Inpatient Penicillin Allergy Delabeling Pilot Project at University HospitalsRainbow Babies and Children's Hospital in Cleveland, Ohio

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Objectives

To verify pediatric patients with reported penicillin allergy in electronic medical record (EMR) by performing current standard of practice oral amoxicillin challenge testing.

Hypothesis:

Pediatric patients with reported penicillin allergy in EMR can be verified by performing current standard of practice oral amoxicillin challenge testing.

Specific objectives:

1. To identify no-risk, low-risk and high-risk patients among pediatric patients with reported penicillin allergy in EMR through a standardized questionnaire.
   Hypothesis: No-risk, low-risk and high-risk pediatric patients with reported penicillin allergy in EMR can be identified using a standardized questionnaire.
2. To be able to delabel pediatric patients with reported penicillin allergy in EMR who are identified as no-risk.
   Hypothesis: No-risk pediatric patients with reported penicillin allergy in EMR can be delabeled using a standardized questionnaire.
3. To be able to delabel identified low-risk pediatric patients with reported penicillin allergy in EMR who are verified not allergic to penicillin by current standard of practice oral amoxicillin challenge testing.
   Hypothesis: Identified low-risk pediatric patients with reported penicillin allergy in EMR using a standardized questionnaire can be verified using current standard of practice oral amoxicillin challenge testing.
4. To be able to provide proper referral guidance to patients identified as high-risk and those who failed oral amoxicillin challenge testing to allergy and immunology for further evaluation and management.
   Hypothesis: Proper referral guidance to patients identified as high-risk and those who failed oral amoxicillin challenge testing to allergy and immunology can be provided for their further evaluation and management.

Background

Penicillin remains a reliable class of antibiotic that addresses majority of infections both in outpatient and inpatient settings. [1,2] It is also one of the cheapest antibiotics to use for empiric therapy for susceptible infections. [3,4] Emerging literature suggests that the number of patients with historical penicillin allergy is an overestimate. A growing number of studies show that only approximately 10 % of patients with historical penicillin allergy are truly allergic after verified allergy testing is done. [1-3,5,7] Despite this, efforts on antibiotic allergy delabeling remains sparse and penicillin allergy remains to be the most common drug allergy reported.

Moreover, few institutions have validated, much less implemented, protocols to determine truly allergic patients who have reported penicillin allergy when diagnosed with infections theoretically susceptible to penicillin.[6] One limitation perhaps is the absence of validated questionnaire that uniformly captures accepted levels of risk especially in the pediatric population.[7] As a result, these patients end up receiving alternative antimicrobial agents that pose a risk for emergence of resistance, development of

unnecessary intestinal dysbiosis and increased economic burden to health care resulting in suboptimal clinical outcome. [1-6]

Thus, identifying patients with no immunologically-mediated penicillin allergy and delabeling them in the electronic medical record (EMR) accordingly will mitigate the use of second-line antibiotics, aid in minimizing development of resistance, ameliorate unnecessary economic burden and overall lead to positive impact in clinical outcome and patient care. In the same way, this process will also identify patients with true penicillin allergy creating a point-of-care opportunity to provide them proper guidance on the importance of Allergy/Immunology followup for further evaluation and management.

Inclusion and Exclusion Criteria

	Inclusion Criteria for screening
1.	Patients 3-18 years old admitted at Rainbow 3, 5 and 6 with penicillin allergy label on EMR identified through TheraDoc database (including patients admitted for antibiotic therapy for an infection)
2.	Patients with available parent/s or legal guardian who can give both written and verbal consent to the oral challenge testing
3.	Patients with available parent/s or legal guardian during the conduct of oral amoxicillin challenge testing
	Inclusion Criteria for oral challenge test
1.	Patients who will be identified as low-risk patients based on the standardized screening questionnaire. Low-risk group patients are those patients with previous reaction not suggestive of anaphylaxis AND not requiring hospitalization for the reaction OR reaction considered non-immunologic (e.g. diarrhea, nausea, yeast vaginitis) OR exposure to penicillin-containing antibiotic after the date of reported reaction with no anaphylaxis and hospitalization AND no serious types of delayed reactions such as Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute interstitial nephritis (AIN), drug-induced hepatitis or other documented organ injury, drug rash eosinophilia systemic symptoms (DRESS), hemolytic anemia, drug-induced cytopenia, and serum sickness. Patients who had delayed reaction (onset more than 24 hours) of isolated, non-progressive
	symptoms (such as rash/hives alone) also belong to this group.

	Exclusion Criteria for screening
1.	Patients who cannot tolerate amoxicillin by enteral route.
2.	Patients with no parents or legal guardian available to give both written and verbal consent to the oral challenge testing
3.	Patients with no available parents or legal guardian during the conduct of oral amoxicillin challenge testing
4.	Patients currently on antihistamine or have received antihistamine in the previous 48 hours
5.	Patients who are critically ill or unable to complete challenge testing due to intercurrent illness
6.	Patients who have been vomiting more than twice in the past 24 hours or are actively vomiting
7.	Patients with respiratory symptoms warranting oxygen therapy or pulmonary finding of wheezing or stridor
8.	Patients identified as having anaphylactic reaction to penicillin in the EMR through TheraDoc system.

	Exclusion Criteria for oral amoxicillin challenge testing
1.	Patients who will be identified as no-risk patients based on the standardized screening questionnaire. No-risk group patients are those patients who are historically labeled with penicillin allergy in the EMR based on family history alone OR those who have tolerated penicillin after a concerning incident without any reaction OR with penicillin allergy label but deny any history of reaction to any form of penicillin on screening questionnaire
2.	Patients who will be identified as high-risk patients based on the standardized screening questionnaire. High-risk group patients are those patients with penicillin allergy label on EMR with previous reaction suggestive of anaphylaxis OR requiring hospitalization/epinephrine administration for the reaction OR reactions considered immunologic (angioedema, joint pains) OR involving serious types of reactions such as Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute interstitial nephritis (AIN), drug-induced hepatitis or other documented organ injury, drug rash eosinophilia systemic symptoms (DRESS), hemolytic anemia, drug-induced cytopenia, and serum sickness. Patients who were previously diagnosed with penicillin allergy by an allergist also belong to the high-risk group.

Number of Research Participants

We will screen approximately 800 patients and enroll approximately 60 patients in our study based on the weekly census of Rainbow 3, 5 and 6 floors over a span of 6 months (September 22, 2021– March 31, 2022).

Recruitment Methods

The research participants will be identified through the TheraDoc database system. TheraDoc database is a clinical surveillance system used to monitor antibiotic stewardship initiatives in healthcare systems. University Hospitals is one of the health care systems that employs the clinical surveillance services of TheraDoc. Patients admitted in Rainbow 3, 5 and 6 floors with penicillin allergy in the EMR will be identified through the TheraDoc system. Based on review of patient's allergy reaction in the EMR, the patient will be deemed potential research participant or not. If the EMR record shows that patient's penicillin allergy does not imply anaphylaxis or indicates an unclear non-anaphylactic reaction, the patient will be included in the patients to be screened through a standardized questionnaire (will be conducted with patient's parent/s or duly designated legal guardian). Screening questionnaire is an integral part in standard of practice allergy delabeling process. The patient/parent or legal guardian will be approached directly in the patient's room by the investigator where questionnaire will be completed. Only patients with parents/legal guardians who are physically present in the patient's hospital room will be screened. Based on assessment of patient's penicillin allergy status through the standardized questionnaire, patients will be identified as belonging to the no-risk, low-risk or high-risk groups. Only patients identified under low-risk group will be eligible to undergo oral amoxicillin challenge testing. Patients belonging to high-risk group will be given proper referral guidance to see allergy/immunology for further evaluation and management. Patients identified as no-risk group will immediately be delabeled in the EMR without oral amoxicillin challenge testing. All contact and communication with the patients and patient's parent/s or legal guardian will be in person.

Setting

The conduct of this research project will be done at Rainbow 3, 5 and 6 floors inside patient's hospital room. The oral amoxicillin challenge testing will also be done in the patient's hospital room.

Consent Process

The study will be obtaining consent from patient's parent/s and/or legal guardian.
Consenting will be split in two parts. A separate consent will be done for screening. This will need to be signed prior to completing the screening questionnaire. If patient is categorized in the low-risk category, a separate consent will be done for the oral amoxicillin challenge testing. The study will also obtain assent from patients 7 years of age or older.

Sharing of Results with Research Participants

The result of the study will be shared with the research subjects as this will have an impact to their future receipt of any penicillin. This will also be formally shared with their PCPs in the form of a letter that contains the oral challenge test result which will be given to parent/s or legal guardian at the end of the procedure. This is to ensure that PCPs will have proper guidance on the use of penicillin in the future. Verbal consent from parent/s or legal guardian will be obtained for study team to be able to share the oral challenge test result to patient's PCP.

Study Design

This will be a single visit study. There will be no randomization involved

Study Procedures

Methods:

Prior to commencement of the study, all study team members will undergo training on the conduct of the oral amoxicillin challenge testing. During this training, the study team members will be educated

about acute adverse reactions of amoxicillin including how to properly identify these reactions and the interventions that need to be done to address them. This will be conducted by a pediatric allergy attending study team co-investigator. A thorough briefing about the study protocol/algorithm will also be done so that a standardized understanding of the algorithm will be established.

The algorithm/procedures on performing the oral challenge testing is based on empirical standard of practice for direct oral antibiotic allergy challenge testing patterned after successful studies that have aimed the same objectives.

1. Over a 6-month period from September 22, 2021 - March 31, 2022, patients aged 3-18 years old admitted with reported penicillin allergy (either by historical report or allergy label on EMR) in Rainbow 3,5 and 6 will be identified through TheraDoc system.
2. Once the patients with penicillin allergy label are identified in TheraDoc, a verbal permission from the primary treating team attending will be obtained before approaching the parent/s or legal guardian. Detailed plan which will include the timing of the conduct of the components of the procedure (from consenting, screening through a questionnaire and oral challenge testing if indicated) will be discussed with the primary treating team in order to coordinate these steps with the patient's primary treatment plan. This is to avoid disruption of the flow of patient's primary medical care. Once verbal consent from the primary team attending is obtained, an informed written consent from the parent/s or legal guardian will be obtained prior to administering the screening standardized questionnaire which the parent/s or legal guardian will be filling out with the assistance of a trained study team member. This screening questionnaire will be used to identify the level of risk of the patient.
3. Identified patients with penicillin allergy in the TheraDoc system will be stratified into three risk groups: no risk group, low-risk group and high-risk group (see inclusion/exclusion criteria) based on responses on the standardized questionnaire.
4. Patients in the no risk group will be automatically delabeled in the EMR. A clinical event note in the chart to document that the patient was delabeled based on historical verification showing absence of any clinical evidence suggesting of any signs and/or symptoms compatible with penicillin allergy (see Appendix C.1). This information will then be communicated to the patient's primary care physician for guidance on future use of penicillin in a form of a letter. Permission from patient and parent/s or legal guardian to communicate the result to the PCP will be obtained. This letter will be handed to the parent/s or guardian for them to hand over to the PCP. Education on the patient's change in allergy status will also be provided to the parents.
5. Patients identified in the high-risk group will not undergo oral amoxicillin challenge testing. Patients in this group that have not been evaluated by an allergist will be referred to Allergy/Immunology (AI) for further evaluation and management. A clinical event note will be written in the chart to document that the patient is identified to have reactions highly compatible with true penicillin allergy by history/screening and that referral was made to AI (see Appendix C.2).
6. Patients identified in the low-risk group will undergo a step-wise amoxicillin oral challenge testing. An extensive anticipatory guidance and explanation to parent/s or legal guardian about the steps of the testing as well as the risks of the procedure will be done prior to initiation of testing. Informed consent from a parent/s or legal guardian of the patient will be obtained to be able to proceed with testing. Assent will be obtained from patients 7-13 years of age.

Before initiating the step-wise oral amoxicillin challenge testing, it will be ensured that these patients have not taken any antihistamine in the previous 48 hours. Any patients with receipt of antihistamine in the previous 48 hours cannot undergo the testing and will be excluded.

The step-wise oral amoxicillin challenge allergy testing will ONLY be conducted during the day shift from 8:00AM-2:30 PM to make sure adequate medical personnel is present should untoward event occurs. Patients who have any of the exclusion criteria will not be eligible to proceed with the challenge testing (see exclusion criteria).

The following criteria also need to be met in order for the challenge testing to be performed:

- Parent/s or legal guardian present during the test
- A medical provider is available on the floor
- Rescue medications (refer to materials/appendix D – ordered and available at bedside prn)

Only patients in the low-risk group who can tolerate enteral amoxicillin will be eligible to proceed to the step-wise oral amoxicillin challenge testing. This step will entail amoxicillin oral challenge test (either by mouth, by nasogastric tube or gastric tube). Patients not able to take the amoxicillin enterally will be excluded. A separate consent form will need to be signed for the oral amoxicillin challenge testing part of the study.

This step is subdivided into two graded steps: administration of 10% of the standard dose followed by administration of 90% of the rest of the standard dose separated by 30 minutes time interval (see Appendix D).

<u>Administration of 10% of standard dose</u>:
A set of baseline vital signs will be obtained by a trained study team member before initiation of step-wise amoxicillin oral challenge allergy testing. If vital signs are normal and no apparent contraindication to perform the test is identified, the testing will be commenced.

Patients will first receive 10% of the standard drug dose in the form of enteral amoxicillin (see Appendix D). A trained study team member will administer the oral amoxicillin dose and closely monitor and observe patients for 30 minutes at the bedside following dose administration for any sign or symptom of drug reaction.

At any point the patient will have any reaction to the initial 10% dose, testing needs to be stopped immediately. A trained study team member needs to assess the patient right away at bedside and should consider giving diphenhydramine by mouth (or by IV or IM as clinically applicable) if reaction does not meet criteria for anaphylaxis (see definition of terms – attached document). Diphenhydramine will be available at bedside prior to initiation of the oral amoxicillin challenge testing. Administration of diphenhydramine will be done by the study team member. The patient needs to be monitored for the next 2 hours postadministration of diphenhydramine for the progression of symptoms. The reaction needs to be documented in the patient's chart specifying the reaction observed and intervention given (see Appendix C.3).

If the patient develops any symptom indicative of anaphylaxis (see definition of terms), epinephrine will be administered right away either by IV or IM (see Appendix D) and a rapid response alert or code will be called as indicated. Epinephrine will be available at bedside prior to initiation of oral challenge testing. Administration of epinephrine will be done by a trained study team member. Inhaled albuterol or supplemental oxygen will be administered if indicated. Administration of both will also be done by the study team member with the assistance of the patient's nurse. The event needs to be documented in the patient's chart specifying the reaction and the intervention given (see Appendix C.3). The patient will need to

be monitored for progression of symptoms for the next 2 hours post-administration of epinephrine so a proper disposition can be made (remain on the floor or transfer to higher level of care)

Any patient who develops any type of reaction at any point during the administration of the initial 10 % dose will be labeled to have failed the test. This will also be documented in the patient's chart accordingly. The patient's penicillin allergy status will then be retained in the chart (see Appendix C.3). The patient will be provided proper guidance and recommendation to follow up with an allergist for further evaluation and management.

Administration of the remaining 90% of standard dose:
If the patient did not develop any reaction to the 10% initial oral dose of amoxicillin following 30 minutes of administration, another set of vital signs will then be obtained by a trained study team member. If vital signs are normal, then the patient can proceed to receive the remaining 90% of the test standard dose of amoxicillin (see Appendix D). A trained study team member needs to be present at bedside for 30 minutes following the administration of the rest of the 90% of the dose. Another set of vital signs will be obtained 30 and 60 minutes following the administration of the rest of the 90 % of the dose.

Administration of the remaining 90% of standard dose: If the patient did not develop any reaction to the 10% initial oral dose of amoxicillin following 30 minutes of administration, another set of vital signs will then be obtained by a trained study team member. If vital signs are normal, then the patient can proceed to receive the remaining 90% of the test standard dose of amoxicillin (see Appendix D). A trained study team member needs to be present at bedside for 30 minutes following the administration of the rest of the 90% of the dose. Another set of vital signs will be obtained 30 and 60 minutes following the administration of the rest of the 90 % of the dose.

If the patient develops any symptom indicative of anaphylaxis (see definition of terms), epinephrine will be administered right away either by IV or IM (see Appendix D) and a rapid response alert or code will be called as indicated. Epinephrine will be available at bedside prior to initiation of oral challenge testing. Administration of epinephrine will be done by a trained study team member. Inhaled albuterol or supplemental oxygen will be administered if indicated. Administration of both will also be done by the study team member with the assistance of the patient's nurse. The event needs to be documented in the patient's chart specifying the reaction and the intervention given (see Appendix C.3). The patient will need to be monitored for progression of symptoms for the next 2 hours post-administration of epinephrine so a proper disposition can be made (remain on the floor or transfer to higher level of care)

Any patient who develops any type of reaction at any point during the administration of the remaining 90 % of dose will be labeled to have failed the test. This will also be documented in the patient's chart accordingly (see Appendix C.3). The patient's penicillin allergy status will then be retained in the chart. The patient will be provided proper guidance and recommendation to follow up with an allergist for further evaluation and management.

If the patient did not have any reaction to the remaining 90% of standard dose at 120 minute-mark following start of challenge testing, then the patient is deemed to not have allergy to

penicillin. The allergy label in the EMR will then be removed with a notation "patient underwent direct oral amoxicillin challenge testing with no reaction on (date)". The patient's vital signs will again be obtained by a trained study team member and recorded for documentation (see Appendix C.4).

The pediatric ID fellow will be present for 30 minutes following each dose of amoxicillin. The study team attending or the pediatric ID fellow will also oversee study team members who are still in residency training through direct supervision during critical portions of the procedure (within 30 minutes of challenge dose administration). The pediatric ID fellow will always be available in person within the campus for the resident team members for every patient challenged throughout the entire duration of the challenge testing. Anytime a patient is challenged, the pediatric ID fellow will be present not more than 3-5 minutes away from the study site and always reachable by a dedicated study team phone. Study team members will also be responsible to attend/respond to any reaction the patient may have that is related to the oral challenge testing procedure.

All vital signs obtained throughout the procedure will be performed and recorded by trained study team members. Administration of the graded enteral amoxicillin doses and rescue medications if indicated will also be performed by the study team members.

7. The result of the oral challenge testing be communicated to the patient's primary care physician for guidance on future use of penicillin in the form of a letter that will be handed to the parent/s or guardian containing the result of the challenge testing. Permission will be obtained from parent/s or guardian before communication of result to PCP. Permission will be obtained during the consent process. Education on the patient's change in allergy status will then be provided to the parents.

Study Timeline
The conduct of the challenge testing will be done only from 8:00 AM – 2:30 PM to ensure availability of full attendance of medical staff in the event untoward issues occur. The single visit from consent to the time amoxicillin oral challenge is done will take an average of approximately 3 hours. Enrollment and conduct of the study will be done over a 6-month period (September 22, 2021 – March 31, 2022).

Data to be Collected for your study
(AFTER consent and HIPAA Authorization have been obtained)
Data that will be collected will include patient's name, date of birth, age, sex, MRN, race (if available), penicillin allergy status (reaction description if stated), PCP's name, PCP's contact information, and the responses of parent/s or legal guardian to the screening questionnaire (see attached Appendix B)

Data Analysis Plan
Descriptive statistical tools will be used to analyze the data. A P-value of of <0.05 will be used to determine statistical significance in the result interpretation.

The primary end point will be verification of patients' penicillin allergy status through direct oral challenge testing with amoxicillin.

Secondary endpoints will be:

1. Identification of patients (no-risk patients and low-risk patients who passed the oral challenge testing) who will then be delabeled in the EMR.
2. Identification of patients (no-risk patients and low-risk patients who passed the oral challenge testing) in order to provide proper guidance to their PCPs regarding use of penicillin in the future.
3. Identification of high-risk risk patients and low-risk patients who failed the oral amoxicillin challenge testing in order to provide them proper guidance on referral to allergy/immunology for further evaluation and management.

Risks to Research Participants
Reasonable foreseeable risks include breach of confidentiality, discomfort, inconveniences both to parent/s or legal guardian and patients. These will be protected against through observance of HIPAA-concordant practices in the conduct of the study as well as efficient and timely performance of challenge testing to avoid consuming too much of patients' time.

Reaction to the intervention is also one of the foreseeable risk to the patients in this study. Potential reactions to the intervention (amoxicillin challenge testing) include skin rash, nausea, vomiting, diarrhea, and very rarely anaphylaxis.

Oral diphenhydramine can potentially cause sedation, sleepiness, dizziness, disturbed coordination, epigastric distress and thickening of bronchial secretions as the most common known adverse reactions.

Epinephrine can potentially cause anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea, vomiting, headache, tachycardia, hypertension and very rarely respiratory difficulties.

Albuterol can potentially cause tachycardia, hyperactivity, hypokalemia, sleeplessness, headache, abnormal heart rate, hypertension, muscle cramps, drying and irritation of oropharynx and sometimes hypersensitivity reaction such as rash or urticaria.

These are ameliorated by proper and strict adherence to the selection criteria stipulated in the standardized questionnaire, strict attendance of medical personnel available at the critical portions of the testing, performing the challenge testing within hours of maximal medical personnel attendance (see attached Appendix E), and making sure that rescue medications are ready at bedside before initiation of the challenge testing.

Provisions to Protect the Privacy Interests of Research Participants
Conversations with parent/s or legal guardian and patients (screening, consenting and disclosure of challenge testing results) will only be done inside the confines of the patient's hospital room with the door closed. Only the study team members would have access to the conduct of the study. Strict adherence to HIPAA guidelines will be observed to protect the patient's privacy.

Potential Benefit to Research Participants
The main benefits of this study to the research participants will be determination of their allergy status to penicillin (will play a big role in their potential for future receipt of penicillin that may be both life-saving and cost-saving) and the need to be referred for a formal allergy/immunology evaluation to verify penicillin allergy status if indicated.

Withdrawal of Research Participants
The patient or the parent/s or legal guardian can opt to withdraw on behalf of the patient from enrollment at any time during the conduct of the study. Research participants as well have the liberty to withdraw from the study anytime. Admission and retention of patients to remain enrolled in the study is purely voluntary.

Alternatives to Participation
Participation to this research project is fully voluntary. The alternative to participation is not to participate.

Costs to Research Participants
The cost of the delabeling procedure will be free to the patient/s. This would otherwise be a relatively expensive procedure if done in an allergist's clinic. The cost of the challenge medications (amoxicillin) will be billed to the patient/s insurance as these are medications used in standard of practice allergy delabeling process and as this study entails standard of practice delabeling procedure. If the patient/s will develop reaction to the challenge testing, the cost of the rescue medications will be part of the patient's standard of care cost and will be billed to the patient/s insurance as well.

Research Participant Compensation
There will be no compensation, in any form, given to research participants.

Provisions to Monitor the Data to Ensure the Safety of Research Participants
Data collection will take place at UH RBC premises. Data will be managed by the PI (Dr. Desai) and co-investigators (Dr. Lim, Dr. Ruda-Wessell, Dr. Lopes, Dr. Miller and Leanne Moore) using REDCap database. REDCap (Research Electronic Data Capture) is a secure web application for building and managing online surveys and databases. Only the study PI (Dr. Desai) and study team members will have access to identifiable private information. The study team will monitor at least every 1- 2 weeks for accuracy and adherence to protocol.

Drugs and Devices
Amoxicillin – standard full dose is 45 mg/kg/dose (maximum total dose 1000 mg) – to be given only by enteral route (naso-gastric tube, oro-gastric tube, gastric-tube) in two graded doses: 10% initial dose and 90% dose.

Indication: "Challenge Dose Amoxicillin" in order

Diphenhydramine - 1 mg/kg PO or IV (maximum dose 50 mg) – 12.5 mg/5 ml formulation and 50 mg/vial preparation

Albuterol – 2.5 mg/3ml nebule

Oxygen – to be given by nasal cannula to maintain oxygen saturation more than 92 %

Normal saline (0.9 % NaCL IV solution) - 20 ml/kg as bolus as needed for hypotension

Epinephrine 1:1000 for rescue medication:
<50 kg: Epinephrine (1mg/mL) at 0.01 mg/kg/dose – will be given as Epinephrine Jr 0.15 mg/0.3 ml auto-injector

>50 kg: Epinephrine (1mg/mL) at 0.5 mg/dose – will be given as Epinephrine 0.3 mg/0.3 ml auto-injector

Additional Information

Please see attached protocol algorithm (Appendix A), screening questionnaire (Appendix B) and clinical event notes (Appendix C).

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