A. Cover Page—Grant ID 36504513

1. Title: **Penicillin Allergy Skin Testing in the Inpatient Setting: "closing the gap"—an initiative to improve infectious disease management, reduce antibiotic resistance, and yield health care savings**

2. Abstract:

This pilot study addresses a significant practice gap in the management of purported penicillin allergy in hospitalized patients. Up to 90% of listed penicillin allergies are invalid; prior data suggest such patients have longer hospital stays, higher rates of resistant nosocomial infections, greater healthcare utilization, and even higher mortality; and a validated and reliable testing method exists; yet, no interventional testing protocol has been implemented on a large scale for inpatient testing. In this study, we will test the feasibility and impact of implementing evidence-based penicillin allergy testing guidelines on a hospital-wide level among patients admitted to our hospital with penicillin allergy. Demonstrable improvements in utilization of broad-spectrum antibiotics, healthcare cost, nosocomial infections, length of stay, mortality, and other metrics as a result of this pilot study may enable implementation of this protocol as an ongoing quality improvement measure at our institution and other major health systems.

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C. Reviewer Comments

Reviewer comments: "While all review panel members were interested by your program and look forward to reading your full proposal, there is a request for more information on the mentoring that will be available throughout the project."

There is a wealth of mentoring available on a number of levels for the planning and support of this work. This includes experts in allergy / immunology, infectious diseases, quality improvement, and inpatient dermatology, all with special interest and expertise in prevention and management of drug reactions, who will provide critical advice and support in facilitation of this project. Additionally, through our resident training program and QI / QA track, the faculty involved in this project will play a key role in mentoring Dr. Caplan, a resident physician who has been involved in the planning and will be involved in the conduct of this study. Specifically, we would highlight those collaborators outside the department of dermatology:

Dr. Phillips is an internationally known expert in severe drug reactions and innovative approaches to drug allergy testing. She runs a specialty referral and research clinic at Vanderbilt University dedicated to the study and clinical applications of drug allergy testing. She is an expert in penicillin testing and provides a wealth of practical experience with respect to design and conduct of studies in this area. Her support and mentorship will be invaluable in making this work a success.

Dr. Fadugba is an allergist at the University of Pennsylvania who is the quality improvement and patient safety lead for her division and regularly performs penicillin skin testing both on outpatients and inpatients as part of the allergy and immunology consult service. She has a special interest in penicillin skin allergy testing and implementation of that testing on a larger scale. Her experience performing penicillin allergy testing on inpatients at our hospital will be invaluable in creating the study protocol, maintaining safety and quality control standards, and interpreting results.

Dr. Hamilton is an infectious diseases specialist at the University of Pennsylvania who is the Director of Antimicrobial Stewardship at the Hospital of the University of Pennsylvania. He has a keen interest and expertise in the subjects of drug allergy and appropriate utilization of antimicrobial resources. His support with respect to implementation of this protocol and hospital-wide antimicrobial administration strategy stemming from the results of allergy testing will be critical to the conduct of this study.

D. Main Section of the proposal

1. *Overall Goal & Objectives:*

The overall goal of this initiative is to improve patient outcomes and save health care dollars by reducing unnecessary use of non-beta-lactam antibiotics prescribed as a result of inappropriate listing of penicillin allergy in the patient record.

This project highlights and directly addresses a substantial practice gap between listed and actual penicillin allergy that exists despite the availability of a validated and available penicillin allergy testing method. We will utilize existing data and the expertise of our study team in the areas of dermatology, allergy, infectious diseases, and quality improvement to implement a hospital-wide strategy for closing this gap. If shown to be feasible and impactful with the help of these pilot funds, the ultimate goal will be permanent implementation of inpatient penicillin skin testing at our health center and beyond, thereby improving outcomes related to infectious diseases, reducing the burden of antibiotic resistance and nosocomial infections, and reducing healthcare expenditures.

These aims are of broad interest to dermatologists, who diagnose and manage drug eruptions, allergists, infectious diseases specialists, hospital administrators, policy makers, and any physician prescribing (as well as any patient receiving) beta lactam antibiotics. The potential impact of this effort is significant.

2. Current Assessment of need in target area

Penicillin allergy is the most commonly reported drug allergy, reported in up to 10% of patients. Such patients are frequently instructed to avoid all beta-lactam antibiotics, including other penicillin derivatives, cephalosporins, and carbapenems. When treated for infections, such patients often receive antibiotics which are broader spectrum, suboptimal, and potentially more toxic. Reported penicillin allergy thus creates significant potential challenges for patient care, both in the inpatient and outpatient settings.

Perhaps nowhere are these challenges felt more acutely than on the inpatient medical ward, where reported penicillin allergy forces providers to use alternative, less-preferred regimens for serious or potentially life-threatening infections, resulting in higher medical costs and longer hospital stays. Meanwhile, antibiotic resistance and antibiotic-associated complications like C. difficile colitis are growing problems to which exposure to alternative antibiotic regimens are a significant contributing factor. Retrospective matched cohort studies have shown that patients with reported penicillin allergy have an increased length of hospital stay and are more likely to develop infection by *C. difficile*, methicillin-resistant *Staph aureus*, and vancomycin-resistant *enterococcus*.

Nevertheless, data suggest more than 90% of patients who report penicillin allergy do not have a true allergy. Additionally, people with a remote history of allergic reaction may become less allergic over time, such that only 20% of patients with a true penicillin allergy continue to be allergic 10 years after the initial reaction. There is therefore significant potential that reported penicillin allergy is inaccurate in the vast majority of patients.

Penicillin skin testing is a validated, commercially available, and easily performed bedside procedure with a negative predictive value approaching 100%. Most patients receiving such testing will have negative results, which greatly simplifies future antibiotic treatment and should improve clinical care outcomes. Based on expert consensus, the American Academy of Allergy, Asthma, and Immunology recommends this approach to validating reported penicillin allergy.

Despite being commercially available, however, penicillin allergy testing is not routine practice in most clinical settings. In recent years, various institutions have examined the feasibility and impact of implementing a protocol for penicillin allergy testing in the inpatient setting. However, a well-defined institution-wide protocol for performing inpatient penicillin skin testing for patients who are likely to require a Beta-lactam agent has not yet been broadly instituted.

Initial analyses based on epidemiologic data and the number of patients admitted annually to HUP (~34,000) suggest as many as 3,400 patients listed as penicillin-allergic may be admitted to our hospital annually. Of these, greater than 3,060 patients likely have no true allergy to penicillin.

Beta lactam allergy label has been found to be associated with several adverse outcomes. A recent retrospective cohort study conducted at the University of Pennsylvania, found that patients with hematologic malignancy (leukemia, lymphoma, myeloma) with beta-lactam allergy label had longer length of hospital stay, increased use of antibiotic classes, higher rates of acute kidney injury and higher rate of *Clostridium difficile* infection than those without this label (manuscript submitted and under revision).

Prior retrospective case-control studies have demonstrated that such patients who receive penicillin skin testing are approximately 90% likely to have a negative test result and are 51.6-81.5% less likely to receive alternative, non-preferred antibiotic therapies.

3. ***Target Audience:***

The target audience for this project is patients admitted to The Hospital of the University of Pennsylvania (a tertiary care academic referral center with approximately 800 beds) with a listed penicillin allergy over a 6-month period. The

target population we propose to enroll are patients who are highly likely to receive an antibiotic and for whom beta-lactams are clearly the treatment of choice, including but not limited to endocarditis, meningitis, bacteremia, and neutropenic fever. These patients will be compared to a contemporaneous, randomly-selected cohort of equal size who will not receive testing. We expect that 80-90% of tested patients will have negative test results, as documented in past studies of inpatient penicillin skin testing. Therefore, there is potential for a large proportion of these patients to have their penicillin allergy label removed. In turn, we expect to be able to demonstrate differences in key metrics such as use of beta lactam agents after skin testing, healthcare cost, rates of antibiotic-resistant nosocomial infections, hospital length of stay, and even mortality.

While this is an interventional study, study procedures are considered low-risk. Published retrospective studies have reported no significant adverse events from penicillin testing interventions. Patients who undergo selection for skin testing will be assessed to ensure that they are low-risk for testing. We will exclude those patients with recent anaphylaxis to penicillin antibiotic and those with serious non-IgE mediated reactions such as Stevens-Johnson syndrome / toxic epidermal necrolysis, for whom skin testing is contraindicated. The potential benefits related to improved infectious outcomes, decreased length of stay, reduction in adverse events related to non-preferred regimens, and reduced health care costs, will outweigh any associated with allergy testing. We anticipate the level of commitment from potential patient participants in this effort will be high, and that most admitted patient approached by our team will agree to participate.

Direct beneficiaries of the outcome of this project will include those patients tested who are shown not to be penicillin-allergic. Successful demonstration of the feasibility of this effort, including improved patient care and cost savings, should lead to institutional funding for implementation of an inpatient-based penicillin testing team on a permanent basis. Over time, such a team has the potential to impact many thousands of patients and reduce the risk to our community posed by antibiotic resistance and nosocomial infections such as *Clostridium difficile*.

Since we intend to publish the results of this effort, successful implementation and demonstration of benefit has the potential to become a model for other centers. Improved patient outcomes and cost savings resulting from performing a readily-available, safe, and validated test will help spur change on a larger scale and help close the current practice gap. Innumerable patients and society as a whole have the potential to benefit from this relatively simple intervention via lower healthcare costs, antibiotic resistance, and nosocomial infections.

4. ***Project Design and Methods:***

The proposed study will be a randomized, controlled interventional study investigating the outcome of penicillin skin testing in a population of patients admitted to a tertiary care hospital.

We will utilize our electronic medical records system to identify in real time patients admitted to the hospital with purported penicillin allergy. With the help of our information technology support staff, we will build an alert system which sends an automatic notification to our team when patients with a listed penicillin allergy are admitted. We proposed to enroll patients who are highly likely to receive an antibiotic and for whom beta-lactams are clearly the treatment of choice.

Members of our team will evaluate potential subjects for eligibility and obtain informed consent to participate in the study. Patients will be randomized either to receive testing or be included instead in a comparator group of controls. For those assigned to undergo testing, trained staff will obtain a detailed allergy history and, when deemed appropriate, administer the validated penicillin skin testing protocol, followed by observed oral challenge, to prove or disprove the presence of true penicillin allergy. We estimate the total time involved for each patient will be approximately 3-4 hours, and this can easily be accommodated during a typical inpatient stay. The team will issue an evidence-based interpretation of the veracity of the patient's penicillin allergy and then, when possible, delist the allergy in the medical record along with notification of test results in the chart system. Patients will be entered into the study and receive testing within 24 hours of the time of hospital admission so that subsequent antibiotic interventions can reflect the outcome of that testing.

Key metrics will include: 1) the number and percentage of true and untrue penicillin allergies in the target population, 2) the use of beta lactam and other antibiotic(s) after receiving skin testing, 3) the actual cost of any antibiotic therapy received, 3) the theoretical cost of an antibiotic regimen to treat the same infections which excludes penicillins, 4) the length of hospital stay, 5) the total cost of the inpatient stay, and 6) patient mortality (both in-hospital and within 30 days post-discharge). These outcomes will be compared to the cohort of patients with listed penicillin allergy who do not receive testing (controls). We will control / adjust for key factors such as age, sex, and Charlson comorbidity index. These outcomes are of paramount interest to policy makers interested in patient safety and quality of care. Demonstration of significant differences in one or more of these metrics will help establish the utility of penicillin testing in the inpatient setting and justify its wider adoption.

We have every reason, based on prior data, to anticipate success of this project. Prior work has demonstrated the accuracy and reproducibility of the testing protocol. Such testing is done routinely in some specialized outpatient testing centers. Models have predicted that routine testing of this nature should produce significant health system savings, if implemented. Our target inpatient patient population is complex and sick, and we anticipate any effects of de-labeling penicillin allergy will be magnified in such a cohort compared to a standard non-acute outpatient population. Consequently, we will be well-positioned to demonstrate a difference between outcomes of the intervention and control groups that justifies implementation of this model at our and other institutions moving forward.

5. Evaluation Design

A significant practice gap exists in which the vast majority of patients thought to be allergic to penicillin are not actually allergic to that medication, yet a simple, validated, and commercially available test which could correct inaccurate allergy designation is not routinely administered to the population of sick and complex inpatients who could benefit most from its use.

In order to determine whether this project adequately addresses the stated practice gap, we will look at both direct and indirect measures of our intervention's impact.

Among direct measures, we will measure the frequency of listed penicillin allergy encountered among patients admitted to our hospital during the study period. Following testing, we will document the number and percentage of true and untrue penicillin allergies in the target population. These two measures together will provide a sense of the scope of the problem in our local hospital and show what potential there is to narrow the gap with respect to eliminating false penicillin allergy designations from patient medical records.

Among indirect measures, we will determine the rate of use of beta lactam antibiotics following testing, the actual cost of any antibiotic therapy received, the theoretical cost of an antibiotic regimen to treat the same infections which excludes penicillins, the length of hospital stay, the total cost of the inpatient stay, and patient mortality (both in-hospital and within 30 days post-discharge). These outcomes can reflect other confounding factors which are independent of antibiotic choice. However, by controlling for key factors such as age, sex, and medical comorbidities and by comparing outcomes to those of a contemporaneous

control population of inpatients with listed penicillin allergy who do not undergo testing, we will determine the impact of our intervention on certain critically important patient quality metrics.

All data will be derived prospectively from our electronic medical record using a standardized form and managed in a secure database using Research Electronic Data Capture (REDCap) tools hosted by the University of Pennsylvania. Descriptive statistics will be used to examine the frequency and distribution of covariates of interest. Comparisons between groups will be made using chi-squared analysis or Fisher's exact test for dichotomous variables and the Student's t-test or Mann-Whitney rank sum test for continuous variables. Logistic regression will be performed to help control for potential confounding variables. All statistical analysis will be performed using STATA 13 (Stata Corporation, College Station, TX).

Based on available literature stating that 90% of listed penicillin allergies are incorrect, we anticipate it will be fairly easy to demonstrate a reduction in listed penicillin allergies in the intervention group compared to controls. With respect to the other metrics of interest, an anticipated 90% reduction in listed penicillin allergies in the intervention group should, in turn, make reductions in utilization of second-line antibiotics, healthcare costs, rates of resistant nosocomial infections, and hospital length of stay demonstrable.

If this effort is successful, we plan to implement it on a larger scale as an ongoing, available service in our hospital. Outcomes of this project will be written up for publication in an appropriate medical journal for broad dissemination. We will present the results at applicable medical conferences relevant to antimicrobial stewardship, drug reactions, and health policy / quality improvement.

6. Detailed Workplan and Deliverables Schedule:

Upon approval of this grant proposal, we will begin preparations for formal construction and implementation of our research protocol. This process will include discussions with key hospital personnel to obtain the full buy-in of all interested parties. One of our collaborators / co-investigators, Dr. Hamilton, the current Director of Antimicrobial Stewardship at the Hospital of the University of Pennsylvania, will be central to this effort. Additionally, an application will be prepared for submission to the Penn IRB for approval.

In addition, we will work with Penn information technology services to construct an auto-flag system within our inpatient electronic medical record system to alert our team of admitted patients with listed penicillin allergy. Similar alert systems already exist for both clinical and research projects within the institution.

Meanwhile, we will work on refining our staffing protocol to ensure we can respond to appropriate enrollment and testing opportunities and ensure adequate oversight. This will occur with the help of Dr. Fadugba in allergy / immunology, which currently administers such testing on a smaller scale, as well as the inpatient dermatology team. The nurse research coordinator will receive any necessary training and will work directly with these investigators.

We anticipate it will take approximately 6 months to put these critical elements in place, receive IRB approval, and be ready to begin enrolling. Once enrollment begins, we anticipate keeping the study open for an additional 6-month period. Total time from study start to completion will be 12 months.

1/1/2018	6/1/2018	1/1/2019
Refine formal protocol	Enrollment begins… →	Presentation of data Internally…
IRB submission	…Enrollment completed	…and at scientific meetings
Discussions with key hospital personnel →		Implementation of full-scale testing at UPenn
…Training of research nurse		Manuscript preparation and publication
		Identify next steps for investigation in this area

E. References

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