plan to Generate R01 Support I propose to submit my first R01 by year 4 of this award (Figure 1) and gain independence from my mentorship team. The first 3 years of this award I will work with my mentors to obtain training and practical research experience to give me the skills needed to be an independent investigator in epi-metabolomics research. In year 4, I will design a R01, multi-site study to validate the profiles established in this proposal through established networks within pediatric emergency medicine and pediatric hospital medicine. The R01 will be needed for the direct development of point-of care tests.

Career Development and Training

Figure 1: Career Trajectory



Mentoring Team and Collaborators: My mentorship team includes prominent researchers in their respective fields. Each has strong records of publication, funding and mentoring (**Table 1 and Mentor Statements**). The mentoring committee has been meeting with me on a *quarterly* basis since 2013 to evaluate career progress and will continue to meet to assess my progress toward the training goals and adherence to the timeline in **Table 2**. I meet with Dr. Shah weekly and I have had monthly meetings with Drs. Shah, Ruddy and Florin (since 2012) to discuss the execution of the prospective pneumonia cohort that Dr. Florin and I developed and that will be leveraged for this K01 proposal. Dr. Stringer and I have met in person 2-3 times per year since 2013 and have had more frequent communication via email and phone throughout the development of this proposal. Dr. Macaluso and I have met monthly since my fellowship in 2011; he continues to guide my career as a molecular-based epidemiologist. Dr. Sucharew and I have met biweekly throughout the proposal development. *These established relationships will ensure the success of the proposed work and my development into an independent investigator.*

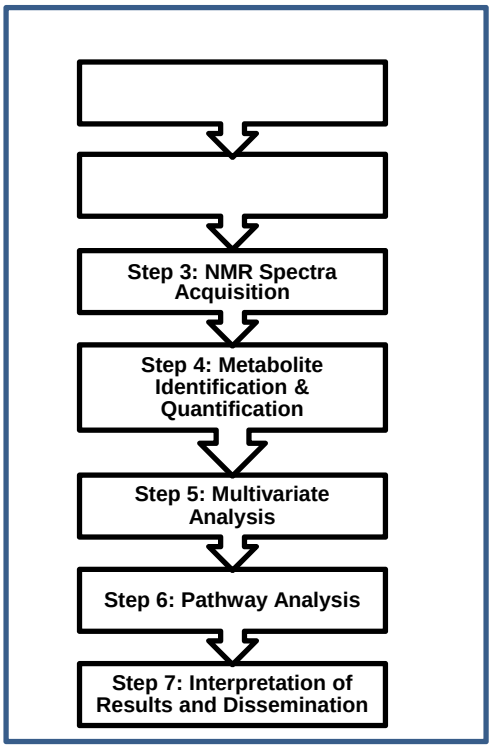
Table 1. Mentoring Committee

Name (Institution)	Associated Aims/Goals*	Meeting Frequency and Format	Area of Expertise and Role
Samir Shah, MD, MSCE (CCHMC, UC) [Primary Mentor]	Research: 1,2,3 Training:1, 3, 4	Weekly meetings (and informally as needed, in person)	**Expertise:** Pediatric community-acquired pneumonia, infectious diseases, hospital medicine, clinical epidemiology, multicenter inpatient studies (Vice Chair of the PRIS Network), leadership skills **Role:** Primary mentor for pneumonia, career guidance, study design and execution, multicenter research
Maurizio Macaluso, MD, DrPH (CCHMC, UC) [Co-Mentor]	Research:1,2,3 Training:3,4	Monthly (in person)	**Expertise:** Advanced epidemiological methods, causal inference, molecular epidemiology **Role:** Career mentor, primary mentor for molecular epidemiology
Kathleen Stringer,	Research: 1,2,3 Training:1, 3, 4	Every other week (by phone/Skype), in person at 3x/year	**Expertise:** quantitative NMR metabolomics, metabolomics study design and execution using biofluids including urine, statistical and

PharmD (UMichigan)			bioinformatics analysis aimed at identifying metabolites of biological relevance, inflammatory lung diseases **Role:** Primary mentor for metabolomics, onsite externship at University of Michigan (3 2-week visits in year 1)
Richard Ruddy, MD (CCHMC, UC)	Research: 1,2,3 Training: 1, 4	Monthly (in person)	**Expertise:** Multicenter pediatric emergency medicine research (nodal PI for PECARN), respiratory diseases in ED, leadership skills, **Role:** Content expertise for pediatric emergency medicine research, career guidance
Heidi Sucharew, PhD (CCHMC, UC)	Research: 1,2,3 Training: 2	Monthly (year 1 and 5, in person) Every other week (years 2-4, in person)	**Expertise:** Cluster analysis, functional data analysis with extension to large scale data such as metabolomics, latent class models **Role:** Statistical mentor on analysis of metabolomics dataset
Additional Collaborators (not on Mentoring Committee)			
Lindsey Romick-Rosendale, PhD	Research:1,2,3 Training:1	Every other week (Years 1-3, in person); Monthly with Dr. Stringer (Year 1-3); Monthly (Year 4-5)	**Expertise:** 6 years of NMR metabolomics experience, complex metabolic pathways involved in diseases/infections **Role:** CCHMC onsite metabolomics expert, guidance in study design, execution and interpretation of NMR metabolomics portion of the proposal
Assem Ziady, PhD	Research:1,2,3 Training:3	Monthly (Year 4-5, in person)	**Expertise:** Proteomic and metabolomics study studies using Liquid Chromatography Mass Spectrometry (LC/MS), inflammatory signaling in children with cystic fibrosis **Role:** LC/MS metabolomics externship in his laboratory in year 4
*Numbers correspond to specific aims (for research) and training goals (below)			

Training Goals:

GOAL 1: Gain experiential and didactic learning in study design and execution of quantitative ^{1}H-NMR metabolomics. *(Key Individuals: Stringer, Romick-Rosendale, Shah, Ruddy)*. My PhD training provided me a strong foundation in epidemiological study design and execution. However, only recently have I had experience designing a prospective cohort (*Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine* (CARPE DIEM)). Specimen collection is the first step in learning the metabolomics work flow **(Figure 2)**. Drs. Shah, Ruddy, Florin and I use a team science approach to execute CARPE DIEM (see letters of support). To accomplish the next steps in the metabolomics work flow **(Steps 2-4, Figure 2)**, collected urine samples will be shipped (50 samples total) to the University of Michigan NMR Metabolomics Laboratory, where, 3 times a year, I will travel to Michigan to prepare and assay samples (steps 2 &3), process spectra (step 4), conduct initial statistical analysis (step 5) and gain experience with pathway analysis (step 6) under the supervision of Dr. Stringer (see letter of support). I will further my expertise by running technical replicates of the same samples in the newly established metabolomics core laboratory at CCHMC under the supervision of Dr. Romick-Rosendale (see letter of support). This strategy will ensure reproducibility of my technique and enable me to independently assay the remaining generated samples. In addition, I will gain a *better understanding of cross-center NMR validation studies*, which is important for future multicenter studies. My hands-on training will also include training in both laboratories in the use of the software, Chenomx (www.chenomx.com), to identify and quantify metabolites from NMR spectra.[12]



GOAL 2: Acquire and apply advanced statistical analytics to large metabolomics datasets. *(Key Individual: Sucharew)*. Through my prior training I have built a strong foundation in statistics that includes regression analysis and longitudinal data analysis. However, to accomplish **Steps 5 and 6 (Figure 2)** I will gain hands on experience performing the analysis for this proposal under the guidance of Dr.Sucharew and using SAS 9.3 (SAS Institute, Cary NC) and MPlus 7.3 (www.statmodel.com). I will take *Structural Equation Modeling* (BE8094) that provides the foundation for pathway analysis, latent variable analysis, mixture models and multi-level models.

GOAL 3: Interpret metabolomics data and its biological context. *(Key Individuals: Shah, Stringer, Ziady, Macaluso).* To achieve **Step 7 (Figure 2),** under the guidance of Drs. Shah and Stringer, I will use current scientific literature to interpret the

identified metabolites from my K01 project and begin planning the logical subsequent aims for the R01 application. In addition, I will gain experience using the bioinformatics tool, Metscape, (http://metscape.ncibi.org/),for metabolomics data interpretation. I will spend 3 months in year 4 in Dr. Ziady's laboratory validating the identity of low abundant metabolites found by NMR using LC/MS.[10] In addition I will learn about designing targeted metabolomics studies using LC/MS in preparation for the R01 application (see letter of support). In parallel, I will also complete the following: *Medical Microbiology* (26MG7003) which discusses host-pathogen interactions; and experiential learning with Dr. Macaluso to discuss criteria for evaluating the medical importance of an identified biomarker in human populations and to address ethical concerns regarding biomarker research.

GOAL 4: Develop leadership and professional skills to execute multicenter studies. *(Key Individuals: Shah, Ruddy,Macaluso)* To continue to develop and strengthen my professional skills I will attend regular monthly meetings of UC's "K Club," which is designed to support K-funded researchers in the transition to independent investigators. I will present findings from this project at national and international meetings. In the fourth year of this award I will take part in an institutional yearly intensive grant-writing workshop to prepare me for writing and submitting an R01. Finally, beginning fall 2015, I have participated as a site co-Investigator in a 2 year, state-wide multicenter study, Children's Hospital's Initiative for Research in Pneumonia (CHIRP). This study collects biological specimens from six children's hospitals within Ohio to develop a genomic "molecular distance to health" score for children with pneumonia.[13] I, in collaboration with Dr. Shah, the site PI, coordinate the enrollment procedures within our institution. This study will give me direct hands-on experience in the organization needed to recruit and collect samples from multiple sites. I will use this experience in developing a multicenter R01 proposal collaborating with inpatient settings and emergency department sites, to validate metabolite profiles identified from this K01 award.

Table 2: Timeline of future training, research and clinical work	**Goal**	**Pre-K01**	**Year 1**	**Year 2**	**Year 3**	**Year 4-5**
Training (in calendar months)			4.8	4.8	3.6	2.4
Courses						
Introduction to Functional Genomics (26GNTD881)	**1**	**X**				
Advanced Statistical Methods in Biomedical Research (BE8064C)	**2**	**X**				
Structural Equation Modeling (BE8094)	**2**		**X**			
Medical Microbiology (26MG7003)	**3**			**X**		
Ethics in Research (26GNTD7003)	**4**				**X**	
Experiential learning						
NMR hands-on learning with Stringer and Romick-Rosendale	**1**		**X**	**X**	**X**	
Multivariate Analysis and Latent Class Modeling with Sucharew	**2**			**X**	**X**	**X**
Advanced Molecular Epidemiological Methods with Macaluso	**3**			**X**	**X**	
LC/MS^2 hands-on learning with Ziady	**3**					**X**
AAMC Early Career Women Faculty Professional Development Seminar	**4**					**X**
Research			6	6	7.2	8.4
	1-4		Aim 1	Aim 1- 2	Aim 2- 3	Aim 2-3
IRB Submission and Approval	1-4	X				
Teaching*			1.2	1.2	1.2	1.2
*I spend 1.2 calendar months total teaching two courses per year: Comparative Effectiveness Research, Advanced Methods in Epidemiology)						
Seminars						
Weekly	Hospital Medicine Research in Progress Meeting, Pediatric Grand Rounds					
Monthly	Division of Biostatistics and Epidemiology Journal Club, Metabolomics Seminar, K-Club					
Conferences (2 annually)						
Infectious Disease Week (Annual Conference of the Infectious Diseases Society of America), Pediatric Academic Societies, Metabolomics Society, European Society for Infectious Diseases Annual Conference, Society for Epidemiologic Research Annual Conference						

3. SPECIFIC AIMS AND HYPOTHESES Community-acquired pneumonia causes substantial morbidity and mortality worldwide.[14] In the U.S., CAP is among the most common and costly causes of hospitalization in young children.[15] Clinical examination and chest radiography do not differentiate between viral and bacterial CAP.[16,17] Conventional diagnostic tests (e.g., sputum cultures) used in adults are not feasible in young children and high yield tests (e.g., lung tap)[18] are too invasive to be routine. Other bacterial diagnostics infrequently identify the causative pathogen (e.g., <7% for blood cultures) limiting their diagnostic utility. Viral tests, while often positive, do not exclude the possibility of bacterial co-infection.[19,20] Therefore, patients with CAP receive empiric antibiotic therapy, which confers no benefit for children with non-bacterial infections, but places children at risk for adverse drug reactions, treatment-related complications (e.g., *Clostridium difficile* colitis) and antibiotic resistance.[21] There is a pressing and unmet need for *non-invasive diagnostic tests that permit accurate and timely clinical decision-making in children with CAP.*[22]

The interaction between pathogen and host results in a unique metabolic profile that is detectable in the host's urine.[7] Quantitative metabolomics can simultaneously detect and quantify metabolites (small molecules, < 1 kDa) in a biological sample using ^{1}H- NMR.[23,24] Quantitative metabolomics testing of the urine is *simple, noninvasive and rapid* (< 1 hour, as opposed to >24 hours for conventional blood culture techniques).[25] We developed a prospective cohort study in our Emergency Department to examine approaches to investigate the etiology of pediatric CAP. Using this cohort, I began investigating the potential for metabolomics to distinguish pathogens in CAP. Over the past 3 years, we enrolled 169 children between 3 months and 11 years of age with CAP. Our preliminary data suggest that distinct urine metabolite profiles cluster by class of pathogen. Evaluating the change in these metabolite profiles in response to antimicrobial therapy also offers a tremendous opportunity to non-invasively gauge appropriateness of initial antibiotic choice. *Urine metabolite profiles may provide a fast, accurate and non-invasive approach for pathogen identification of CAP in children representing a critical innovation in the severely limited current practice*.

My *long-term goal* is to become an independent investigator in infectious diseases epidemiology with a focus on translating bench science research to bedside application. *The overall objective of this application is to combine robust clinical data (e.g. smoking exposure, antibiotic receipt) with metabolomics data using advanced statistical and metabolomics methodologies to inform pathogen-detection in childhood CAP.* I will use a clinical database and specimen biorepository from an established, funded, and fully-operational prospective cohort study of children with CAP. I will acquire knowledge and skills in systems biology sciences and their application to clinically challenging infections such as CAP. To accomplish this objective, I will pursue the following specific aims:

1. **To characterize the sources of variability in the urine metabolite profiles of healthy children.** The *primary hypothesis* is that between subject variability will be larger than within subject variability in the metabolites in the urine of healthy children and the highest proportion of variance will be attributable to age and sex.

2. **To determine and compare the urine metabolite profiles of children with viral or bacterial CAP with those of healthy children.** The *primary hypothesis* is that urine metabolite profiles of children who have viral pneumonia will be uniquely different from those of healthy children. In addition, urine metabolite profiles of children who have *Streptococcus pneumoniae* (the most common bacterial pathogen) or *Mycoplasma pneumoniae* (the most common atypical bacterial pathogen) will be distinct from those of healthy children.

3. **To evaluate longitudinal changes in the urine metabolite profile of children with CAP compared with healthy children.** The *primary hypothesis* is the magnitude of change in the metabolome of a child with viral or bacterial CAP will be greater than the diurnal fluctuation of the metabolome in a healthy child. A *secondary hypothesis* is that longitudinal changes in metabolite patterns of children with CAP will differentiate response from non-response to antibiotics.

Successful completion of these aims will generate preliminary data on distinct metabolite profiles associated with bacterial and viral pneumonia. These findings will inform an R01 application for a large scale, multi-center, validation study that includes more diverse microbial causes of CAP to advance the development of point-of-care diagnostic tests. *This study will further the field of CAP by introducing a method to differentiate bacterial and viral pathogens thereby increasing targeted antibiotic therapy for children*.

4. RESEARCH STRATEGY

4.A. Significance and Scientific Premise In the U.S., most cases of CAP are caused solely by viruses (73-85%) with the remaining 18% caused by bacteria or bacteria-virus co-infections.[26,27] However, CAP is the most common bacterial infection in children, with over 3 million cases each year.[28] In young children, the annual total estimated direct medical costs exceed $1 billion for pneumonia-related hospitalizations.[15,28] Although there are many factors that contribute to this high cost, the major driver is the use of extensive diagnostic testing.[15] Practice variation in the use of diagnostic tests highlights the absence of a gold standard,[29,30] there is no currently available single test that can distinguish viral from bacterial CAP. Therefore biomarkers, such as white blood counts and serum procalcitonin levels are ordered to aid in the decision whether to initiate antibiotic therapy.[20,31] These biomarkers are not sensitive for bacterial CAP (sensitivity <50%).[20,32] The numerous bacterial and viral pathogens that can cause CAP, the lack of a true gold standard diagnostic test and the limited evidence to support a particular diagnostic approach for managing children with CAP contribute to the variation in care. The national pneumonia guideline highlights the need for better diagnostics in CAP by encouraging research on developing "diagnostic tests that are noninvasive yet sensitive and specific in documenting clinical disease caused by single pathogens or combinations of pathogens."[33]

Currently, children with CAP are treated empirically with antibiotics based on age, signs and symptoms, and radiographic imaging, all of which have poor specificity for etiology.[34] This approach leads to overtreatment of children who may have viral CAP, for which antibiotics have no benefit, and under treatment of children with more virulent pathogens such as *Staphylococcus aureus,* for whom conventional antibiotics such as ampicillin are ineffective.[33] The individual consequences of untargeted therapy include overuse of antibiotics, which place children needlessly at risk for common antibiotic side effects (e.g., allergic reactions, diarrhea) to severe complications (e.g., colitis caused by *Clostridium difficile*) and bacterial resistance. Children with *C. difficile* infection experience a 6-fold higher risk of mortality than uninfected children, even when controlling for underlying medical diagnosis.[35] These consequences of unnecessary antibiotic use underscore the need for more efficient and effective diagnostic tools. Identifying a group of metabolites that are by-products of a specific pathogen/host disease process provides a novel and timely aid in the diagnosis, treatment and overall management of CAP in children.

4.B. Innovation: The proposed research is innovative because it uses an unbiased approach, the potential to identify all pathogens with one approach, that integrates robust clinical phenotype data with quantitative NMR metabolomics using novel statistical methods to address the clinically challenging problem of pediatric CAP diagnostics. The advantages of NMR for pathogen identification in children with pneumonia include: 1) rapid results- it takes < 1 hour to process and run a specimen by NMR; 2) non-invasive testing- it can be performed on urine; and 3) simple processing- NMR analysis of urine does not require extraction as required in other biological samples.[36] Only recently has NMR been applied as an analytical platform for metabolomics.[37] Establishing a metabolite profile for a given disease such as CAP can be used to direct targeted metabolomics studies and ultimately the development of point-of-care tests. Currently used microbiologic techniques, ones developed 150 years ago, often take >48 hours to produce results, long past when the patient was initially cared for in the ED. For many acute infections such as CAP, it is impractical and possibly harmful to delay treatment while awaiting a test result. The data from this proposal are expected to drive the development of a quick and reliable diagnostic tool for detecting etiology of CAP in children that will permit targeted management of the most common serious bacterial infection in children.

4.C. Approach

4.C.1. Overall Research Design

CARPE DIEM Cohort: The proposed study, *Metabolomics Evaluation of the Etiology of Pneumonia (MEEP)*, is part of a fully-funded and operational, prospective cohort study of CAP severity and etiology that I co-developed entitled *Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine* (CARPE DIEM). The external funding for CARPE DIEM supports patient recruitment and specimen banking through 2017. We have enrolled 360 children with CAP since initiation of patient recruitment in July 2013 with a majority (n=169) able to provide a urine sample **(Table 3).** A funded K01 award will enable me to assay and analyze the urine specimens, aid in establishing me in the fields of metabolomics and infectious diseases epidemiology, and provide pilot data for an R01 to validate metabolomics profiles.

Table 3: Description of CARPE DIEM Cohort (n=169)	
Age*	N (%)
3 months--1 year	25 (14.8)
1-5 years	93 (55)
6-11 years	51 (30.2)
Male	99 (58.6)
Race	
White	110 (65.1)
Black	52 (30.8)
Other	7 (4.2)
Ethnicity	
Hispanic	6 (3.6)
Season of ED visit	
Winter	53 (31.4)
Spring	33 (19.5)
Summer	32 (18.9)
Fall	51 (30.2)
Exposed to smoke**	64 (37.9)
Antibiotics prior to ED presentation	39 (23)
* Age groups based on the child's immunological and general physiological stage in development.[8] **Smoking exposure is defined as 1 or more person living at the same residence as the patient who smokes.	

Patient Recruitment and Specimen Collection for CARPE DIEM: Trained clinical research coordinators (CRC) staff the ED 12-16 hours/day 7 days/week to identify potential patients. Enrolled patients provide blood, urine, and nasopharyngeal (NP) swab samples. *A strength of this study is that all covariates used in the analysis for all aims are collected prospectively and are available in the medical record. For patients enrolled to date there is no missing data* **(Appendix A).** Specimen processing and storage is facilitated by the Cincinnati BioBank Core Facility (CBCF). For hospitalized patients, blood specimens and urine samples are also collected prior to discharge as a second time point and 14 days after discharge for a third time point (Time points discussed in Aim 1 and 3).

MEEP Healthy Control Cohort: Children, 3 months to 11 years, visiting the Fairfield Primary Care Clinic, a CCHMC-affiliated clinic, for annual check-ups will be eligible as part of the control group **(see letter of support from Dr. Morehous)**. Patients will be excluded if they have had a lower respiratory tract infection <7 days before the visit or have any additional exclusion criteria as described for CARPE DIEM. NP swabs and urine will be collected. Data on the control cohort will include applicable variables as in CARPE DIEM (**Table 3**).

Sample Collection and Storage: The CBCF will receive and store all specimens for this proposal. At the time of collection, NP swabs are placed in viral transport medium and skim milk-tryptone-glucose-glycerin (STGG) for pneumococcal PCR testing[38], and frozen at -80°C. Urine samples are collected in urine collection cups coated with 10% sodium azide (NaN3) solution; NaN3 is added to inhibit bacterial growth in the sample.[39] Urine samples are centrifuged for 10 minutes and the supernatant is then aliquoted into 1 mL cryovials and stored at the CBCF (-80°C) until assayed. Use of urine samples are discussed in **Sections 4.C.2c, 4.C.3c, and 4.C.4c**.

Urine Sample Processing and Acquisition of ^{1}H- NMR Data: De-identified samples (n=50) will be shipped frozen on dry ice to UM using a next-day express service in year 1. Case and control samples will be randomly batched and processed to minimize artificial effects arising from day-to-day variation in NMR runs. However, unlike LC-MS, NMR is not prone to high day-to-day variability.[23,24] All samples are frozen and will be thawed at room temperature on the day of NMR assay only. Urine metabolites are negligibly influenced by long term freezer storage or shipment on dry ice.[12] The pH of each sample will be measured and if necessary, NaOH or HCl will be added to achieve a pH of 7.0± 0.25.[12] A volume equivalent to 10% of the total sample volume of 4,4-dimethyl-4-silapentane-1-sulfonic acid (DSS) will be added as an internal standard. We will acquire one-dimensional ^{1}H-NMR spectra of urine samples using the first increment of the standard NOESY pulse sequence on a four-channel Varian (Varian Inc., Palo Alto, CA) Inova-500 MHz NMR (UM) or on a Bruker 600 MHz spectrometer (NMR-Based Core at CCHMC). [12,40,41] We will specify parameters such as pulse sequencing to acquire accurate spectra from both NMR spectrometers.[12] Sample preparation by the PI will occur under the supervision of Drs. Stringer and Romick-Rosendale **(see letters of support).** [12] All spectra will be recorded at 25°C. For this proposal, the original raw ^{1}H-NMR spectra will be processed using Chenomx software (NMR Suite 8.0; Chenomx Inc., Edmonton, Alberta, Canada), [12,40] which includes chemical shift referencing, shimming, phasing, and baseline correction followed by identification and quantification of metabolites.[42,43] NMR is a unique platform in that every metabolite has its own distinct NMR spectrum, so metabolite identification and quantification for abundant metabolites can be done reliably across platforms without a secondary analytic platform needed to validate the metabolite. However, the identity of any statistically significant metabolites will be confirmed by 2D NMR. For these compounds as well as any that are of low abundance (< 5μM), I will also conduct analytical confirmation using LC/MS with Dr. Zaidy (**Section 2, training goal 3**). Before statistical analyses, quantified NMR metabolite data will be normalized to account for the influence of metabolites present in either high or low concentrations. [12]

Data Management Clinical data will be extracted from the same Epic electronic medical record for both the case and control groups and imported into a REDCap database.[44] Metabolomics data will be expressed as one record per study ID per identified metabolite.

4.C.2.Specific Aim 1: To characterize the sources of variability in the urine metabolite profiles of healthy children.

4.C.2a. Rationale The human metabolome can be affected by external factors (e.g. diet and medications) as well as biological factors (e.g. age and sex). In adults metabolites that differentiated [redacted] were mostly the result of changes in energy metabolism (e.g. creatinine) as males have more muscle mass than women.[40,45] In pre-pubescent children the difference in muscle mass is much less pronounced than adults making it unclear the impact of [redacted] on child's metabolome. Diet in adults have demonstrated that there is greater variability in the metabolome between subjects than within subjects.[46,47] However this variability was deemed insignificant in comparison to the variability that exists when evaluating disease progression.[47] In addition, age may be an important predictor in changes of metabolites over time in adults.[40,46] Likewise in children annual variation in the metabolome as the child aged was found.[48] Due to the sparse pediatric literature on healthy children it is unclear which factors have the greatest effect on a child's metabolome day to day.

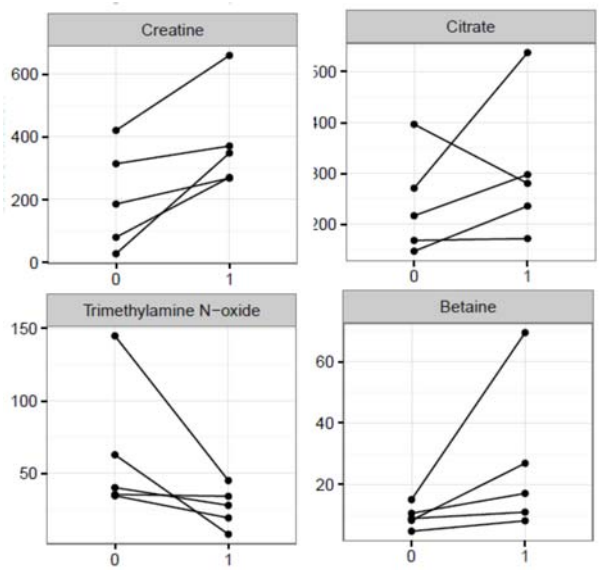


Figure 3: Changes in metabolite concentrations over time. The y-axis is the concentration of the metabolite (uM); the x-axis is the time point, "0" is baseline, "1" is 24 hours after the first time point. Each line represents a unique child.

4.C.2b.Preliminary data A convenience sample of five healthy children provided two morning urine specimens 24 hours apart. Three subjects were female, and the age ranged from 5-7years old. Similar to a previous study we found large changes in creatine, citrate, trimethylamine N-oxide, and betaine over time **(Figure 3).** However, the magnitude of the changes in metabolite concentrations from our data is less than that of the previous study. This may be due to the tight age range or short time frame in which samples were collected. Additional healthy controls will allow us to determine the extent to which external and biological factors influence a child's metabolome over time.

4.C.2c. Methods

Biological Specimens: Urine samples, from healthy children who provide urine samples at 3 time points will be eligible for inclusion in the analysis. The three time points are: 1) at the time of enrollment (T0); 2) 24 hours post enrollment collected at home by the patient (T1); and 3) 14 days' post enrollment collected at home by the patient (T2). The time points were chosen to demonstrate acute changes in the metabolome. Patients will receive a home urine collection kit during enrollment and will be given three options to return the sample: 1) Mail the sample back with the provided box and shipping label; 2) Drop off the sample at their primary care office, which has a daily courier service to CCHMC; or 3) Drop off the sample at CCHMC **(Appendix B)**. From previous studies at CCHMC, a return rate of >90% of samples was demonstrated.[49] Therefore using an established protocol from the Centers for Disease Control and Prevention for home urine collection and our local experience we believe it will be feasible to collect three time points.[50]

Statistical Analysis: First, descriptive statistics (e.g. paired t-tests) and graphics (i.e. stick plots) will be used to evaluate metabolite concentration at each time point. Metabolite concentrations will be transformed if necessary to achieve a normal distribution. Only metabolites that are reported in at least 90% of the samples will be included in the analysis. For each metabolite, we will estimate the between-subject and within-subject variability by using linear mixed models. Metabolite concentration will be the dependent variable and a random effect will be included for subject and time nested within subject.[51,52] Using these variance components, we will estimate the intraclass correlation (ICC), the ratio of between-subject variance and total variance. We will also include fixed effects for age and sex, and examine the proportion of the variance attributable to each of these covariates. To account for multiple testing which arises due to metabolites from the same child we will use false discovery rate procedures, such as Benjamini-Hochberg procedure. We will illustrate the distribution of the variance components and ICCs among all metabolites and describe the proportion of metabolites that are associated with age and sex by the false discovery rate procedure.

Sample Size: We performed a log-normal power analysis to estimate the differences in metabolite concentrations between [redacted]. The difference is defined as the linear t-contrast between logs of the geometric means derived from the mean concentrations of the metabolite. We examined power to detect the geometric mean ratio with p<0.01 for a coefficient of variation (CV) of 0.5 within each group. With a planned enrollment of 125 healthy controls, we estimate 110 (~90%) will provide at least 3 samples and be eligible for inclusion in Aim 1 analysis. We anticipate 65 (59%) will be male and 45 females and allow us to have 80% power to detect a geometric mean ratio of 1.38.

4.C.2d. Expected Outcomes The main outcome is the change in metabolite concentration over three time points (i.e. T2-T0; T2-T1; T1-T0).

4.C.2e. Potential Problems and Alternative Strategies Although NMR is highly reliable in identifying metabolites it is possible that certain metabolites are unable to be quantified accurately. From our preliminary data, 7 metabolites out of the initial 50 metabolites identified had random missing patterns for 3 of the samples. Therefore, as a subanalysis we will impute the missing concentration of the metabolite if it has between 10-30% missing in the dataset.[53,54]

4.C.3.Specific Aim 2: To determine and compare the urine metabolite profiles of children with viral or bacterial CAP with those of healthy children.

4.C.3a. Rationale Viruses, particularly respiratory syncytial virus and influenza, are thought to account for most (73-85%) cases of CAP in children.[26,27] However, antibiotic treatment is more common than the prevalence of bacterial pneumonia suggests due to clinicians' inability to distinguish viral from bacterial etiologies.[4] Conventional microbiological techniques such as blood, sputum or pleural fluid cultures demonstrate high specificity but are positive in very few children.[55,56,57] Therefore, I will use multiple molecular and microbiological tests to increase the accuracy of identifying bacterial infection **(see section 4.C.3c).** Metabolomics studies have distinguished different etiologies of CAP; however, those studies are limited by small sample sizes.[25,58] Slupsky et al identified unique metabolite patterns excreted in urine of adults with pneumococcal infection (n=8) and *Mycoplasma pneumoniae* (n=9); these metabolites were significantly different from those in healthy adult control samples (n=115).[25] In other studies, distinct metabolites appeared in the urine of children with severe pneumonia (n=11) but not in controls.[7,58] These initial studies are limited by the inclusion of only hospitalized patients, the lack of any viral testing, and the lack of clinical data. **4.C.3b. Preliminary Data** In my preliminary data from CARPE DIEM, urine samples from children with CAP (n=39) were frequency matched by age and sex with samples from healthy children (n=14) and yielded 50 named and quantified metabolites by NMR. I compared healthy controls with viral (n=29) **(Figure 4A)** and bacterial CAP (n=10) **(Figure 4B)** by partial least squares-discriminant analysis (PLS-DA). This resulted in distinct groups with potentially important metabolites identified through the variable importance in projection (VIP) score and large fold differences in the concentrations of metabolites **(Figure 5)**. Potential metabolites that may differentiate bacterial and healthy

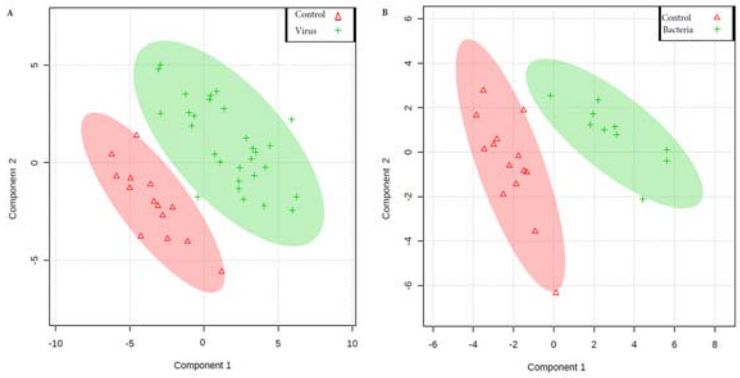


Figure 4: PLS-DA score plots of quantitative 1H-NMR metabolomics of urine from pediatric healthy controls (n=14) (red) compared with patients with pneumonia either due to virus (n=29) (green, 4A) or bacteria (n=10) (green, 4B).

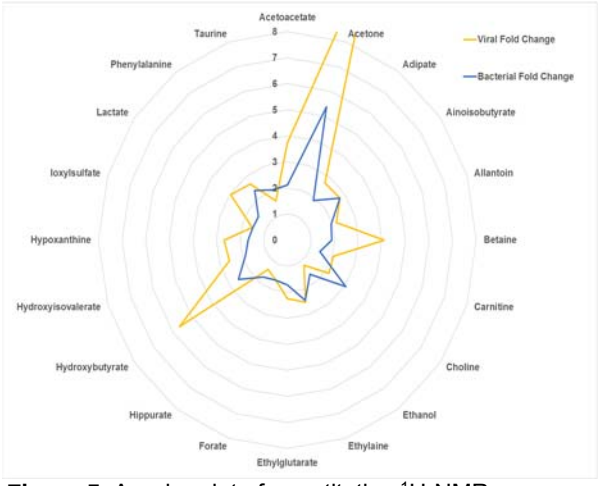


Figure 5: A radar plot of quantitative [1]H-NMR metabolomics of urine from pediatric patients with pneumonia due to bacteria or virus and healthy controls. Each circle represents a 2-fold difference from the class of pathogen and healthy control. The smallest circle is the reference circle indicating no difference between healthy control and class of pathogen. The viral class is indicated by the orange line and the bacterial class is the blue line.

samples included methylnicotinamide, taurine, acetone, choline, citrate, and methylgultarate. Alternatively, potential metabolites important in differentiating viral and healthy samples included hypoxanthine, methylgultarate, acetone, betaine, and phenylalanine. It is possible that metabolites that are identified in both analyses (e.g. methylgultarate and acetone) are indicators of infection regardless of pathogen, and that non-overlapping metabolites such as taurine and betaine are indicators of bacterial versus viral pathogens, respectively. Collectively, these data, although preliminary, provide additional support for the utility and feasibility of NMR metabolomics to differentiate CAP etiology. Here, I propose a more definitive study to corroborate and extend these findings using a substantially larger sample size, overcoming the limitations of prior studies.

Table 4: Etiology Definitions

Viral Etiology

Anticipated Prevalence: 60-75%

NP Swab Positive for Virus*

AND

NP Swab Negative for bacteria**

AND

Negative cultures from collected sources

Bacterial Etiology

Anticipated Prevalence: 5-10%

NP Swab Negative for Virus*

AND

Blood/Pleural Fluid Culture Positive for Bacteria***

OR

NP Swab Positive for Bacteria**

AND

Procalcitonin (PCT) indicative of bacterial infection (≥ 1.5ng/mL)

Viral/Bacterial Co-Infection Etiology

Anticipated Prevalence: 5-10%

Viral Classification AND Bacterial Classification Criteria Met

Unknown Etiology

Anticipated Prevalence: 15-20%

NP Swab Negative for Virus and Bacteria

AND

Culture Negative from collected sources

Footnote

*Includes: Influenza A/B, Parainfluenza 1/2/3, Respiratory Syncytial Virus (RSV) A/B, Human Metapneumovirus, Enterovirus/Rhinovirus, Adenovirus, Coronavirus, Human Bocavirus

**Includes: *Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumoniae*

***Includes: *Streptococcus pneumoniae, Haemophilius influenza, Staphylococcus aureus, Streptococcus pyogenes, Klebsiella pneumoniae*

4.C.3c. Methods Pathogen Classification: Specimens from the CARPE DIEM study or from the control cohort will be included in the analysis. Final viral and bacterial classifications will be determined as defined in **Table 4**.[26,33,55,59] We will define bacterial pneumonia as a nasal swab positive for bacteria and a procalcitonin (PCT) of >1.5 ug/mL which has moderate sensitivity and specificity to diagnose bacterial infection.[59] PCR to detect pneumococcal autolysin A (lytA) and pneumococcal surface adhesion (psaA), pneumococcal surface antigens, will be performed on all NP swabs [60-66] and will be considered as either present or absent in the sample and of course cases with blood or pleural culture positive for pneumococcus will be classified as positive **(Table 4)**. Currently of the 169 urine samples collected the majority of patients (60.4%) had only a virus detected **(Table 5).** A subset of samples will be classified as "unknown" and be further analyzed using 16S rRNA on blood samples to identify bacteria at the genus level.[67-69]

Statistical Analysis of Metabolomics Data: Descriptive statistics will be conducted and continuous variables will be transformed if necessary to achieve a normal distribution. Case samples will be analyzed with age- and sex-matched controls.

The first stage of analysis will include a crude examination of the metabolite data. Principal component analysis (PCA) and PLS-DA, multivariate statistical methods, will be perfomed which transform a large set of correlated data (e.g. individual metabolites) into a smaller number of uncorrelated principal components while maintaining variability within the data. PCA and PLS-DA allow for a visual display of the clusters that are inherent in the dataset by creating a scores plot (**Figure 4**), and a loading plot, which shows which metabolites are the most important in deciding the clusters.[70] We will use the results of the PCA to guide the number of latent variables or PLS components of the PLS-DA classification procedure. The second stage is to use PLS-DA is to optimize separation of the metabolomics data between the three groups with an analytic advantage of being able to handle highly collinear and noisy data common in metabolomics. Through this approach, we will obtain VIP score and

Table 5: Etiology from CARPE DIEM Cohort (n=169) *

Overall Pathogen Classification	N (%)
Virus Only	102 (60.4)
Bacteria Only	21 (12.4)
Viral and Bacterial Co-infection	12 (7)
Unknown Etiology	34 (20)
Specific pathogens identified**	N (%)
Influenza A/B	12 (7.1)
Parainfluenza 1/2/3	6 (3.6)
Respiratory Syncytial Virus A/B	32 (18.9)
Human Metapneumovirus	11 (6.5)
Enterovirus/Rhinovirus	57 (33.7)
Streptococcus pneumoniae	17 (51.5)
Mycoplasma pneumoniae	14 (42.4)
Staphylococcus aureus	2 (6.1)

*Etiology determined as defined in Table 4.
**Note one patient may have multiple pathogens identified therefore percentages were calculated based on number of specimens with the identified pathogen divided by total number of pathogens identified in that class (Virus or Bacteria) of pathogen.

regression coefficients to identify the most important variables in separating groups.

The third stage of analysis will use analysis of covariance (ANCOVA) to compare groups with respect to individual metabolite concentrations with clinical and demographic characteristics included as covariates. Covariates with a p-value <.10 in 1-to1 regressions will be considered statistically significant and examined in the final model. The final model will indicate whether or not the means of the metabolite concentrations between each group are significantly different by examining t-contrasts from the model. The t-statistic from each contrast will be used to compare groups. To account for multiple testing I will use false discovery rate procedures, (i.e. Benjamini-Hoceberg procedure).[71] As an exploratory analysis, I will conduct pathway analysis via Metscape to construct metabolic networks using the differentiating metabolites to aid in the interpretation of the data.[70]

Sample Size: We performed a log-normal power analysis where the difference was defined as the linear t-contrast between logs of the geometric means derived from the mean concentrations of the metabolites identified from our preliminary study. We examined power to detect the geometric mean ratio with $p<0.01$ for a coefficient of variation (CV) of 0.5 within each group. An enrollment of 250 cases with 175 (70%) estimated to be viral and 125 healthy controls would allow us to have 80% power to detect a geometric mean ratio of 1.21.

4.C.3d. Expected Outcomes We expect to identify and quantify the concentrations of approximately 50-60 metabolites in each urine sample.[12,72]

4.C.3e. Potential Problems and Alternative Strategies It is possible that results from lytA and psaA will be discordant for detecting *S. pneumoniae.* In that situation I will use a Latent Class Modeling (LCM) approach which estimates a probability of pneumococcal infection in cases when a true gold standard is not available for all cases (e.g. limited blood or pleural fluid cultures for each case).[62,73] Cases with positive blood or pleural culture for pneumococcus will be included in the model as known disease cases. The LCM will be implemented using Mplus 7.1.

4.C.4. Specific Aim 3: To determine longitudinal changes in the urine metabolite profile in children with CAP compared with healthy controls.

4.C.4a Rationale and Preliminary Data Assessing the physiological response to antibiotic therapy is challenging because the etiology of pneumonia is usually not known and antibiotics are prescribed empirically. In addition, traditional culture techniques are substantially less sensitive and less specific in detecting bacterial pathogens when the samples are collected after the patient receives antibiotic therapy.[74] Therefore, measuring longitudinal changes in metabolite patterns will aid in differentiating response from non-response to antibiotics; and determining the effect of different antibiotics on the identified metabolomics profile. Samples will be collected at 3 time points from children with CAP: 1) at the time of presentation in the ED; 2) 24 hours post exposure to antibiotics to allow for response to the infection if bacterial which will be collected on the inpatient service; and 3) 14 days post discharge to determine a non-infected state of the metabolome collected at home by the patient. Samples from controls are described in 4.C.2c. **4.C.4b. Preliminary Data** In my preliminary data, I compared changes (delta) in metabolite concentrations for urine samples taken at the first 2 time points on each of 7 hospitalized patients from CARPE DIEM and from 5 healthy controls (from Aim 1). Patients with CAP had larger changes in their metabolite profiles over 24 hours compared with healthy controls (**Figure 6**). All patients with CAP received ampicillin within the 24 hours of their first urine sample. Choline is a known metabolite of aminopenicillins, however had one of the smallest changes among all the metabolites.[75] In addition other metabolites (e.g. betaine and citrate) that were identified in the preliminary analysis in Aim 2 have consistently greater changes in patients with CAP than healthy controls.

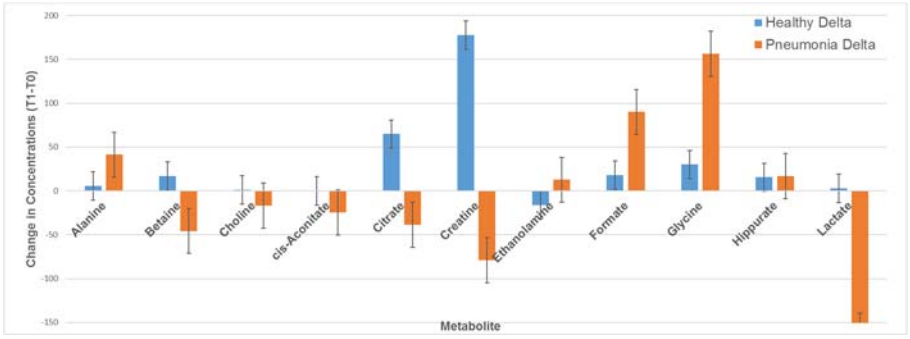


Figure 6: Changes in metabolite concentrations over time. The y-axis is the change in concentration of the metabolite (uM); the x-axis is the individual metabolites. Orange bars indicate pneumonia subjects and blue bars indicate healthy subjects. Black bars indicate standard errors.

4.C.4c Methods

Biological Specimens: Urine samples, from cases and controls, who provide samples at 3 time points will be eligible for inclusion in the analysis.

Statistical Analysis: First, descriptive statistics and graphics will be used to evaluate metabolite concentration at each time point by group (i.e. viral, bacterial, healthy). Metabolite concentrations will be transformed if necessary to achieve a normal distribution. For each metabolite, we will utilize a linear mixed model with normalized metabolite concentration as the dependent variable. The models will include a between- subject variable (group) with 3 levels (group: viral, bacterial, and healthy control) and one within-individual variable (time) with 3 levels (baseline, 24 hours, and 14 days) along with covariates. Our primary goal will be to assess overall group effects and group by time interactions. Group differences in changes over time, will be tested using least square means contrasts.[52]

Sample Size: We calculated power to detect differences in longitudinal changes between 2 groups, cases and controls. Assuming a log-normal distribution, we examined the smallest geometric mean ratios between the 2 groups that would be detectable and assumed a CV of 0.50 and t-contrasts corresponding to the geometric mean ratios for power calculations. We have sufficient power (80%), with an alpha of 0.01, to detect a geometric mean ratio of 1.61 for our anticipated sample of 50 cases and 50 sex and age matched healthy controls, having data at all 3 time points.

4.C.4d. Expected Outcomes The outcome of interest is the change in the metabolite concentrations at each time point across groups.

4.C.4e. Potential Problems and Alternative Strategies As multiple therapies (e.g. bronchodilators) can be administered within the time frame of sample collection for patients in CARPE DIEM, we will include time-varying covariates for each therapy to better evaluate the influence of these therapies on the temporal changes in the metabolite profiles. In addition, it is possible that we only receive two time points from cases or controls therefore a subanalysis will be conducted including these samples with the cohort of children with all 3 time points.

4.C.5. Timeline and Future Directions The timeline for the research and training goals are outlined in **Table 6.** The metabolites identified in Aim 2 will be the foundation for a targeted approach using LC/MS to validate the metabolite profiles in a multicenter study. Data generated from Aim 1 and 3 will be used as preliminary data to further investigate the response to therapy over time compared with normal changes. The strength of this study is the identification of candidate metabolites that will ultimately be translated to point-of-care tests for rapid pathogen identification for children with CAP.

Table 6: Timeline of Proposed Research Activities

	Pre-Grant	Y1	Y2	Y3	Y4	Y5
IRB Approval	X					
Case Patient Recruitment (n)	175	75				
Control Patient Recruitment (n)		75	50			
NMR Work Flow (n of samples)*	81	100	350	175		
16S rRNA				X		
Statistical Analysis				X	X	X
Dissemination of Results				X	X	X
R01 Application						X
Training Goal		1	2, 3	2,4	3,4	3,4

*N's include 3 time points for Aim 1 and 3. In Year 1, technical replicates (n=50) will be assayed at two sites.

TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH

The responsible conduct of research was a significant part of my graduate school training. I completed two ten week courses on public health ethics and epidemiological research methods that were taught by a historian and ethicist in the School of Public Health at Drexel University. The course topics included understanding bioethics, legal basis of public health, ethical considerations in health disparities, ethical failures in the past and present human subjects' research and new challenges to ethical research. In addition doctoral seminars were held on conflict of interests, data sharing and roles and responsibilities of individuals versus institutions during the scientific process. During my post-doctoral fellowship, I participated in multiple group discussions on topics related to ethical research in the clinical pediatric setting. I have also completed the on-line Collaborative IRB Training Initiative (CITI) Program during graduate school and fellowship and I will continue to keep my CITI training current during this award and my scientific career. The CITI program includes training in all facets of human subject's research, including IRB regulations, informed consent, and research with protected populations, and research involving children. The CITI training is the industry standard human subjects training, with funding from DHHS and over 1.3 users from over 1,130 institutions worldwide. This training maintains our institutional compliance with NIH's RCR Notice #NOT-OD-10-1019.

Preparation of IRB Proposals and Protocol Management (~12-15 hours over two years)

CCHMC's research community structure supports the responsible conduct of research, as evidenced by having received full accreditation from the Association of the Accreditation of Human Research Protection Programs in 2008.The institutional review board assigns "research compliance specialists" to each division. This allows for close relationships between each division and the IRB, as well as facilitating the development of research protocols through open dialogue between researchers and the IRB. Additionally the IRB at CCHMC has Standard Operating Procedures (SOPs) which will be applied as is relevant to my research. These include the SOPs on obtaining informed consent, documentation procedures, and participant recruitment and protection. The SOPs were designed to optimize protection of research subjects and promote ethical conduct of research. Throughout the course of this award, I will review these SOPs with my mentors and utilize them when appropriate. Finally, all research will be reviewed by co-mentors as well as by our division scientific review process and the IRB to confirm both the scientific validity and the responsible conduct of all proposals.

Seminar on Ethics in Research and Scientific Integrity (24 hours over 5 years)

Additional training will be gained through my attendance at the University of Cincinnati's (UC) Center for Clinical and Translational Science seminars which routinely offers forums and workshops on trending topics including ClinicalTrials.gov in regards to intellectual property ownership, biorepositories and research ethics.

Human Subjects Protection Symposium (8 hours every two years)

UC and CCHMC also offer a yearly, one-day "Human Subjects Protection" symposium that addresses topics relevant to pediatric research which I attended in 2012 and will attend again in 2017.

Formal coursework (10+ hours over 5 years)

I will complete a course offered by the UC entitled "Ethics in Research / Scientific Integrity" (26 GNTD 730 001). Lectures and group discussions will focus on topics including mentoring, record keeping, Institutional Review Boards (IRBs), authorship, and scientific misconduct. In addition, annual metabolomic workshops such as those at the University of Alabama and at the University of Michigan include sessions specifically regarding ethics in "-omics". These sessions include discussions on what constitutes scientific misconduct, data storage of -omic data, appropriate data retention as required by the NIH and NSF, data sharing and reporting both with the scientific community and with the study participants. These sessions are also incredibly useful in presenting the most recent regulations surrounding -omics data as the field and the regulations surrounding this type of subject data is ever changing. As discussed in my training plan I will attend these –omics workshops throughout the award period.

Division of Hospital Medicine Faculty Educational Conference (~24 hours over 2 years). Clinical and research faculty and staff in the Division of Hospital Medicine meet approximately once per month (as part of our weekly faculty meetings) to discuss research topics relevant to the responsible conduct of research including study design, IRB relationships, presentation formats, and data management. Dr. Armand Antommaria, an Associate Professor in the Division of Hospital Medicine and Director of the Ethics Center at CCHMC leads quarterly sessions focused on ethics in research and clinical care. Dr. Antommaria begins each session with a broad topic and then refines his approach after a needs assessment of the faculty and fellows. Attendance at these training-pertinent conferences is required and tracked.

Re: **Mentorship Plan and Statement from Primary Mentor: Samir Shah, MD, MSCE**

Dear Study Section Members:

It is with great pleasure and enthusiasm that I write this letter in support of Dr. Ambroggio's K01 proposal, "Metabolomic Evaluation of the Etiology of Pneumonia" (MEEP). I am Professor of Pediatrics at the University of Cincinnati College of Medicine. I also serve as the Director of the Division of Hospital Medicine and hold the James M. Ewell endowed chair at Cincinnati Children's Hospital Medical Center (CCHMC). I have known Dr. Ambroggio for over 7 years during her time as a graduate student at Drexel University. I currently serve as Dr. Ambroggio's primary mentor and division director. During this time we have developed a rich relationship, collaborating on multiple publications focused on the management of pneumonia in children. I have always been impressed with her insight and understanding of the clinical decision making process. She has spent time rounding with pediatric hospitalists and infectious diseases specialists both at Children's Hospital of Philadelphia and at CCHMC. I believe that her experience shadowing pediatricians, collaborating with pediatricians within multiple specialties through different research studies, attending weekly pediatric grand round lectures and her exposure to many facets of clinical medicine have provided her with a deep understanding of the intricacies of diagnosing and managing pneumonia from an individual patient level as well as from a health care systems level. It is this combination of her clinical understanding and her research acumen that makes her an exceptional candidate for this K01 award.

As an infectious diseases pediatrician, my own research has focused on factors associated with severe disease in children diagnosed with community-acquired pneumonia in the hospital settings. I served as Associate Chair of the writing committee and co-first author on the recently published national pediatric pneumonia guidelines, jointly sponsored by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. I have a strong track record of extramural funding, (~$10 million as PI or co-investigator) and a productive record of publishing (>200 peer-reviewed manuscripts).

Mentoring talented junior faculty is a priority in my career and as a result I had the privilege of receiving the prestigious national Miller-Sarkin Mentorship Award from the Academic Pediatric Association in April 2015. I have served as the primary research mentor for over 45 trainees, ranging from medical students and residents to doctoral students, fellows, and junior faculty. Virtually all of my former mentees have been successful at securing academic positions with many receiving extra-mural research funding. It is in this context that I can confidently say that Dr. Ambroggio is clearly one of the best and most talented young researchers with whom I have worked. My own research, combined with my mentorship experience, provides me with the expertise necessary to guide and monitor Dr. Ambroggio's progress toward accomplishing her proposed research agenda, and becoming an independent investigator.

Dr. Ambroggio has been extremely successful in her academic career thus far. During her graduate training, she clearly stood out from her peers at Drexel University and the University of Pennsylvania where I was faculty at that time, in terms of initiative, inquisitiveness and an affinity for epidemiological and statistical methodology. As such she was awarded the Outstanding Promise Doctoral Award in Physical and Life Sciences from Drexel University upon receiving her PhD. PhD candidates from fields such as biochemistry, engineering, and nursing are eligible, however only one award is given per year and, prior to Dr. Ambroggio, had never been given to a PhD candidate in Epidemiology. I recruited her as a post-doctoral fellow to CCHMC in 2011 and very quickly Dr. Ambroggio developed strong collaborations with faculty in the Department of Radiology to investigate ultrasonography as alternate imaging modality compared with chest radiography to detect pneumonia in children. As a first year fellow, she received a highly competitive grant from the Thrasher Research Foundation for early investigators and led a team of seven faculty members, including four radiologists, to perform chest ultrasounds, chest radiographs and chest computed tomography scans on children with diagnosed pneumonia.

During her first month as faculty Dr. Ambroggio received an internal Trustee Award to fund and co-lead the development of the infrastructure needed to collect biological samples, including urine, blood and nasal swabs, from children with radiographically-confirmed pneumonia in the emergency department. The study, called *Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine* (CARPE DIEM), will be leveraged in this K01 proposal. Dr. Ambroggio and I meet monthly with Dr. Todd Florin and Dr. Rich Ruddy from the Division of Emergency Medicine to discuss study progress and provide senior and peer research mentorship formally and informally. All four investigators have distinct interests and career

paths, but a unified focus on improving CAP outcomes, which allows for complementary expertise in approaching our research questions. The CARPE DIEM infrastructure is funded to enroll through end of fiscal year 2017 using funds from the Gerber Foundation grant and the Ohio Governor's Research Fund. These funds ensure that the cost of study enrollment infrastructure, general study management, and sample collection is covered during the recruitment periods in the K01. The K01 award funds will be critical to support the NMR spectral acquisition of the urine specimens collected as part of CARPE DIEM and for the collection of control samples from healthy patients. The team science approach for CARPE DIEM has resulted in Dr. Ambroggio (as the lead author) over the past couple of years in collaboration with Drs. Florin, Ruddy, Stringer and myself to submit abstracts to national and international conferences where she has been able to present preliminary results.

In addition, Dr. Ambroggio has had the opportunity to become a site co-investigator in a multicenter study entitled "Children's Hospital's Initiative for Research in Pneumonia (CHIRP)". The goal of CHIRP is to develop a genomic "molecular distance to health" score for children with pneumonia. This 6 hospital study is exposing Dr. Ambroggio to the processes needed to collect biological samples from multiple sites. This opportunity will enable Dr. Ambroggio to construct an effective multicenter study collaborating with the PRIS and PECARN network as part of a R01 application at the end of her K01 award.

As the primary mentor on this K01, I am extremely invested in Dr. Ambroggio's success and thus will provide her with clinical content expertise in pediatric pneumonia as well as the appropriate environment, resources, and mentorship necessary for her to success. Dr. Ambroggio's long term research program focuses on improving diagnostic capabilities for common childhood infections using a combination of epidemiologic and metabolomics methodologies that are clearly distinct from my own program, which focuses on improving resource utilization for CAP and determining the comparative effectiveness of different treatments. Dr. Ambroggio will lead all aspects of the proposed studies including the preparation and assay of the urine samples in Dr. Stringer's and Dr. Romick-Rosendale's laboratory, the identification, quantification and analysis of the metabolomics data she generates. I will personally supervise her development throughout the period of the award as I have great confidence that she will develop into a successful independent investigator. The two of us meet regularly with weekly formal meetings and additional informal meetings to discuss her research progress and career development. Formal meetings will continue at least weekly during the initial years of this grant and then transition to bi-weekly meetings in years 3-5 as Dr. Ambroggio develops greater independence. Additionally, we have adjacent offices and I am available to her on an "open door" basis. Our one-on-one mentoring sessions will continue to focus on progress towards completing the proposed research, manuscript writing, abstract submission to national meetings, career development and grant identification and writing. In addition we have been and will continue to meet with Drs. Ruddy, Macaluso, Sucharew and Stringer (by phone) on a quarterly basis to discuss Dr. Ambroggio's overall career and research trajectory. By years 4-5, Dr. Ambroggio will have developed the required skillsets to pursue an independent research career, including her own R01 application, and independence on manuscript publications without me as a senior author.

CCHMC has a formal process for annual faculty evaluation that includes a review of progress towards meeting the previous year's goals, as well as the establishment of new goals for the coming year. I will provide the primary guidance to Dr. Ambroggio in this process, and the goals and progress towards goals will be shared with the entire advisory committee. Dr. Ambroggio and I have created specific goals including 2-4 publications per year for the duration of the award. Committee meetings occur every 4 months with her scholarly oversight committee to guide Dr. Ambroggio in achieving both her research and career development aspirations as well as to discuss her strategies in achieving her goals. As her primary mentor, I will also complete the required evaluation for her annual NIH progress report. In addition as the Director of the Division of Hospital Medicine, where Dr. Ambroggio holds a primary appointment, I will continue to ensure that she has at least 75% of her time protected for research and research training specific to this award, with an additional 10% effort devoted to teaching two epidemiology courses per year at the University of Cincinnati. While I have great confidence in Dr. Ambroggio, her ongoing dedicated research time is not contingent on the success of this application. I will also support her by providing professional fees that can be used for the K award in excess of allowable costs such as for travel and registration to scientific conferences.

In conclusion, it is a true pleasure to serve as a primary mentor for Dr. Ambroggio for this award. Dr. Ambroggio has shown herself to excel in everything she has done to date including 19 publications (10 as

first author, 15 in relation to pneumonia) and 10 grants (5 as PI), and I am absolutely confident that she will continue to do so. In summary, Dr. Ambroggio has enormous potential to succeed as an independent investigator and to be a national leader in the field of infectious disease epidemiology. I offer my most enthusiastic and unreserved support for Dr. Ambroggio.

Sincerely,

Samir S. Shah, M.D., M.S.C.E.
James Ewell Professor, Department of Pediatrics, University of Cincinnati College of Medicine
Director, Division of Hospital Medicine, Cincinnati Children's Hospital Medical Center

Re: **Mentor Statement from Co-Mentor: Maurizio Macaluso, MD, DrPH**

Dear Study Section Members:

I am writing to convey my strong commitment to serve as the co-mentor for Dr. Ambroggio's K01 and to work closely with her primary mentor, Dr. Samir Shah, to ensure Dr. Ambroggio's success in completing the proposed research and career development plan. I believe that her plan will help her establish herself as an independent investigator in infectious diseases epidemiology and metabolomics. I am Professor of Pediatrics and Environmental Health at the University of Cincinnati and Director of the Division of Biostatistics and Epidemiology of Cincinnati Children's Hospital Medical Center. I am also the director of the Biostatistics, Epidemiology, and Research Design core of the UC Center for Clinical and Translational Science and Training (CCTST). In my thirty-year career in public health research, including my experience as a Professor of Epidemiology at the University of Alabama, my leadership position as Distinguished Consultant and Branch Chief at the Centers for Disease Control and Prevention in Atlanta, and in my present position, I have led large and diverse research groups. I have mentored many master level students, 15 doctoral students in epidemiology and related disciplines, Epidemiologic Intelligence Service Officers, Public Health Fellows and Preventive Effectiveness Research Fellows resulting in over 60 joint publications out of 200 publications (H-index: 39). I believe that my background enables me to provide depth and breadth of mentorship, and complements well the expertise of the primary mentor and other aspects of her training plan.

I have known Dr. Ambroggio for four years, since she joined the Division of Hospital Medicine at Cincinnati Children's as a post-doctoral research fellow. I served as the epidemiologist co-mentor with Dr. Shah, her primary clinical research mentor. During the interview process that led to her selection as a post-doctoral fellow I was impressed by her strong foundations in epidemiologic research methods and in her biological foundation in regards to infectious diseases. She joined the program with a clear research focus on advancing the diagnosis and treatment of community-acquired pneumonia, but also with the desire to expand her horizons into novel diagnostic methods. Soon after joining CCHMC she developed a coherent research program including a study of the comparative effectiveness of alternative antibiotic regimens in the treatment of community-acquired pneumonia and a comparison of the diagnostic accuracy of chest ultrasound and x-ray receiving funding from an Early Career Award by the Thrasher Fund in her first year as a post-doctoral fellow. Her determination, early success as a post-doctoral fellow and potential as an independent investigator led to a joint faculty recruitment by my own Division and the Division of Hospital Medicine.

Dr. Ambroggio's proposal to use metabolomics methods to identify pathogens in children diagnosed with community acquired pneumonia is reflective of a transition in the field of epidemiology to focus on translating bench science to bedside application. She is well positioned to succeed in this proposal as she has a strong foundation in study design, statistical analysis, and molecular and cellular biology. However, -omics epidemiology and specifically metabolomics, is a subset of epidemiology that is not taught in the majority of graduate programs. As her co-mentor I will ensure that Dr. Ambroggio receives timely and appropriate assistance with methodological aspects of her work. Overall, I believe, Dr. Ambroggio has assembled an outstanding group of mentors and advisors who whose expertise is complementary to ensure her success in accomplishing the proposed research and in her overall career as an independent investigator and future leader in the fields of epidemiology and metabolomics. Dr. Ambroggio's proposal has the potential to significantly and positively impact diagnostic tools for detecting pathogens in community-acquired pneumonia in children.

I am committed to fostering Dr. Ambroggio's career development, by supporting her while she strengthens her already well developed research skills, develops leadership and management skills and transitions from a mentored investigator position, to an externally-funded, independent investigator role. As she outlined in her career development plan, I will meet with her monthly during the period of performance of the award and more frequently as needed. I will be an active participant in the progress toward the goals outlined in this proposal and I look forward to learning from our collaborative effort into the adaptation of epidemiologic methods to the area of metabolomics. I strongly believe that Dr. Ambroggio is a talented junior scientist who can become a leader and that the proposed K01 plan will ensure her success. Thus, I highly recommend her for your consideration and hope that you will support her application for this award.

Sincerely,

Maurizio Macaluso, MD, DrPh, FACE; Professor of Pediatrics and Environmental Health, University of Cincinnati College of Medicine; Director, Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center

Re: **Mentor Statement from: Kathleen Stringer, PharmD**

Dear Members of the Review Committee,

It is my great pleasure to write a letter in strong support of Dr. Ambroggio's K01 application entitled "Metabolomics Evaluation of the Etiology of Pneumonia". Dr. Ambroggio is an exceptional candidate and I am enthusiastic to provide this recommendation on her behalf. I have known Dr. Ambroggio for two years. We first met in the summer of 2013 at the University of Alabama's (UAB) NIH-funded 1st Metabolomics Workshop where I was serving as an invited speaker and Dr. Ambroggio was an attendee. Dr. Ambroggio's keen interest in metabolomics and its application to her research in pediatrics was readily apparent. We had a number of one-on-one discussions about metabolomics at the meeting. These fruitful conversations naturally extended beyond the workshop and have continued on a regular, monthly basis as we have worked together to construct her K01 application. Together we have developed the application's study design and a standard operating procedure for the study's sample collection so that reliable, high quality metabolomics data will be generated. Dr. Ambroggio has spent time over the past two summers in my laboratory understanding the different aspects of metabolomics study design. During this time we jointly generated the preliminary metabolomics data included in this application. Throughout our interactions in and outside of the laboratory it is evident that Dr. Ambroggio has a steep learning curve for this field and will be successful in her endeavors in this field of research.

I am uniquely qualified to serve as Dr. Ambroggio's metabolomics mentor on her K01 application. I am a Professor of Clinical and Translational Pharmacy at the University of Michigan's College of Pharmacy. My research is focused in fibrin-inflammatory lung diseases, which includes the study of the rare, most often, pediatric illness, plastic bronchitis. I have also conducted a number of metabolomics studies using a range of biofluids, including urine. Most often I utilize quantitative NMR metabolomics with statistical and bioinformatics analyses aimed at identifying and quantifying metabolites of biological relevance. My research program is supported by grants from NIGMS and metabolomics supplements from NIGMS and NIMH. I have over 60 peer-reviewed publications. I have mentored numerous students and post-doctoral fellows and was recently named a Distinguished Mentor by the University of Michigan's CTSA. Based on my mentoring experience, I can confidently say that Dr. Ambroggio is clearly one of the best trainees I have encountered. Dr. Ambroggio is insightful, smart, highly organized, efficient, and very motivated. As an example we recently were invited to write a metabolomics review of sepsis.

Dr. Ambroggio has designed a robust study, collecting relevant clinical data that are essential during the analysis phase of the study. As outlined in the training plan, Dr. Ambroggio will undergo intensive training in my laboratory during three 2-week visits in the first year. During this time Dr. Ambroggio will gain hands-on experience in processing and running her samples by NMR under my guidance and with the aid of the NMR spectromist, Dr. Larisa Yeomans and our laboratory technician, Cora McHugh. Dr. Ambroggio will gain experience with Chenomx (chenomx.com) software as well as Metscape 2 (www.metscape.ncibi.org), a plugin for Cytoscape (www.cytoscape.org), and other publicly available netware tools.

We will also work closely with Dr. Sucharew, the biostatistician on the project, on statistical analysis and interpretation of the data. My knowledge and training in clinical pharmacy will be extremely helpful in the interpretation of the results from this proposal as many children with community-acquired pneumonia will have received antibiotics. Deciphering the influence of pharmacotherapy on the metabolome is of critical importance in furthering knowledge of community-acquired pneumonia. In addition to this time, I will continue having scheduled bi-weekly phone calls with Dr. Ambroggio throughout the period of the award, with a joint monthly phone call with Dr. Ambroggio and Dr. Romick-Rosendale to discuss study progress, Dr. Ambroggio's ability to reproduce the data generated in my lab and other facets of cross-center NMR validation studies.

I have also participated in Dr. Ambroggio's quarterly mentorship team meetings over the past three years and have been able to interact with her outstanding group of mentors and advisors, including Dr. Shah. I believe that our collective expertise will afford Dr. Ambroggio an intensive career development experience that I am confident will lead to her research independence in the fields of metabolomics and epidemiology. I look forward to my continued involvement in the research and career development of this talented individual.

Sincerely,

[redacted]

Kathleen A. Stringer, PharmD
Professor of Clinical and Translational Pharmacy
College of Pharmacy, University of Michigan

Re: **Mentor Statement from: Richard Ruddy, MD**

It is with great enthusiasm that I write in support of the K01 application of Lilliam Ambroggio, PhD, MPH as one of her co-mentors. I have known Dr. Ambroggio for three years, since her second year of fellowship at Cincinnati Children's Hospital Medical Center. Her zealousness and passion to improve clinical outcomes for children with pneumonia through implementing evidence based guidelines to investigating emerging diagnostic tools has been evident from the beginning. During her first year as faculty, she secured a highly competitive internal Trustee award, and together with Dr. Todd Florin, developed a prospective research study of children with community-acquired pneumonia who present to the emergency department including an associated biorepository. Dr. Ambroggio and Dr. Florin, under the supervision of Dr. Shah and I, have enrolled 248 children since enrollment began in July 2013. *The feasibility of this study has been clearly demonstrated.* Enrollment will continue through July 2017 with funding by the Gerber Foundation and the Ohio Governor's Research Fund, both of which Dr. Ambroggio is a co-Investigator. This well established and funded prospective study entitled Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine (CARPE DIEM) will provide Dr. Ambroggio with the biological samples and robust clinical data she needs to complete the research and training aims outlined in her K01.

Academically, I am a Professor of Pediatrics in the College of Medicine at the University of Cincinnati and was the Division Director of Emergency Medicine in the Department of Pediatrics until June of 2015. My research focuses on defining the role of diagnostic testing on management decisions in the emergency department. My current research investigates respiratory illness and febrile young infants who are at low risk of serious bacterial infection. I am the principal investigator of one of six research nodes of pediatric emergency departments in the Pediatric Emergency Care Applied Research Network (PECARN), the first federally-funded multi-institutional network for research in pediatric emergency medicine. We are funded through 2019 I will continue to advise Dr. Ambroggio in respiratory illness content, in enrollment and quality metrics for her study patients as well as her aspirations for this work to be multicenter through PECARN. That includes nodal and network wide studies which may help expand Dr. Ambroggio's metabolomics investigation to a larger population of children in a future R01 award. I am excited to continue to play the role as mentor and advisor to her work the next 5 years.

Dr. Ambroggio has developed a strong mentorship team that has been meeting quarterly as part of her scholarly oversight committee since she became faculty in 2013. In this time I have had many opportunities to communicate with Drs. Shah, Macaluso, Sucharew and Stringer in the development of this award as well as

the pathway for Dr. Ambroggio to establish herself as an independent investigator studying pediatric infectious diseases.

In conclusion, I believe that Dr. Ambroggio's leadership, analytical skills, and ability to form strong relationships across disciplines combined with her scholarly accomplishments in the past and in the future will make her one of the leaders in the field of infectious diseases epidemiology. This K01 will move her forward as an independent investigator in this field. I am fully committed in providing Dr. Ambroggio the support that is needed for her to successfully accomplish her research aims as outlined in her application as one of her mentors.

Sincerely,

Richard M. Ruddy, MD
Professor of Pediatrics, University of Cincinnati College of Medicine
Medical Director, Cincinnati Children's Hospital Medical Center - Liberty

Re: **Mentor Statement from: Heidi Sucharew, PhD**
Dear Members of the Review Committee,
It is with the utmost support that I write this letter for Dr. Ambroggio's K01 proposal "Metabolomics Evaluation of the Etiology of Pneumonia", as her statistical mentor. Dr. Ambroggio developed a strong foundation in statistical methods during her PhD and I believe that she is extremely capable of learning and applying the statistical methods outlined in her proposal for her current research aims. In our interactions over the past four years since her arrival at CCHMC, she has been impressive in her attention to detail, calm, and thoughtfulness in solving design and methodological problems. She has been successful as a junior faculty member and the formation of a well-rounded mentoring team that has been meeting quarterly over the past three years demonstrates her initiative and leadership abilities.
I am an Assistant Professor of Pediatrics in the Division of Biostatistics and Epidemiology at CCHMC with a methodological expertise in structural equation modeling, latent class variable analysis (e.g. statistical methods applied to imperfect gold standards) and cluster analysis. My recent areas of interest include latent profile analysis of infant neruobehavior and of individual NIH stroke scale scores for mortality prediction. I have collaborated and mentored many clinical fellows and faculty since beginning at CCHMC. I will advise Dr. Ambroggio in advanced statistical techniques such as cluster analysis and when an imperfect gold standard is available to estimate the sensitivity and specificity of a multiple diagnostic tests. Dr. Ambroggio's proposed career development and training plan builds on her existing expertise and complements the proposed research. Additionally, her training plan will prepare her to transition to become an extramurally-funded, independent investigator focused on diagnostics using metabolomics methodology and advanced statistical analysis for pediatric infectious diseases. I will continue to meet with her monthly for the first year of the grant and then bi-weekly in years 2-4, however I am always available for informal meetings as needed.

The rapidity with which Dr. Ambroggio developed collaborative relationships and garnered recognition for her work at CCHMC is just the beginning of a trajectory that promises to lead her to become an independent investigator. The proposed research constitutes a deliberate and thoughtful set of studies that follows naturally from her prior work. This work will provide Dr. Ambroggio with the necessary data and research skills to submit and successfully complete a future R01-funded application. I look forward to my continued involvement in the research and career development of this talented individual.

Sincerely,

Heidi Sucharew, PhD
Biostatistician, Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center
Assistant Professor of Pediatrics, University of Cincinnati College of Medicine

Cincinnati Children's

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Division of Pathology and Laboratory Medicine

David P. Witte, M.D.
Division Director

Paul E. Steele, M.D.
Medical Director

Michael L. Baker, MD
Staff Pathologist

Kevin E. Bove, M.D.
Staff Pathologist

Margaret H. Collins, M.D.
Staff Pathologist

Anita Gupta, M.D.
Staff Pathologist

Robert Lorsbach, M.D., Ph.D.
Staff Pathologist

Richard McMasters, M.D.
Staff Pathologist

Lili Miles, M.D.
Staff Pathologist

Lindsey Romick-Rosendale, Ph.D.
Mass Spectrometry

Kenneth Setchell, Ph.D.
Mass Spectrometry

Shiva Shanmukhappa, Ph.D.
Research Pathologist

Amy Sheil, M.D.
Staff Pathologist

Rachel Sheridan, M.D.
Staff Pathologist

Jerzy W. Stanek, MD, Ph.D.
Staff Pathologist

Keith F. Stringer, M.D.
Medical Education

Dehua Wang, M.D.
Staff Pathologist

Mika Warren, M.D.
Staff Pathologist

Kathryn Wikenheiser-Brokamp, M.D., Ph.D.
Staff Pathologist

(513) 636-4261 Anatomic
(513) 636-3924 Fax
(513) 636-4686 Mass Spec
(513) 636-7853 Fax

Dear Members of the Review Committee:

It is with great pleasure that I support Dr. Ambroggio's K01 training goals related to ^{1}H-NMR quantitative metabolomics experimentation. *As the Director of the newly established NMR-based Metabolomics Core Facility at Cincinnati Children's Hospital Medical Center, I can ensure the committee that Dr. Ambroggio will have the necessary resources at her disposal to accomplish the specific aims proposed in her study titled "Metabolomic Evaluation of the Etiology of Pneumonia", in addition I will gladly provide intensive laboratory training in collaboration with the training she receives from Dr. Stringer as outlined in her K01 training plan.* The Metabolomics Core Facility is supported by the Cincinnati Children's Research Foundation (CCRF), therefore, Dr. Ambroggio will only be charged $30 per sample for time on the NMR; however, all other reagents needed for urine preparation and assay will be provided free of charge as well as access to Chenomx NMR Suite software for the identification and quantification of metabolites. I will meet with Dr. Ambroggio every other week for the first three years of the award and then monthly in years 4-5. In addition I will be on monthly phone calls with Drs. Stringer and Ambroggio during the period of award to discuss progress of Dr. Ambroggio's training and any potential barriers that may arise in regards to sample preparation, spectral analysis, or data interpretation.

The NMR-Based Metabolomics Core Facility is conveniently housed in the basement of the R building on the CCHMC main campus. The facility includes a wet lab, freezer space and has 3 full-time employees, including myself. The CCRF at CCHMC has purchased a new Bruker 600MHz NMR spectrometer, which is fully automated and optimal for metabolomics analysis of biological fluids. The instrument is equipped with a 96-well SampleJet autosampler and is ideal for high-throughput NMR data acquisition of patient samples. The spectrometer uses the same techniques as the NMR spectrometer in Dr. Stringer's laboratory. Thus, Dr. Ambroggio should easily be able to transfer techniques learned at one facility to the other. I and my staff have the necessary expertise and analytical capabilities to assist Dr. Ambroggio in carrying out this important research endeavor. Although Dr. Ambroggio will be performing all aspects of the Metabolomic Work Flow as described in her training plan, my staff and I will be available for supervision and guidance as she performs each step. I am also available for informal meetings with Dr. Ambroggio to discuss day to day questions while she is running her own samples for this award.

In closing, I offer my utmost support to Dr. Ambroggio in her K01 research and training goals. I am completely committed to the success of her proposal and training experience in the Metabolomics Core. Dr. Ambroggio is an exceptional investigator and this K01 will provide the necessary skills and experience to allow her to transition to an independent investigator.

Sincerely,

[redacted]

Lindsey Romick-Rosendale, PhD
Assistant Professor of Pathology
Director, NMR-Based Metabolomics Core Facility

Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue, Cincinnati, OH 45229-3039 | 513-636-4200 | www.cincinnatichildrens.org

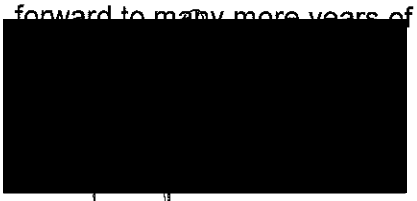
Dear Members of the Review Committee:

I write this letter in strong support of Dr. Lilliam Ambroggio's application, "Metabolomic Evaluation of the Etiology of Pneumonia". I am a pediatric emergency medicine attending physician and Assistant Professor in the Cincinnati Children's Hospital Medical Center (CCHMC) Division of Emergency Medicine. I received my MD from the University of Rochester School of Medicine & Dentistry in 2005 and completed pediatric residency, chief residency, and a fellowship in pediatric emergency medicine at the Children's Hospital of Philadelphia from 2005-2012. During my fellowship, I also received a Master's of Science in Clinical Epidemiology from the University of Pennsylvania.

Over the past three years Dr. Ambroggio and I have worked in collaboration with Dr. Samir Shah and Dr. Richard Ruddy to develop the study infrastructure for *Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine (CARPE DIEM)*, a prospective cohort study of children who present to the emergency department with pneumonia. Dr. Ambroggio's study will utilize this existing study for her K01 research and training aims. Dr. Ambroggio is the co-principal investigator, I am the principal investigator and Drs. Shah and Ruddy are senior mentors on the project. The four of us meet monthly to discuss overall study execution and progress on each one of the multiple aims of the study. This collaborative approach has allowed Dr. Ambroggio and me to develop independent research interests from each other and also from our senior mentors, while taking advantage of the exceptional mentorship from our 2 senior mentors. Dr. Ambroggio and I also meet weekly with our team of research coordinators to monitor study enrollment and progress. Dr. Ambroggio is responsible for inpatient sample collection and procedures. As the principal investigator, I am responsible for ED enrollment and lead the study operations for CARPE DIEM. In addition, we meet every 2 weeks with our data management team to develop and maintain the complex study database that includes clinical, laboratory, radiographic, biobank and survey data from multiple databases.

As we have developed distinct career interests, Dr. Ambroggio and I have benefitted tremendously from our close collaboration. Dr. Ambroggio's research is focused on using a systems biology approach that integrates epidemiological and metabolomics methodology to improve diagnosis of children with common infectious diseases. Her K01 training is focused on NMR-based metabolomics experimentation and advanced statistical methodology. My research program focuses on the use of clinical and translational methods, focused on predictive modeling and use of existing and novel biomarkers to improve the diagnosis and outcomes of pediatric pneumonia and other common infections in the acute care setting. Thus, we have a common goal in improving the outcomes for children with pneumonia however we are using substantially different approaches within the CARPE DIEM infrastructure to achieve this goal.

On a personal note, Dr. Ambroggio has been a wonderful peer collaborator. We have developed a relationship based on honesty and transparency which has led to higher quality research and productivity for each of our distinct paths. I believe Dr. Ambroggio's collaborative spirit, in addition to her outstanding epidemiological abilities, will make her a leader in her field. She is an exceptional candidate for this K01 award and I look forward to many more years of productive collaborations and peer mentorship.



Todd Florin, MD, MSCE
Assistant Professor, UC Department of Pediatrics
Cincinnati Children's Hospital Medical Center

Fairfield Primary Care Clinic
3050 Mack Road
Fairfield, OH 45014
513-636-8259

May 29, 2014

Dr. Lilliam Ambroggio
Cincinnati Children's Hospital Medical Center
3333 Burnet Ave ML 9016
Cincinnati, OH 45236

Dear Lilliam,

I am writing this letter to provide the strong commitment of Fairfield Primary Care Clinic to your proposed grant application titled "Metabolomics Evaluation of the Etiology of Pneumonia". I believe that there is great utility of a diagnostic test that can distinguish viral from bacterial pneumonia for children diagnosed with community-acquired pneumonia. I believe you have developed an innovative proposal using metabolomic methodology to accomplish this goal. As the medical director of Fairfield Primary Care Clinic, I will be the main contact on behalf of the other pediatricians within the clinic. Our clinic will be involved in the biological sample collection from healthy children who are visiting the clinic for routine well-child visits, and I am committed to work with you throughout this entire process.

Fairfield Primary Care Clinic is a primary care clinic with 8 providers, representing 4 Full-Time Equivalents, and is directly affiliated with Cincinnati Children's Hospital Medical Center. Due to our affiliation the protocol detailing the sample collection and extraction of clinical information from CCHMC's electronic medical records will be reviewed and approved by the Institutional Review Board at CCHMC. Our practice has approximately 56% minority patients and about 90% of our patients have Medicaid insurance. This is representative of the population that visits the emergency department on the main campus of CCHMC.

I look forward to working with you and your study team on this important endeavor.

[redacted]
Medical Director, Fairfield Primary Care Clinic

Assem G. Ziady, Ph.D.
Associate Professor of Pediatrics

Department of Pediatrics,
Division of Pulmonary Medicine
Cincinnati Children's Hospital Medical Center

3333 Burnet Avenue
MLC 2021
Cincinnati, OH 45229
Office R6391

T: 513-803-9094; F:513-803-4820
email: assem.ziady@cchmc.org

Dear Members of the Review Committee,

I am writing this letter in strong support of Dr. Lilliam Ambroggio's K01 award proposal, "Metabolomic Evaluation of the Etiology of Pneumonia". Dr. Ambroggio has identified a major gap in the management of community-acquired pneumonia (CAP), specifically the ability to identify the etiology causing pneumonia in children. Her proposal is thoughtful in its investigation of using quantitative NMR to distinguish bacterial and viral pathogens in children with pneumonia. As she indicates in her K01 training plan the logical next step is a R01 application to validate these profiles using a targeted approach such as tandem Liquid Chromatography-Mass Spectrometry (LC/MS^2). I am happy to train Dr. Ambroggio in using LC/MS in my laboratory during the 4^{th} year of her award. This will give her the practical expertise needed to add mass spectrometry to a multi-faceted approach in preparation for her future R01 application.

I recently joined faculty at Cincinnati Children's Hospital Medical Center in the fall of 2014 as an Associate Professor in the Division of Pulmonary Medicine. Prior to arriving, I was an Associate Professor and Associate Director of Cystic Fibrosis Basic and Translational Research within the Department of Pharmacology at Emory University. I also serve as a member of the Cystic Fibrosis Foundation Biomarker Consortium. My research program focuses on investigating inflammation in chronic lung disease and interventions that can modulate this inflammation. A central approach in our studies is the use of mass spectrometry for proteomic and metabolomic analysis of inflammation and the laboratory houses a state of the art LCMS ion trap mass spectrometer for these analyses. I will train Dr. Ambroggio on the study design, development and execution of targeted metabolomics studies using mass spectrometry.

As a PhD trained epidemiologist, Dr. Ambroggio brings a unique expertise that is lacking in the field of metabolomics. This field is moving toward clinical application for which population-based studies are invaluable. I believe that Dr. Ambroggio is an excellent candidate for this K01 award and look forward to providing her with the practical learning needed for her to accomplish this and future proposals. In addition I believe she will develop into a leader in the field with whom I hope to collaborate.

Sincerely,

[redacted]

Assem G. Ziady, Ph.D.
Associate Professor

Department of Pediatrics, Cincinnati Children's Hospital Medical Center
Division of Pulmonary Medicine

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DESCRIPTION OF THE INSTITUTIONAL ENVIRONMENT

Cincinnati Children's Hospital Medical Center (CCHMC) is a free-standing children's hospital with 629 beds and over 30,000 annual admissions that houses the Department of Pediatrics for the University of Cincinnati College of Medicine (UC). CCHMC is the primary provider of inpatient, subspecialty and emergency care in Greater Cincinnati and the surrounding counties serving over 2 million people. CCHMC is ranked second nationally among US pediatric institutions receiving NIH funding, having received $129 million in overall sponsored program awards in fiscal year 2015. The Cincinnati Children's Research Foundation (CCRF) was established in 1931 with an endowment that would exclusively support research. Currently this endowment exceeds $2 billion, and continues to support research today. CCHMC is the largest pediatric research institution in the nation, with nearly 1.5 million square feet of research space. The CCRF has a proven record of producing high-quality research and supporting the development of junior faculty through career development programs, and a commitment to collaboration. CCRF has 724 faculty members engaged in basic, clinical and translational research. In 2015, CCRF faculty authored >2,000 published manuscripts. In addition, junior faculty have access to all available academic programming at UC, including tuition remission and library resources. UC's Center for Clinical and Translational Science and Training (CCTST) is located on the CCHMC campus. It provides data management, bioinformatics support, and research nurses to aid in specimen collection for patients and grant development, through a Clinical and Translational Science Award and other mechanisms. Additionally, the CCTST sponsors a "K club" designed to provide both senior and peer mentorship to assist K-award recipients in achieving their research and career goals, as well as promote successful transitioning to R01 funding. The Office for Faculty Development offers relevant seminars for faculty, including a monthly grantsmanship series addressing challenges in writing grants and managing funds. CCHMC has an active Women's Faculty Association (WFA) that was developed in 1984. The overall goal of the WFA is to promote career development, advancement and recognition of women in the Department of Pediatrics. The WFA also provides an opportunity for women faculty to meet, network, and participate in informal mentoring activities. A major goal is to advance the careers of women in science. ***Division of Hospital Medicine,*** directed by Samir S. Shah, MD, MSCE, includes 45 academic faculty members and 7 fellows. The division includes 3 clinical services and cares for > 25,000 encounters each year, which is one-fourth of all patients hospitalized at CCHMC. Divisional faculty received ~$1 million in direct annual grant support in FY16 and collaborate regularly with faculty in 17 other CCHMC divisions on groundbreaking research initiatives. The Division is dedicated to providing travel support to all faculty members who have research abstracts accepted for presentations at national meetings. ***Division of Pediatric Emergency Medicine,*** directed by Dr. Stephen Porter is responsible for managing two large emergency departments (ED) and four urgent care facilities with annual visits of over 163,000 pediatric patients. This research will take place in the primary emergency department, a Level 1 Trauma Center, which had over 92,000 visits in 2014 and >1100 visits for pneumonia. The Division has 42 full-time faculty members with a research agenda to improve healthcare delivery among the ED population and was awarded over $1.67 million in research funding in 2014. This Division has a sophisticated infrastructure of research personnel who assist investigators with all aspects of their research. ***Division of Biostatistics and Epidemiology,*** directed by Maurizio Macaluso, MD, DrPH, was established to advance the capacity of CCHMC for clinical, translational, and population-based research that contributes to improving child health. The Division includes 98 faculty and staff who have received over $11.69 million in grant funding through collaborative and individual grants. The Division provides collaborative support to 54 research divisions at CCHMC. Division faculty members are also independently funded from the National Institutes of Health and other sources. ***NMR-Based Metabolomics Core,*** directed by Lindsey Romick-Rosendale, PhD, has a fully equipped laboratory within the Division of Pathology and Laboratory Medicine at CCHMC. The lab is fully equipped to process urine samples and conduct the proposed metabolomics experiement. Dr. Romick-Rosendale has direct access to a Bruker IVDr 600MHz spectrometer and Chenomx NMR suite 8.0 software to aid in spectral analysis. ***Ziady Laboratory,*** located at CCHMC is directed by Assem Ziady, PhD and houses a Tandem Liquid Chromatography-Mass Spectrometer and a fully equipped laboratory (~800 sq. ft) to process biofluid samples such as urine and blood specimens. ***Stringer Laboratory, University of Michigan,*** directed by Kathleen Stringer, PharmD, has a fully equipped laboratory (~500 sq. ft) in the College of Pharmacy on the central University of Michigan campus. Her lab is fully equipped to process urine samples and conduct the proposed metabolomics experiments. Dr. Stringer's laboratory shares the same building as the Biochemical NMR core laboratory allowing Dr. Stringer direct access to a state-of-the-art Varian 500 NMR spectrometer. It is a "research grade" instrument capable of performing all of the solution NMR techniques being proposed. The Stringer Laboratory processed and in collaboration with Dr. Ambroggio analyzed the samples used for preliminary data in this proposal.

Cincinnati Children's

UNIVERSITY OF Cincinnati

Department of Pediatrics

Margaret Hostetter, MD
BK Rachford Professor and Chair
Director, CCRF
Chief Medical Officer, CCHMC

Vice Chair for Research
Louis Muglia, MD, PhD

Associate Chair for Clinical Affairs
Chief of Staff
Derek Wheeler, MD

Associate Chair for Community Health
Robert Kahn, MD, MPH

Associate Chair for Education
Thomas DeWitt, MD

Associate Chair for Finance
Lori Stark, PhD

Associate Chair for Liberty Campus
Richard Ruddy, MD

Associate Chair for Outcomes
Evaline Alessandrini, MD

Associate Chair for Promotion and Academic Affairs
Jessica Kahn, MD

Associate Chairs for Research
Tracy Glauser, MD
Jeffrey Whitsett, MD

Cincinnati Children's Research Foundation

Vice President, Finances
Jana Bazzoli

Vice President, Research Operations
Kristine Justus, PhD

June 16, 2016

National Institutes of Health
Center for Scientific Review
Bethesda, Maryland

Dear Members of the Review Section:

It is my great pleasure to write a letter in support and institutional commitment for the application of Lilliam Ambroggio, PhD, MPH for a K01 award titled "Metabolomic Evaluation of the Etiology of Pneumonia". We were excited to recruit Dr. Ambroggio to the Division of Hospital Medicine and Biostatistics and Epidemiology, as an Assistant Professor of Pediatrics, in August 2013 after the completion of her post-doctoral training.

Dr. Ambroggio has been an exceptionally successful junior faculty member. She has assembled an outstanding team of experienced mentors who bring diverse skillsets. She has also obtained internal and external funding for her work, including a highly competitive Trustee Award to develop pilot data for her K01 application, and has presented her research at national and international conferences. This K01 award would provide her with the opportunity to develop advanced skills in metabolomic experimentation and statistical methodology and to develop a deep understanding of etiology detection, which can lead to targeted antibiotic therapy for childhood pneumonia and, ultimately, other serious infections.

The Strategic Plan 2020 for the Department of Pediatrics is focused on accelerating discovery, innovation and translation in the biomedical sciences. To this end the Department has supported institutional cores to propel the –omics field forward. In July 2014 we established a NMR-based Metabolomics Core directed by Dr. Lindsey Romick-Rosendale in which Dr. Ambroggio will spend part of her time training. Along with Dr. Ambroggio's post-doctoral training in quality improvement science and systems management, this background differentiates her from the candidate who has standard training in infectious diseases research. Talented faculty members such as Dr. Ambroggio have the potential for driving discovery science from the bench to implementation at the bedside.

Dr. Ambroggio is at the end of her third-year as a full-time, salaried Assistant Professor, and her retention is not contingent upon receipt of the K01 award. I assure the selection committee that the Department of Pediatrics will guarantee her time for research at 75% or more of full time professional effort. Her remaining 25% effort will be dedicated to fellow, graduate and undergraduate teaching and other research efforts that are aligned with her research goals.

As Director of the Cincinnati Children's Research Foundation at CCHMC and Chair of the Department of Pediatrics at the UC College of Medicine, I assure you that Dr. Ambroggio has the necessary resources, such as office space, networked computers, and access to core facilities (e.g. Cincinnati Biobank Core Facility), travel and education funding, administrative support, and grants management to conduct her research in a successful and efficient manner. I am committed to the mentoring of junior faculty and support Dr. Ambroggio's mentors with dedicated effort to work with mentees and pursue other educational and academic developmental tasks. Furthermore, our institutional affiliation with the UC Center for Clinical and Translational Science and Training, will provide Dr. Ambroggio with additional resources to support her research and career development.

This K01 award will be just the first step in a fruitful independent research career with the potential to improve care of children diagnosed with pneumonia by detecting the specific etiology of the pneumonia and subsequently targeting therapy. As such, Dr. Ambroggio is an outstanding candidate for a K01 career development award and I support her application with the greatest confidence of success.

Very truly yours,

[redacted]

B.K. Rachford Professor
Chair, Department of Pediatrics
Director, Cincinnati Children's Research Foundation
Chief Medical Officer, Cincinnati Children's Hospital Medical Center

12. PROTECTION OF HUMAN SUBJECTS

Multiple precautions, described below, have been put in place to protect participants in the studies proposed for this application. **Except where a specific group is listed (i.e. case group or control group), precautions apply to all participants being enrolled as part of the entire proposal.** This protocol has been approved under CCHMC IRB #2014-1290.

1. Risk to Human Subjects: Involvement, Characteristics, and Design.

a. Human Subjects Involvement and Characteristics

Inclusion Criteria
Patients will be eligible for enrollment in the control group if they:

- Are 3 months to 11 years of age;
- Are being seen at a CCHMC-affiliated primary care clinic for a well visit
- Have not had a documented LRTI in the past 7 days

Patients will be eligible for enrollment in the case group if they:

- Are 3 months to 11 years of age AND
- Have signs and symptoms of lower respiratory tract infection as defined by at least one of the following: new or different cough, new or different sputum production, chest pain, dyspnea/shortness of breath, documented tachypnea, abnormal findings consistent with LRTI on examination (e.g. crackles, rhonchi, wheezing, dullness), or acute respiratory failure requiring mechanical ventilation; AND
- Have a new focal infiltrate on chest radiograph

Exclusion Criteria
Patients will be ineligible for enrollment in either control or case group if any of the following is present or anticipated:

- Lack of parental consent and/or child assent for children 11 years of age.
- Hospitalized ≤14 days before the study ED visit
- Immunodeficiency or immunosuppression, including malignancy, chronic corticosteroid use
- Chronic pulmonary disease, including cystic fibrosis, tracheostomy-dependent patients
- Congenital cardiac disease
- Sickle-cell disease
- Neuromuscular disorders
- History of aspiration or aspiration pneumonia at any time in the potential subject's medical history

b. Sources of Materials

The study will be conducted within the ED and when applicable on the Hospital Medicine service at CCHMC or at a CCHMC-affiliated primary care clinic. Trained clinical research coordinators (CRC) who staff the ED 16 hours per day for 4 days per week and 8-12 hours per day for 3 days per week will initially identify patients with respiratory-related chief complaints, such as "cough," "difficulty breathing," "shortness of breath," "respiratory distress," "fever," "pneumonia," or "wheezing." These subjects will then be screened using the protocol inclusion and exclusion criteria. Eligible subjects will be approached to obtain informed consent in the ED. Trained CRC from Hospital Medicine (HM) will screen subjects using the protocol inclusion and exclusion criteria for the control group at the CCHMC-affiliated primary care clinic. HM CRCs will be available 8 hours per day for 5 days a week for recruitment.

Emergency Department OR Primary Care Clinic Phase
After consent is obtained, research staff will collect demographic and historical information from the patient and/or parent. Attending physicians will complete a case report form assessing clinical symptoms, motivations for disposition decisions and patient severity. All data will be recorded in a secure database in the REDCap system. Research staff will also provide nursing staff with the specimen collection tubes to obtain the necessary blood, urine, and/or nasopharyngeal samples as detailed by the research protocol. For easily obtained samples, such as urine in an older child, the CRC will provide the specimen containers directly to the patient for collection. Specimen collection will occur as part of routine care as much as possible (e.g. blood samples will be collected at the time of IV placement). Any collection procedures not part of routine care will occur only with consent of the parents and/or patients.

Specimen processing and storage will be facilitated by the CBCF. Clinical data, such as vital signs, history and physical exam findings, test results, will be extracted from the electronic medical record into the REDCap database. All patients will have the following tests performed as part of either their clinical care or the research protocol if not obtained as part of their clinical care: c-reactive protein (CRP), procalcitonin, blood culture, and respiratory viral panel. Clinicians caring for enrolled patients will be blinded to all study laboratory results, with the exception of positive blood culture results.

Hospital Phase for Case Samples Only
For those patients admitted to the hospital from the ED, daily clinical data will be extracted from the EPIC, the electronic medical record, into the REDCap database. A Hospital Medicine CRC will review the REDCap database regularly to check for any enrolled patients that were admitted. A HM CRC will collect blood and urine samples prior to the patient being discharged from the hospital.

Follow-Up Phase
All patients enrolled in the study will receive a follow-up phone call approximately 7-10 days after their ED visit to assess clinical symptoms and disease course.

c. *Potential Risks*
There is minimal risk associated with this protocol. This study does not involve any medications or therapies. The primary risks associated with this protocol are those related to sample collection including blood and other biological specimen collection procedures, which are typical procedures in a hospital setting. Potential discomforts associated with a blood draw are bruising and possible infections. There is potential discomfort associated with a nasopharyngeal swab. Every effort will be made to minimize these risks. Additionally, this research also carries a minimal risk of loss of data confidentiality/security. Section 2.b., below, describes the ways in which we will mitigate exposures to risks. These risks will be presented to the patient and parent prior to enrollment, and if the subject is interested in study participation, informed consent will be obtained. Alternatively, a potential subject can receive standard care if they choose to not enroll in the study.

2. Adequacy of Human Subjects Protection
a. Recruitment and Informed Consent
During the research study, potential participants will be screened for possible eligibility, approached in the CCHMC ED or primary clinic and presented the opportunity to participate in the study. After determining eligibility and interest in the study, research study staff will review the consent document with the parent or legally authorized representative (LAR), and the patient. The consent document is prepared to account for participant consent, parental permission, participant assent, and HIPAA Authorization. In cases where the patient is not able to consent for himself/herself, the parent or LAR will provide parental permission for their child to participate in the research study. When the parent or LAR provides written permission, the child (if appropriate) will be asked to provide written assent. Written assent will be documented for participants 11 years of age and older. The consent is written in a way that agreeable participants have the opportunity to deny the collection of specimens which the participant and/or parent does not allow to be collected as part of their participation in the research study. This study was approved by the CCHMC IRB on April 24, 2013 (IRB # 2012-4959).

b. *Protection against Risk*
Blood and Biological Specimen Collection
When possible, blood draws and other sample collections from patients will coincide with sample collection for clinical care. Potential risks associated with obtaining nasopharyngeal samples include a brief period of discomfort when the swab is inserted into the nose to collect the sample. Urine collection is non-invasive and is collected in a bag or cup depending on developmental stage of the child.

Data Confidentiality
Data will be entered into a secure electronic database. Risks associated with loss of electronic data confidentiality/security will be mitigated through the utilization of standard CCHMC research network security process to ensure that only authorized CCHMC personnel have access to the research data.

Consistent with CCHMC information security policies, no individually identifiable information will be transmitted outside CCHMC's secure research network environment. Additionally, no identifiers will be used in publications.

3. Potential Benefits of the Proposed Research to the Participants and Others

There are no potential direct benefits for the participants, as the data derived from this study will not be used for clinical decision making for each individual patient. Overall, the potential benefits will be improvement in clinical care provided to patients with CAP, in that identification of CAP severity and etiology may result in less antibiotic therapy, more appropriate antibiotic therapy when required and improved clinical prediction of prognosis.

4. Importance of Knowledge to be Gained

There is currently no accurate method to predict CAP severity or etiology in children using either clinical scores or biomarkers. This can result in overtreatment with antibiotics, unnecessary hospitalization, or delays in appropriate treatment in patients who are at risk for CAP-related morbidity. There is an urgent need for accurate and reliable tools to predict which children with CAP will develop severe disease or complications requiring hospitalization and which children will require aggressive antibiotic therapy. Completion of the aims outlined in this proposal will identify pathogens within broad classes of disease, viral and bacterial, which cause CAP. We expect this to result in a key positive impact by facilitating observational and interventional studies in children with CAP, with the ultimate goal of targeting antibiotic therapies for children diagnosed with bacterial CAP while reducing use of unnecessary antibiotics in children diagnosed with viral CAP.

5. Data Safety and Monitoring Plan

A Data Safety Monitoring Board will not monitor this study because this is a minimal risk and non-therapeutic protocol. There is no research study intervention. The principal investigator and study team will review any unanticipated problems related to data safety or adverse events, and the principal investigator or study personnel will report unexpected adverse events according to CCHMC IRB policy. Any serious adverse event will lead to a cessation of enrollment until the relationship between the adverse event and the study conduct is determined. All serious adverse events will be reported to the IRB within 48 hours and other adverse events will be reported on an annual basis at time of continuing review by the IRB.

14. INCLUSION OF WOMEN AND MINORITIES

No study subject will be excluded based on [redacted] on race/ethnicity. Based upon the known demographics in the Emergency Department at CCHMC and the Fairfield Primary Care Clinic, we expect the study population for both aims to be approximately 48% female, 48% white, 45% black or African American and 96% identifying as non-Hispanic ethnicity.

PHS Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

OMB Number:0925-0001 and 0925-0002
Expiration Date: 10/31/2018

***Study Title:** Metabolomic Evaluation of the Etiology of Pneumonia

***Delayed Onset Study?** ❑ Yes ☑ No

If study is not delayed onset, the following selections are required:

Enrollment Type ☑ Planned ❑ Cumulative (Actual)

Using an Existing Dataset or Resource ❑ Yes ☑ No

Enrollment Location ☑ Domestic ❑ Foreign

Clinical Trial ❑ Yes ☑ No

NIH-Defined Phase III Clinical Trial ❑ Yes ☑ No

Comments: 250 patients with pneumonia and 125 patients without any known infections will be recruited for this study.

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	0		0	0					**0**
Asian	1	1		0	0					**2**
Native Hawaiian or Other Pacific Islander	0	0		0	0					**0**
Black or African American	79	83		0	0					**162**
White	83	90		1	1					**175**
More than One Race	12	14		5	5					**36**
Unknown or Not Reported										
Total	**175**	**188**		**6**	**6**					**375**

15. INCLUSION OF CHILDREN

Children are the focus of this research. We plan to include children, 3 months to 11 years of age, in all the studies outlined in this research proposal. All participants will require parental consent, as well as child assent for children 11 years old. All studies are considered minimal risk.

16. Vertebrate Animals

Vertebrate animals will not be used to conduct this study.

17. Select Agent Research

There will be no hazardous biological agents or toxins that are used as part of this study.