Recommendations for selecting drug–drug interactions for clinical decision support

An audio interview that supplements the information in this article is available on AJHP’s website at www.ajhponline.org. Readers can also access this interview through AJHP’s augmented reality (AR) feature by launching the Layar app and scanning this page with their mobile device.

**Purpose.** Recommendations for including drug–drug interactions (DDIs) in clinical decision support (CDS) are presented.

**Summary.** A conference series was conducted to improve CDS for DDIs. A work group consisting of 20 experts in pharmacology, drug information, and CDS from academia, government agencies, health information vendors, and healthcare organizations was convened to address (1) the process to use for developing and maintaining a standard set of DDIs, (2) the information that should be included in a knowledge base of standard DDIs, (3) whether a list of contraindicated drug pairs can or should be established, and (4) how to more intelligently filter DDI alerts. We recommend a transparent, systematic, and evidence-driven process with graded recommendations by a consensus panel of experts and oversight by a national organization. We outline key DDI information needed to help guide clinician decision-making. We recommend judicious classification of DDIs as contraindicated and more research to identify methods to safely reduce repetitive and less-relevant alerts.

**Conclusion.** An expert panel with a centralized organizer or convener should be established to develop and maintain a standard set of DDIs for CDS in the United States. The process should be evidence driven, transparent, and systematic, with feedback from multiple stakeholders for continuous improvement. The scope of the expert panel’s work should be carefully managed to ensure that the process is sustainable. Support for research to improve DDI alerting in the future is also needed. Adoption of these steps may lead to consistent and clinically relevant content for interruptive DDIs, thus reducing alert fatigue and improving patient safety.

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Drug–drug interactions (DDIs) can cause preventable patient harm and require proper management. Many electronic prescribing and medication information systems include interruptive alerts and noninterruptive information as forms of clinical decision support (CDS) to warn clinicians that potential DDIs exist based on a patient’s medication history. DDI alerts most commonly occur during the prescriber medication order entry or the pharmacist dispensing/verification process. The Centers for Medicare and Medicaid Services (CMS) included DDI screening in its guidelines for achieving meaningful use of electronic health records (i.e., CMS Meaningful Use Core Measure 2). Today, every pharmacy and increasing numbers of physician offices and healthcare organizations in the United States use some form of health information technology (IT) that includes DDI alerts. The content of the vast majority of DDI decision support systems in the United States is created, maintained, and sold by drug knowledge base vendors that use their own approaches for evaluating and classifying the clinical importance of DDIs. Studies have demonstrated substantial variability in DDI-alerting performance across...
More research is needed to determine if filtering of drug–drug interaction alerts can be done safely.

**KEY POINTS**

- A national panel should be established to evaluate drug–drug interaction evidence and make recommendations as to what interactions should be included in clinical decision support systems.
- The term contraindicated should be reserved for those drug pairs whose coadministration should not be permitted under any circumstances.
- More research is needed to determine if filtering of drug–drug interaction alerts can be done safely.

The work group met monthly via webinars from January 2013 to February 2014, with in-person meetings held in Washington, DC (May 2013), and Phoenix, Arizona (September 2013). Recommendations were developed by consensus after completing a literature review on methods and best practices for establishing consensus in decision-making. Draft questions were proposed by two members, and the entire group modified and addressed the following key questions:

1. What process should be used to develop and maintain a standard set of DDIs?
2. What information should be included in a knowledge base of standard DDIs?
3. Can/should a list of contraindicated drug pairs be established?
4. How can DDI alerts be more intelligently filtered?

The focus of this project was DDIs. Many other types of interactions (e.g., drug-food, drug-herbal product, drug-disease) were recognized but were considered outside the scope of this project. Many of these interactions share similar characteristics, but we did not attempt to address all of the issues across all types of interactions. Recommendations in this article may be relevant to these other types of interactions.

**Key question 1: What process should be used to develop and maintain a standard set of DDIs?**

As part of a larger conference series to improve the quality of CDS for DDIs, 20 individuals with expertise in DDIs, clinical pharmacology, CDS, and establishing healthcare quality initiatives were invited and agreed to participate in this project. The work group’s primary goal was to recommend principles and processes for including DDIs in drug safety alerts that would ultimately guide the development and maintenance of a standard set of DDIs for CDS. Members represented diverse backgrounds such as academia, drug knowledge base vendors, drug information compendia, clinicians, professional societies, the Office of the National Coordinator for Health Information Technology (ONC), and the Food and Drug Administration (FDA).

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are constantly being brought to market, an ongoing process is needed with governance and infrastructure to ensure that a standard set of DDIs is regularly updated and reflects current evidence and newly discovered DDIs. This undertaking is not trivial and requires substantial resources.

In light of these issues and ongoing challenges, we recommend forming a national consensus panel of experts to create and maintain a standard set of clinically relevant DDIs for CDS systems, with oversight by a national organization to ensure that the process is transparent, systematic, and evidence driven (Figure 1). Key elements for developing trustworthy clinical recommendations include ensuring that expert panelists consider relevant evidence, involving relevant stakeholders, providing opportunities for public comment, documenting panelist and external reviewer comments and responses, and actively managing conflicts of interest.25-28

**National process with centralized oversight.** We recommend selecting a centralized organizer or convener, such as an academic unit or a professional association or organization (e.g., American Society of Health-System Pharmacists, American Society for Clinical Pharmacology and Therapeutics, American Medical Informatics Association) with full-time staff, to serve as the driving force to assemble the panel and disseminate information.29,30 The goal should be to maintain the evidence base and decision algorithms for the "public good"; therefore, public funding must support this venture to align and promote collaboration among the public and private sectors. We recommend that a standard set of DDIs for use in CDS should be created and maintained independently of reimbursement decisions. This evidence base could be established so that it is accessible as a Web service, allowing its use by many providers and healthcare systems.

We recommend that a panel of experts be created and include individuals with clinical expertise and skills in evaluating DDIs. Because of concerns of being too prescriptive, we recommend that members of the inaugural panel define the following attributes: the appointment process, terms of

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**Figure 1.** Systematic process for developing a standard set of drug–drug interactions for clinical decision support (CDS).
membership, procedural rules (e.g., voting policies and procedures), the framework for executing the steps involved in grading recommendations, policies for managing potential conflict of interest, and the policies and procedures of a comprehensive and transparent DDI selection process (e.g., methods for evidence summary and presentation, balloting procedures).

Use of expert advice is particularly important because the types and quality of evidence available for DDIs differ substantially from other areas of clinical practice. Furthermore, research indicates that expert advice improves the acceptance and value of DDI alerts. Experts should have a background in clinical pharmacology, pharmacokinetics, pharmacoeconomics, medication safety, clinical experience in relevant clinical subspecialties, health IT, and human factors engineering.

**Evidence synthesis.** We recommend a systematic process for assembling DDI evidence, similar to approaches used for systematic reviews and practice guideline development. Qualified experts should summarize the evidence and provide a quality assessment of this evidence for presentation to the national expert panel for deliberation. Another work group associated with this initiative has developed a new evaluation tool—the DRUG Interaction Evidence Evaluation (DRIVE) instrument—to establish sufficient evidence for DDIs that may require clinical management. Before widespread use, the instrument should undergo testing and validation. That said, the DRIVE instrument or other approaches should be incorporated into the process to provide clinicians a clear rating of the overall quality of evidence, with graded recommendations for clinical management.

**Grading recommendations for risk management.** A major challenge in assigning a recommended action to DDIs is defining the hierarchy of graded risk-management recommendations in such a way that, despite the often weak nature of DDI evidence, confidence can be placed in the recommendations to adequately support them. The hierarchy of graded risk-management recommendations should be presented in a manner that is comprehensible to a wide range of users. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach has been adapted to DDIs and could be further refined for this process. Although the graded DDI recommendations will be advisory in nature, we expect that the approach used by the organizer/convener will promote trust among prescribers and pharmacists so recommendations can be confidently applied.

**Community feedback on DDI recommendations.** We recommend that a Web-based process be created and maintained to solicit input concerning the classification of DDIs. Input from numerous stakeholders, including clinicians, healthcare and quality organizations, government agencies, IT vendors, and pharmaceutical companies, is strongly encouraged. Broad-based feedback is essential for both maintenance and quality improvement in managing the knowledge base. It should be easy for prescribers, pharmacists, and other clinicians to submit petitions to the panel to add or reevaluate drug combinations (e.g., upgrading or downgrading classification). Requests to remove or add DDIs should be evaluated based on their clinical and scientific merits.

**Subsequent evaluation, reevaluation, and updates.** Periodic and timely updates of the standard set of DDIs are essential. We recommend updates at least annually, given the dynamic nature of DDI knowledge acquisition, and we defer to the expert panel for specifications of the process. We also recommend that the standard set of DDIs be aligned with other national initiatives—both public and private (e.g., quality organizations)—when creating quality metrics for healthcare organization quality assessments, including such organizations as the Pharmacy Quality Alliance and the National Quality Forum.

**Key question 2: What information should be included in a knowledge base of standard DDIs?**

Based in part on recommendations by Floor-Schreuder et al., we formulated a list of information to be included, along with the interacting drug pairs, in a standard set of DDIs to optimally guide clinicians in mitigating or preventing harm. These include the classification of seriousness, clinical consequences, frequency of harm and exposure, modifying factors, interaction mechanism, recommended action (with strength of recommendations), and evidence (with quality ratings).

**Classification (seriousness rating) and meanings.** The classification system for DDIs must reflect and include an explanation of medical logic so the justification is intuitive to the end user (provider/pharmacist). Information on the criteria used to classify drug pairs should be readily accessible. We recommend that classification terms (e.g., major, moderate, minor) be clearly defined, easily recognized, transparent, and simple. Many organizations and individuals refer to classification of DDIs by the severity of the interaction. We prefer the more precise term seriousness, defined as the extent to which an adverse reaction can or does cause harm. Severity is a more ambiguous term and describes the intensity of an adverse reaction in an individual. For example, a headache may be severe but not serious. Seriousness, severity, and selected other terms related to DDIs have been defined by others.

The overall classification of an interaction should be driven by the seriousness and frequency (when available) of the potential clinical outcome, taking the clinical management recommendation(s) and strength of evidence into account. We recommend that CDS systems for DDIs use no more than three categories of se-
dangerousness. The rationale is to simplify and increase the consistency of these classification systems. The highest seriousness category should include interruptive alerts for DDIs requiring clinician action. The middle category should be reserved for DDIs requiring some form of clinician notification but that do not necessarily need to be an interruptive alert. The lowest seriousness category should include clinically inconsequential DDIs that generally should not be included in notification systems.

Clinical consequences and frequency. The potential adverse clinical consequences for the patient as a result of coprescribing the interacting drugs should be clearly described. For example, simply stating that ciprofloxacin may increase the blood levels of theophylline is insufficient. The clinical effects of theophylline toxicity, such as nausea, vomiting, cardiovascular instability, and seizures, should be provided with the CDS information. Clinicians can make better therapeutic decisions for specific patients when the potential clinical consequences are clearly identified.

When available, the frequency or incidence of adverse outcomes associated with a specific DDI should be stated in numbers (e.g., 1/1000). A verbal scale may be necessary, recognizing that numerical values are often unavailable and that estimated frequencies are often ranges of measures of central tendency (e.g., means) with wide variability from different studies. One example is the standard frequency groupings for adverse effects used by the European Medicines Agency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

There are several impediments to identifying frequency estimates, such as underreporting, the nature of DDI evidence, and variability in the seriousness of adverse outcomes. Adverse reactions resulting from DDIs are likely to be underreported, and the majority of clinical evidence is currently derived from pharmacokinetic studies and case reports. Epidemiologic evidence is infrequently published and, for most DDIs, evidence is sufficient to make only rough estimates of the incidence of adverse outcomes. In the near term, frequency is unlikely to be a commonly populated field, but clinicians should be informed that the rate of adverse events is unknown when not available.

Modifying (risk or mitigating) factors. The risk of harm associated with a DDI is a function of both the seriousness and frequency of the event combined with individual patient susceptibility. Risk factors increase patient susceptibility, and mitigating factors decrease susceptibility. For example, risk factors for hyperkalemia among patients taking angiotensin-converting enzyme inhibitors and potassium-sparing diuretics include renal impairment, diabetes mellitus, and elevated baseline potassium levels. Providing clinicians with information about factors that modify patient susceptibility is essential for assessing the risk of patient harm. For most DDIs, however, factors that modify the risk of an adverse outcome are often not known. Research shows that providing clinicians with alerts containing patient-specific risk factors can reduce the risk of injury.

Known modifying factors (e.g., genetic information, ethnicity, concomitant diseases) should be included in DDI alerts; when these factors are not known, the lack of information should be stated.

Interaction mechanism. We recommend that clinically relevant information regarding interaction mechanisms, such as differentiating between pharmacokinetic and pharmacodynamic effects, should be included with the standard set of DDIs. This information may be useful to assess patient risk and identify reasonable therapeutic alternatives.

Recommended actions for DDIs in CDS. Providing a statement of possible harm without recommending a corresponding action is generally not an effective way to change clinician behavior. Clinicians may resist an alert when an acceptable alternative is not offered. We strongly recommend that CDS systems provide actionable recommendations—that is, guidance on ways to mitigate or avoid the potential for harm, especially when a clinician’s workflow is interrupted to display a potentially serious DDI. This guidance could include a recommendation to closely monitor the patient while taking the combination therapy. When the benefits of both medications outweigh the risks, it is critical to convey to the clinician strategies to minimize the potential for adverse outcomes, such as specific monitoring (e.g., vital signs, laboratory tests, therapeutic drug monitoring) and dosage adjustments (e.g., 50% dose reduction). However, if the seriousness of the interaction dictates that the drugs should not be used together, the clinician must be presented with the option to discontinue one or both medications. As described previously, clear indications of the strength of the recommendations should accompany clinical advice.

Evidence. Providing access to the evidence is a critical component of weighing the risks and benefits of coprescribing drugs that have the potential to result in a DDI. Unfortunately, information about many DDIs is based on limited evidence, such as a few case studies and perhaps pharmacokinetic evaluations. We recommend that DDI alerts should indicate the quality of evidence (with definitions), summarize the evidence briefly, and provide access to references from the primary literature when possible. Beyond the evidence to substantiate the existence of a DDI, evidence ratings should also be provided, when available, for adverse effects, frequency, risk factors, and management strategies. In addition to ratings for the quality of evidence, links to primary sources should be accessible through the knowledge base. Another work
group associated with this project has recommended links to primary references through PubMed Identifier (PMID) numbers for PubMed or similar systems in other abstracting databases.22

Key question 3: Can/should a list of contraindicated drug pairs be established?

It is important to recognize that there has been inconsistent use of the term contraindicated in various drug information sources. Contraindicated DDIs are those for which no situations have been identified where the benefit of the combination outweighs the risk.3 Using this definition, there are no circumstances where an override is an acceptable action for contraindicated DDIs. In a review of contraindicated DDI alerts from a commercial knowledge base, Hatton et al.14 suggested that most contraindicated drug pairs were not absolutely contraindicated and could be downgraded. For example, according to sildenafil’s product labeling, sildenafil is contraindicated in patients who regularly or intermittently use organic nitrates.50 Therefore, many CDS systems produce DDI alerts identifying the combination of sildenafil and nitrates as contraindicated. However, evidence indicates that sildenafil and nitrates can be used together intermittently with adequate separation of doses (e.g., nitroglycerin may be considered 24 hours after sildenafil dosing) or with appropriate blood pressure monitoring.51,52 Classifying an interaction as contraindicated should be done judiciously and perhaps infrequently, as only a small set of drug combinations are absolutely contraindicated. FDA is aware of this issue and is making steps to limit the use of the term contraindicated or inferred contraindication in product labeling information. For example, rather than using the term contraindicated, the labeling of ibrutinib warns prescribers to “Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition” and provides specific instructions on how to manage the interaction.53 Many times the contraindication may reflect avoidance of simultaneous administration, but this clarification needs to be included in the CDS notification. In other situations, it may be appropriate to classify coadministration of two products as contraindicated based on extrapolation from other medications with similar pharmacologic properties (e.g., use of a novel antidepressant in combination with a monoamine oxidase inhibitor). Furthermore, a separate contraindicated classification should not be used for DDI alerts.

Key question 4: How can DDI alerts be more intelligently filtered?

In an effort to reduce alert fatigue, many organizations have locally customized or revised alerting rules.62 However, implementation and modification of commercially developed CDS may result in unnecessary or error-inducing conditions that may need to be addressed at the organizational level.54,55 Evidence is lacking on how to best filter DDI alerts. Consequently, healthcare organizations should use an interprofessional committee, including physicians and pharmacists, to periodically review frequently overridden alerts and suggest safe and effective ways for either suppressing alerts of low value or changing their presentation format.56 Individual users should be able to provide feedback to the committee about the system at any point in the care process as part of a continuous improvement process. It is unclear whether individual clinicians should be allowed to turn off specific alerts that they consider uninformative or whether entire classes of alerts could be safely suppressed for particular specialists who may not need the same level of support as generalists.42 When adjusting drug administration times could circumvent the DDI, an alternative approach would be to allow a prescriber to defer or forward an alert to a pharmacist for review during order verification. We considered the question of whether organizations should identify a group of expert professionals that should be exempt from DDI notifications. However, there is no research to support that this approach protects patient safety.57

Keeping in mind the “five rights” for health IT medication safety (right information, right person, right CDS format, right channel, right time in workflow),58 there are situations in which DDI notification is repetitive or irrelevant. For example, in some systems, DDI alerts may be generated for refills or continuations of existing medications. Changes in dosing, strength, and time of administration and transfer between inpatient units can result in repetitive alerts that contribute to alert fatigue. Some experts advocate the ability to suppress alerts at the time of renewal of previously tolerated medication combinations for the same patient.59,60 Patients with long-term use of certain medications may have demonstrated their capacity to tolerate them, and suppressing alerts for refills might be an option in some circumstances.61 We do not provide recommendations on this issue due to the paucity of evidence. We encourage organizations that design or modify CDS rules to evaluate outcomes and report the effectiveness and safety of such modifications to the medical community.

Filtering alerts by increasing the specificity of trigger rules may help to decrease irrelevant, interruptive messages.62,64 More-sophisticated rules need to be developed to enable intelligent alerting. Ideally, DDI alerts should be patient specific, taking into account age, sex, genetics, body weight, allergies, serum drug levels, renal function, comorbidity, and other mitigating factors.65 Table 1 provides an overview of situations in which a particular DDI alert may be intelligently ignored for a specific patient. We recognize the challenges posed by incorporating mitigating factors into DDI alerts and that there is of-
ten insufficient clinical evidence to improve patient specificity for many interactions. As CDS systems become more sophisticated, developers are encouraged to take context into account when designing alerts. Given the current state of the evidence, we do not support indiscriminately “turning off” alerts and recommend that modifications to DDI alerts be made cautiously, with careful evaluation to ensure that patient safety is not compromised. Furthermore, suggestions for strategies to actively monitor for signs of harm for patients on concomitant therapies that may result in a DDI should be incorporated into CDS systems.

Discussion

This article presents recommendations from a national work group on approaches to improve CDS for DDIs. We believe that implementing these recommendations will provide substantive improvements to current systems. Foremost, employing a systematic process with graded recommendations and full transparency for a nationally vetted, standard set of clinically relevant DDIs will build trust among clinicians and foster collaboration among healthcare organizations and IT vendors. The threat of liability often dominates the decision to list a drug pair as having the potential to result in a DDI, even when evidence or even plausibility is lacking. We believe a systematic process will help mitigate liability risk and may reduce alert burden and ultimately improve patient safety. Currently, no well-defined, broadly accepted standard exists for grading the quality of a body of evidence for a DDI and providing strengths of recommendations for patient risk-management strategies. In addition, research is needed to develop new approaches that will allow further refinement of DDIs, such as the consideration of patient characteristics when determining if or how to trigger the appearance of a DDI alert. Filling these unmet needs is important for the provision of widely accepted and consistent DDI alerts.

Creating and maintaining a list of DDIs are resource-intensive, time-consuming, and continuous processes. The task faced by a central organizer or convener to create and maintain the proposed knowledge base and standard set of DDIs is enormous. Much oversight will be required to coordinate evidence evaluation and continual updates. Decisions should be

Table 1. Examples of Mitigating Factors Allowing for Intelligent Filtering of Drug–Drug Interaction (DDI) Alerts

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<th>Mitigating Factor</th>
<th>Example(s)</th>
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| Drug dosage or duration| • Dose and/or duration of object or precipitant drug may be insufficient to result in an adverse outcome.  
• A few doses of an NSAID during ACE inhibitor antihypertensive therapy are unlikely to result in clinically important increased blood pressure. |
| Timing of administration| • With some DDIs involving gastrointestinal absorption, administering the affected drug (e.g., ciprofloxacin) at least 2 hr before or 4–6 hr after the binding agent (e.g., ferrous sulfate) can often circumvent the interaction. |
| Route of administration| • Some routes of administration may avoid the interaction.  
• With some DDIs involving gastrointestinal absorption, administering the affected drug parenterally (e.g., ciprofloxacin) may circumvent the interaction (e.g., with ferrous sulfate).  
• Topically applied medications (e.g., erythromycin ophthalmic ointment) may not achieve sufficient systemic concentrations to interact.  
• Caution is needed for drugs with significant absorption when administered by nonsystemic routes (e.g., inhaled fluticasone with CYP3A4 inhibitors can lead to hypothalamic–pituitary–adrenal axis suppression). |
| Sequence of therapy    | • The sequence (order) of starting therapies can influence the risk of a DDI.  
• When an object drug is given long term and its dosage is carefully adjusted (e.g., warfarin), adding a precipitant drug (e.g., amiodarone) requires careful monitoring.  
• The likelihood of a DDI is usually low when starting an object drug with careful dosage adjustment (e.g., warfarin) for a patient already on long-term therapy with the precipitant drug (e.g., amiodarone). |
| Pharmacogenomics       | • Pharmacogenomics can influence the risk of a DDI.  
• Patients who are poor metabolizers of CYP2D6 are unlikely to have a clinically significant interaction between venlafaxine and a CYP2D6 inhibitor (e.g., diphenhydramine). |
| Indication             | • In some cases, drug combinations with potentially serious DDIs may be purposely and safely coprescribed by experienced clinicians.  
• Starting allopurinol in a patient on azathioprine can result in potentially fatal bone marrow suppression.  
• Allopurinol and azathioprine can be beneficial for inflammatory bowel disease when carefully managed and monitored by a gastroenterologist. |

ACE = angiotensin-converting enzyme, CYP = cytochrome P-450 isozyme, NSAID = nonsteroidal antiinflammatory drug.
subject to periodic review along with regular review of underlying methods to remain current with evolving scientific knowledge. Support and buy-in from (or adoption by) the major stakeholders will be essential to the success of the endeavor. To minimize issues of bias, we recommend that public funding take the lead in supporting these administrative efforts. The standard set of DDIs should be aligned with other national initiatives—both public and private (e.g., quality organizations)—when creating quality metrics for healthcare organizations.

Given the cost and difficulty of securing continued public funding, the primary challenge in implementing our recommended process is sustainability. An innovative public–private partnership is needed with endorsement and support from all relevant stakeholders, including government agencies, professional organizations, drug knowledge base and compendia editors, and healthcare systems. Currently, there is no process in place that brings the collective knowledge of DDI experts, including knowledge base and compendia editors, together to reach consensus on DDIs that should be included in warning systems. Collaboration and pooling of limited resources will be necessary to maintain a current standard set of DDIs to protect patient safety.

Much work is needed to provide evidence-based recommendations for other changes to implementing DDI alerts (e.g., filtering alerts, turning off alerts). Table 2 lists areas of future research that would support modifications to DDI alerting systems. Although filtering alerts by provider type is often suggested in the literature, we recommend that modifications to systems be evaluated before implementation to ensure that patient safety is not compromised.

**Conclusion**

An expert panel with a centralized organizer or convener should be established to develop and maintain a standard set of DDIs for CDS in the United States. The process should be evidence driven, transparent, and systematic, with feedback from multiple stakeholders for continuous improvement. The scope of the expert panel’s work should be carefully managed to ensure that the process is sustainable. Support for research to improve DDI alerting in the future is also needed. Adoption of these steps may lead to other changes to implementing DDI alerts, thus reducing alert fatigue and improving patient safety.

**Disclosures**

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**References**


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