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Addressing the challenges of penicillin allergy delabeling with electronic health records and mobile applications.

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Abstract

Allergy labels are common, often incorrect, and potentially harmful. There are many opportunities for clinical decision support (CDS) tools integrated in the electronic health record (EHR) and mobile apps to address the challenges with drug allergy management, including penicillin allergy

delabeling (PADL). Effective delabeling solutions must consider multidisciplinary clinical workflow and multistep processes, including documentation, assessment, plan (e.g., allergy testing and referral), record update, drug-allergy alert management, and allergy reconciliation over time. Developing a systematic infrastructure to manage allergies across the EHR is critical to improve the accuracy and completeness of a patient's allergy and to avoid inadvertently relabeling. Improving appropriateness and relevancy of drug-allergy alerts is important to reduce alert fatigue. Using alerts to guide clinicians on appropriate antibiotic use may reduce unnecessary beta-lactam avoidance.

To date, EHR CDS tools have facilitated non-allergists to provide PADL at the point of care. A mobile app was shown to support PADL and provide specialist support and education. Future research is needed to further standardize, integrate, and evaluate innovative CDS tools in the EHR to demonstrate patient safety, clinical utility, and facilitate wider adoption.

Keywords

Penicillin allergy, Penicillin allergy delabeling, clinical decision support, electronic health records, mobile telephone applications, antimicrobial stewardship, patient safety.

Abbreviations

PADL Penicillin allergy delabeling
EHR electronic health records
CDS clinical decision support
AAAAI American Academy of Allergy, Asthma & Immunology
ADR Adverse drug reaction
HSR Hypersensitivity reaction
NLP natural language processing
BPA Best practice alert
HLA Human leukocyte antigen
SJS Stevens–Johnson syndrome
TEN toxic epidermal necrolysis
NICE National Institute for Health and Care Excellence
iOS iPhone operating system

Introduction

Drug allergies documented in the electronic health record (EHR), including penicillin allergies, are common and often incorrect (1) with 15% of hospitalized patients(2, 3) and 6-10% of the general population(4, 5) reporting a penicillin allergy. Of these individuals, 94% can tolerate penicillin after formal allergy testing, and many of the intolerances during testing are not representative of serious allergic responses.(6) Incorrect penicillin allergy labels are recognized as both a public health concern and a medication safety issue because of the many associated harms which include increased multidrug-resistant infections and increased mortality.(1, 7) Allergy testing has traditionally been delivered by allergists, but the paucity of allergy specialists

worldwide (8, 9) and the traditional resource intensive testing methods have limited wider deployment of penicillin allergy delabeling (PADL).(10) Less resource intensive delabeling methods, such as delabeling on history alone or after a drug challenge without prior skin testing, make PADL more assessable to non-allergists. The endorsement of non-allergists delivering PADL, and the development of toolkits to support non-allergists, creates an opportunity for the wider adoption of PADL and safe delabeling on a broader scale. (1, 11-14) This does require healthcare systems to incorporate new infrastructure, workflows and novel tools to facilitate allergy management, some of which can be integrated with the EHR.(15, 16)

To design, develop and implement effective delabeling solutions, it is important to recognize the broader clinical multidisciplinary workflow and how delabeling fits within these pathways. Elements of allergy management that lend themselves to EHR solutions include the following major components and processes: 1) Documentation, 2) Assessment, 3) Plan (e.g., allergy testing strategy/referral ordering), 4) Record Updates, 5) Drug-Allergy Alert Management, and 6) Allergy Reconciliation. Each step is key to maintain quality care with minimal adverse drug events, reduced healthcare costs, and better health outcomes.(1, 17)

In defining the workflow for allergy record maintenance and outlining the associated EHR functions, it is evident that there are multiple opportunities for EHR and decision support to guide allergy management and PADL effectively (Figure 1). Computerized clinical decision support (CDS) in the EHR is a key potential component of the toolkits that have been developed to support non-allergists delivery of PADL.(1) Incorporating PADL decision support at the point of care would likely enhance the identification, assessment, and selection of the most appropriate testing strategy for patients whilst concurrently providing education for both healthcare workers and patients. Point of care antimicrobial stewardship decision support tools have been successfully incorporated into mobile phone apps.(18) The many identified challenges with penicillin allergy delabeling, from diagnosis to updating records, could be addressed by ‘information technology’.

In this article we explore the role of EHR and applications in allergy management and PADL. We acknowledge the term allergy here is used incorrectly as most patient allergy entries in the EHR are not true immune-mediated reactions, but incorrectly labeled as an allergy. For each major step in the process (as shown in Figure 1), we discuss the current status, unmet needs, and possible innovative solutions.

EHR Technology and Innovation

Figure 1

1. Allergy Documentation

Accurate and complete allergy documentation in the EHR is essential to guide clinical decision making. The EHR allergy section (or “allergy list”) determines how health care professionals document allergies by providing defined data entry fields that characterize the allergy.(16, 19) Allergy information can be entered through structured (dropdown lists or checkboxes) fields or as

free text.(19) Structured fields support CDS that notify the physician of allergy risks prior to prescribing a potentially unsafe medication.

There are currently no consensus guidelines on documentation of allergies in EHR systems and previously published recommendations from informatics societies and allergy specialists have not been widely adopted.(20-23) A workgroup within the Adverse Reactions to Drugs, Biologicals and Latex Committee of the American Academy of Allergy, Asthma & Immunology (AAAAI) was formed to publish guidelines for allergy documentation in the EHR, and this document is in press.(24) Core elements of the drug allergy history include details related to the patient (e.g. symptoms, date of reaction, exposure since), medication (e.g. specific generic drug name, route of administration, timing of reaction) and treatment (e.g. management and time to resolution).(25) To date, the allergy section in most EHRs contain fields for documenting allergens, reaction(s), reaction type (intolerance vs. allergy), and reaction severity, and therefore do not meet the suggested core elements of a drug allergy history.(19) In addition, many allergy entries are incomplete, inaccurate, or blank.(19, 26) When examining entries for beta-lactam allergies, only 40% stated the specific beta-lactam antibiotic and only 23% described the reaction.(27). In another study less than half of the documented reactions contained a reaction description and only 18% described the severity.(28) Incomplete documentation influences future prescribing behavior, with providers more likely to adopt a cautious approach and prescribe alternative antibiotics when vague or minimally descriptive allergy entries were provided.(27) Empowering prescribers with validated EHR functions that facilitate accurate structured allergy history taking and where appropriate, PADL, will reduce the current practice of unnecessarily avoiding penicillins.

Although standardized training on how to document allergies in the EHR is necessary, this will not be sufficient alone as there are numerous EHR vendors across the U.S., Europe and other countries using a broad array of terminology and definitions. This lack of standardization results in frequent free-text entries, which cannot be used in algorithmic CDS. Standard definitions are essential to support both provider training and information technology across EHR vendors. Although this review focuses specifically on penicillin allergy, the definitions in Table 1 could be utilized for all medication reactions.

Table 1.

Although there are a variety of advances that may prove to be helpful to enhance the EHR allergy field, including natural language processing (NLP) algorithms discussed below, a new fine-tuned approach is necessary. Introduction of standardized data elements (e.g. coded value sets mapped to a standard medical terminology) for critical information will minimize variability in documentation among providers and thereby support better prescribing practices.(27) One study by Goss, *et al.* used a NLP tool called Medical Text Extraction, Reasoning, and Mapping System (MTERMS) to develop a comprehensive set of allergy reactions for the reaction field.(29, 30) They identified over 700 reactions from free text in allergy entries with a 98.0% precision and 95.6% recall, demonstrating the rich variety of reactions and importance of comprehensive value sets to capture reaction details while coding information. Wang, *et al.* continued this line of study by building a dynamic picklist that auto-populates appropriate reactions.(31) This simplifies data entry by facilitating efficient, partly automated reaction documentation and can be incorporated into EHR systems broadly.

Improving documentation of the detail and the type of reaction is important because improper classification of intolerances as allergies is common.(32) In a majority of records, intolerances were miscategorized as an allergy (33) and although penicillin is often safe in patients who report an intolerance, physicians are more likely to avoid prescribing penicillin if the intolerance is recorded as an "allergy". Redesigning the binary allergy or intolerance label in EHRs may be a valuable intervention. One suggestion is to redefine the entire allergy module in the EHR as "Adverse reactions" to minimize erroneous entries classified as an allergy.(24) A general improvement may be to place greater emphasis on detailed reaction documentation that can be used to classify allergy or intolerance by trained providers or after allergy validation. Ultimately, the EHR design influences allergy labelling and should be augmented to label only true penicillin allergies as such.

2. Assessment

Drug allergy diagnosis and evaluation results in more appropriate antibiotic prescribing and increased patient safety. Implementing CDS tools in the context of drug allergy management would support non-allergists to diagnose drug allergy correctly and prescribe appropriate antibiotics to improve antimicrobial stewardship and reduce health care–associated expenditures.(34-37) Such tools also have the potential to serve as an efficient triaging platform that appropriately streamlines and prioritizes patient referrals for allergist assessment and testing.(38)

There have been many successful attempts to establish risk stratification pathways, (5, 35, 39-42) including pathways intended for non-specialist PADL in hospitals (43, 44), which utilize decision support tools, such as the 'Drug Allergy App' - a diagnostic algorithm designed to be used on mobile platforms.(38) The risk stratification criteria and the testing methods have varied, with some patients delabeled on history alone and others a direct oral challenge test or after skin testing followed by oral challenge test.(43-45) The literature to date demonstrates the safety and efficacy of non-specialist PADL and it is supported by many national and global organizations.(1, 11, 14, 45) The outcomes have overall been positive with very few adverse reactions, of which all were mild (44), and approximately 25 to 30% of patients with penicillin allergy were able to be delabeled using clinical history alone.(8)

Digital tools such as the "Drug Allergy App" have the potential to improve and extend the functionality and the usefulness of EHRs.(8, 37, 38) Algorithms built into the EHR, when designed appropriately, particularly co-designed with experts in drug allergy, may encourage and allow clinicians to engage with PADL that is embedded into the clinical workflow. Implementing these algorithms will require thoughtful attention to the allergy history taking questions, the clinician acceptability and confidence in the algorithm recommendations, and the validation of the algorithms and CDS tools.

3. Plan

The penicillin allergy assessment plan is determined by the outcome of the allergy risk assessment, based on the allergy history, coupled with patient factors, to determine the most appropriate allergy

testing method. Algorithms have proven to be helpful in assessing patients to identify who would benefit from allergy testing,(46) who would be most appropriate for skin testing with challenge testing (47) or direct drug provocation test (48). An EHR-based algorithm has been developed to automatically screen patients admitted to the hospital and identify those with a documented penicillin allergy who were prescribed high value broad-spectrum antibiotics and were eligible to test, leading to targeted testing by pharmacists.(46) Multidisciplinary interventions that integrate clinical expertise with informatics technology have been reported to improve allergy evaluation with 80-96% of patients testing negative leading to removal of the penicillin allergy label. (46-48). The studies used algorithms that promoted appropriate allergy testing which led to reduced second-line antibiotic use. In the U.S. alone, the majority of penicillin allergies are unverified with only approximately 15,000 penicillin allergy tests performed a year.(49) Staffing shortages, scarce testing resources, and lack of education contribute to the underutilization of allergy testing.
The use of algorithms and CDS provides non-allergists with access to allergist expertise at the point of care, addressing some of the unmet need for allergist delivery of PADL and training of non-allergists.

In addition to identifying patients who are eligible for allergy testing, placing referral orders and updating the allergy records with test results are equally important steps that EHR functionalities can support. Low referral rates and infrequent allergy testing are partly attributable to limited time and lack of familiarity with testing and referral process.(50) To encourage referrals for formal allergy evaluation by specialists, best practice advisories (BPA), another CDS tool used in EHRs, can be designed to assist clinicians with referral orders. One BPA was dedicated to automatically filling out the referral order for patients with a penicillin allergy and providing patient instructions for allergy testing.(51) The BPA paired with educational programming increased the referral rate from 2% to 20% at Rady's Children Hospital in a 9-month period.

Even when an antibiotic challenge test is completed, over half (55%) of the records were not appropriately updated (also see below).(52) An alert was created to appear on the order entry screen 24 hours after the test was administered for the Partners Healthcare System and would cease either after 72 hours or when the provider overrode the alert. With this alert, allergy records were updated more promptly, and allergy updates increased from 51.3% to 66.7% across the healthcare system. These forms of CDS alerting tools facilitated allergy evaluation and allergy record editing by automatically filling out the referral order and bringing attention to test results that need to be updated.

4. Record Updates

EHR features can be developed to readily identify allergy discrepancies and assist clinicians in updating allergy records in a timely fashion. Ortega, *et al.* and Lo*, et al.* demonstrate the unique capabilities of NLP to analyze clinical notes and provide data-driven clinical recommendations.(53, 54) With an NLP tool, Ortega, *et al.* were able to effectively identify over 260,000 allergy records (~16% of total allergy records) with discrepancies that included free-text reactions that were not encoded, duplicate entries, and entries associated with three or more alert overrides. Greater study of the discrepancies also revealed that 36 penicillin allergies were not updated despite negative challenge test results. Lo, *et al.* further examined the application of NLP to identify challenge test discrepancies in patients' allergy records. With 96.1% precision, the NLP

algorithm analyzed clinical notes and identified a greater number of allergy entries that did not correspond to the challenge test result compared to flowsheets alone (5.0% vs 2.0%).(54) They developed a pilot reconciliation module that employed this NLP algorithm to showcase the potential discrepancy and suggest an action to the provider. Piloted with real-time EHR data, over 90% of the recommendations suggested that allergy entries should be deleted based on the challenge test results, 59% of which were related to penicillin allergies. In this case, the EHR was far from a static platform used to document allergies; it can and should be reimagined as dynamic tool that can reinforce robust allergy documentation, facilitate PADL and prevent relabeling.

5. Drug-Allergy Alerts

Delabeling penicillin allergies in a safe and effective way will reduce excessive alerting and thereby alert fatigue. Clinicians have described that allergy alerts often lack clinical relevance and are not sufficiently targeted.(15) As a result, over 80% of inpatient alerts and 77% of outpatient alerts are overridden.(55) Based on 10 years of data at an integrated healthcare system, documented penicillin allergies accounted for approximately 7% (n=66,215) of all drug allergy alerts.(56) One study found that nearly 7 alerts occurred per encounter for patients with a documented penicillin allergy, and of those patients, 49% had prior penicillin exposure.(57) These findings indicate that EHR technology must be better adapted for detailed allergy documentation and the administration of clinically relevant alerts.(58)

Several hospital systems are implementing interventions to reduce the number of non-specific alerts. Alerts can be tiered based on severity such that only severe reactions, such as anaphylaxis, initiate alerts. EHR systems that tier alerts have been shown to decrease alert overrides when compared to EHRs that do not tier alerts (100% acceptance vs. 34% acceptance of alerts).(59) Buffone*, et al.* retrospectively reviewed the impact of altering alerts so that they were displayed only when prescribing the medication in the allergy record or medications with similar side chains.(28) They found there to be no reports of anaphylaxis, demonstrating that alerts might be dispensed with more discretion. Macy*, et al.* studied the effects of removing cephalosporin alerts in a health system with over 4 million patients who received an antibiotic treatment. (60) In a similar vein, their findings demonstrated that without frequent alerting, cephalosporin prescribing increased by 47% and did not result in a significant difference in new adverse reactions, including anaphylaxis, and unsuccessful treatment regimens. While general caution must be exercised before removing alerts, Macy, *et al.* confirms that many alerts are not clinically relevant and still alter clinician behavior.

Rather than removing alerts, another suggestion is to have CDS alerting systems factor in prior exposure to beta-lactams and include such information in the alert itself.(57) In doing so, providers may be more likely to consider patient history, change prescribing behaviors, and even consider updating the allergy record if needed. Some PADL interventions have added progress notes to describe the allergy testing and the results before deleting the allergy record. Going further and attaching an alert that displays this information when providers try incorrectly to re-label patients might prevent incorrect relabeling of delabeled patients. (61, 62)

6. Allergy Information Reconciliation

Allergy information is often documented in diverse sections of EHR, which includes the allergy list, medication discontinuation section, flowsheets, allergy test results, problem lists, and clinician notes. Systematically reconciling allergy information across the EHR is critical to improve the accuracy and completeness of a patient's allergy list. For instance, allergy entries can automatically be populated to the allergy section for patients predisposed to reactions due to existing diagnoses or genetic markers.(16) An example includes screening for the HLA-B*1502 allele prior to initiating treatment with carbamazepine in patients with Asian ancestry due to the risk of SJS and TEN.(63) For unverified allergy entries associated with high severity or reactions documented in other disparate EHR sections, intelligent EHR features can be developed to recommend allergy testing or specialist referral. A research team at the Mass General Brigham has developed an allergy reconciliation tool, which is able to automatically detect allergy information discrepancies documented across different EHR sections and provide actionable recommendations to clinicians to update allergy records via a user interface with the EHR. (53, 54, 64)

It is important to recognize allergy reconciliation and delabeling efforts are related to EHR interoperability. Health information exchange (HIE) is a growing healthcare priority to support continuity of care and encourage strategic resource utilization.(3) Previous studies estimated utilization of Care Everywhere, a record exchange tool for the EPIC EHR, to be approximately 1.5%-6.8%.(3) Clinicians have reported that finding previous exposures to medication with Care Everywhere is time-consuming and often difficult to do without clear denotation of prior exposure and allergies.(57) For that reason, accurate allergy lists and standardized documentation are necessary to share important patient information successfully.(65) Delabeling allergies should be considered a joint initiative to promote safer prescribing practices across institutions. Because allergy testing resources, clinical time, and expertise are limited, sharing allergy test results and updated lists may guide prescribing practices in other institutions. Developing the infrastructure to reconcile allergies across institutions may improve identification of updated, reliable allergy list information when providing care.

Beyond the EHR - Mobile and Web Applications

Innovative interventions have demonstrated that a well-constructed mobile CDS tool can support penicillin-allergy delabeling, facilitating easy access to CDS in diverse clinical settings.(38) A decision support tool needs to be quick and easy to use at the point of care. This is ideally suited to a mobile device application with simple questions that the practitioner can complete while they are with the patient. Ideally the questions should be clear and quick to answer without any ambiguity. The outcomes provided would similarly need to be clear, non-ambiguous and ideally aligned to national and international guidance, such as the NICE drug allergy guidance.(4) User feedback during development of these tools is important to ensure usability of the final application.

There are various mobile platforms that support applications. In June 2021 iOS accounted for 53.66% and Android accounted for 46% of the market in North America.(66) Any mobile application should therefore be developed for both the iOS and Android platforms to ensure equity of access to most mobile device users. Alternative options for mobile application development could include web applications, which provide the advantage of being able to be run on any internet connected device with a web browser. A web application is also more likely to be able to be integrated into hospital systems and therefore be accessible on the hospital computers and possibly

within the EHR. Hospitals may have poor or limited mobile signal related to building construction, and this factor may need to be considered when selecting the platform on which to develop an application.(67) There are clear advantages of having access to the same decision support tool on the users' mobile device, computer, and within the EHR for consistency.

Currently, although there are several validated CDS tools,(68-70) we are aware of only one validated mobile app based tool.(38) Additionally, a web application based approach has demonstrated increased use of penicillin and cephalosporin antimicrobials in patients reporting penicillin allergy.(71) The validation of any decision support tool would need to reassure the end user that the tool was safe, and the risk of missing a potentially life-threatening allergy history is low regardless of the platform on which it runs.

Allergy Phenotype

An accurate description and documentation of a patient's clinical allergy phenotype in the EHR would facilitate the use of CDS and allow for appropriate use of necessary first line medications, especially antibiotics like beta-lactams. Electronic phenotyping is the factual description of clinical characteristics that can facilitate accurate drug allergy classifications using logical algorithms. The electronic phenotype can then be analyzed electronically to appropriately classify the drug reaction. Also, electronic phenotyping refers to the identification of patients with defined clinical characteristics which can be searched for within a structured digital platform, usually an EHR, via logical expressions and operators.(72) Therefore, electronic phenotyping can facilitate accurate drug allergy classifications using logical algorithms. As an example; the drug allergy app utilizes electronic phenotyping to support the classification of previous drug reactions.(38) The interaction between clinical and electronic phenotypes would be led by allergists and immunologists. (Figure 2.).

Figure 2.

Conclusion

There are many opportunities for EHR and mobile decision support tools to guide allergy management and facilitate penicillin allergy delabeling by non-allergist specialists. To optimize CDS use and patient outcomes, internationally agreed guidelines on documentation of allergies in EHR systems and precise definitions for adverse drug reactions are required. This will enable incorporation of CDS into EHR and, thereby, augment clinical decision making and further optimize the delabeling process. Innovations and applications for improving drug allergy documentation and management would reduce the burden of incorrect penicillin allergy labels, reduce unnecessary referrals to allergy services, streamlining allergists care for those that require allergists input and together will enable the appropriate use of antibiotics to more patients.

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Adverse drug reaction (ADR)	Any unintended effect of a drug. ADRs include all reactions to drugs including non-immune mediated intolerances, immune-mediated hypersensitivity reactions (HSRs), Drug allergy, and contraindications as discussed below.(20)
Drug intolerances	Drugs that are not tolerated by specific individuals. These are ADRs that do not carry the same predictability and risk as immune-mediated reactions.(20) Intolerances include reactions such as nausea, headache, or fatigue.(21) If entered in the EHR allergy section, patient aversions or preferences for avoidance of specific drugs, and other agents should be coded as intolerances.(24)
Drug hypersensitivity reactions (HSRs)	Immune-mediated ADRs that can be immediate or delayed in onset. Prior studies identified hives, itching and angioedema as the most common symptoms of immediate HSRs. Delayed HSRs were most frequently documented as causing rash, but delayed HSRs also include severe cutaneous adverse reactions such as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction eosinophilia and systemic symptoms (DRESS).(23)
Drug Allergy	Historically reserved for HSRs with an IgE mediated mechanism (e.g. anaphylaxis to penicillin) .(22) Currently, drug allergy is considered synonymous with drug HSRs and includes all immune-mediated drug reactions.

Contraindication	A specific situation in which a drug should not be used because it may be harmful (e.g. abacavir if patient has HLA B57 01, or ACE inhibitors in ACE-inhibitor induced angioedema)
Unknown	This should be used when the reaction type cannot be specified given the information known. For example, when a reaction occurs that may be an intolerance or HSR. Unknown can also be used when the person entering the allergy does not feel comfortable choosing a reaction type, although overuse of this reaction type will lead to missing data and will not improve EHR allergy module quality. Unknown is also appropriate when patients are not aware of any historical details related to the adverse drug effect.

Table 1. Standard drug reaction definitions

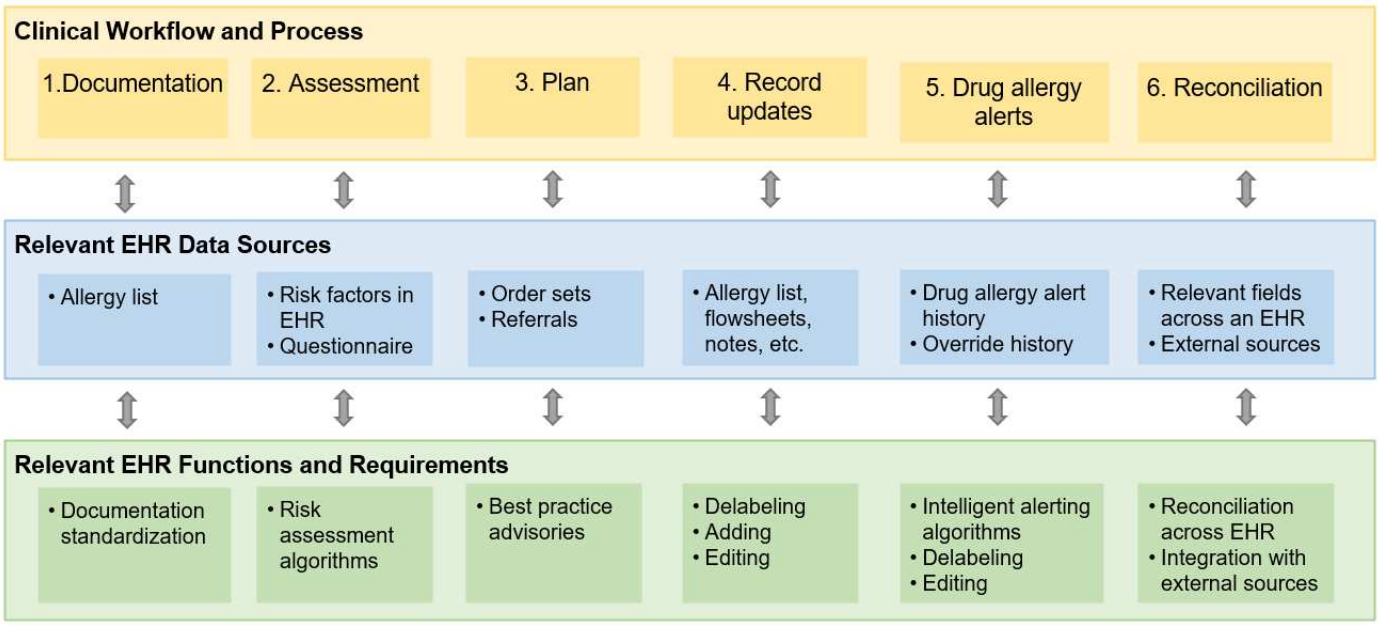

Figure 1. Drug allergy documentation and management process with relevant EHR functions

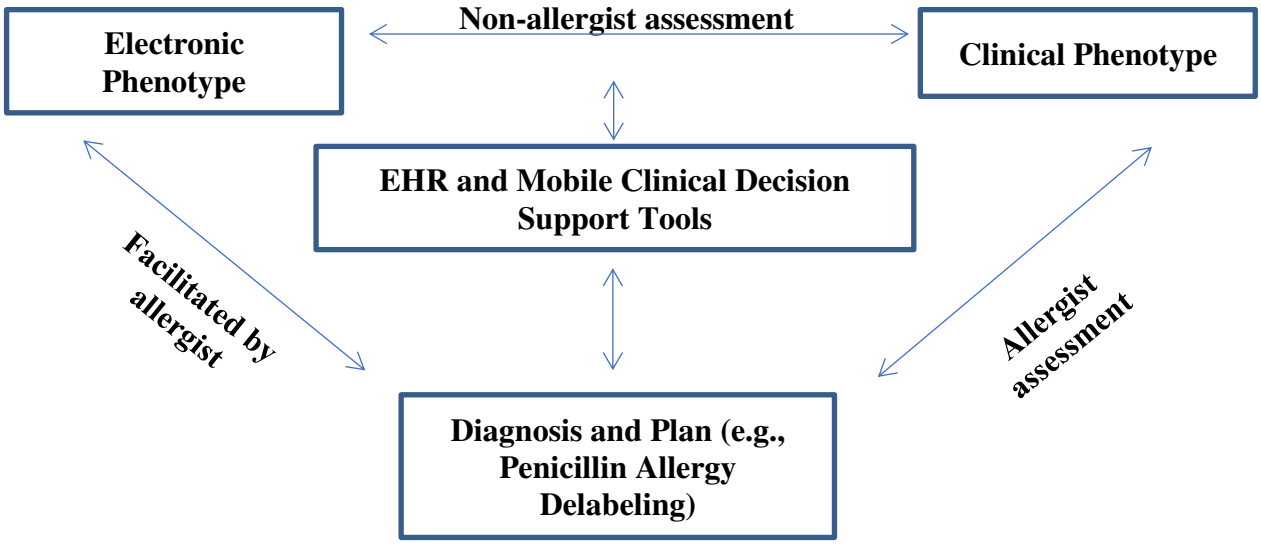

Figure 2. summarize the roles of allergists and non-allergists in designing, assessing, and facilitating accurate drug allergy classifications and penicillin allergy delabeling if appropriate via clinical decision-support.