



# GUIDANCE FOR THE 2025 LEAPFROG CPOE EVALUATION TOOL



**Contents**

Introduction ..... 3

Summary of Changes from the 2025 Leapfrog Hospital Survey ..... 3

Description of the CPOE Evaluation Tool ..... 4

Order Checking Categories ..... 4

General Guidance ..... 6

    Hard Stops vs. Disruptive Alerts ..... 6

Guidance for specific Order Checking Categories ..... 6

    Inappropriate Medication Combinations<sup>1-5, 7-8</sup> ..... 6

    Drug Diagnosis<sup>9</sup> ..... 7

    Drug Age<sup>10-13</sup> ..... 8

    Drug Laboratory and Drug Monitoring<sup>14-16</sup> ..... 8

    Excessive Dosing ..... 9

    Excessive Alerts<sup>6</sup> ..... 9

Clinical Decision Support References ..... 10

References ..... 12



## INTRODUCTION

To achieve Leapfrog's [Computerized Physician Order Entry \(CPOE\) Standard](#), each adult and general hospital must (1) ensure that licensed prescribers enter at least 85% of inpatient medication orders via a computer system that includes decision support software to reduce prescribing errors, and (2) demonstrate, via a test, that its inpatient CPOE system can alert physicians to at least 60% of frequent serious medication errors known to cause harm to patients. To fulfill the second requirement of our standard, hospitals use Leapfrog's CPOE Evaluation Tool to complete an Adult Inpatient Test.

Upon successful completion of an Adult Inpatient Test, a hospital's responses are immediately scored and available to view and print. These CPOE Test results are available within the CPOE Evaluation Tool from April 1 to November 30. For record-keeping purposes, hospitals are advised to print and save a copy of the results. Archived results from prior year's tests can be accessed until November 30 by logging back into the CPOE Evaluation Tool from the [Hospital Survey Dashboard](#). See "Step 7 of 7: View Results" in the [CPOE Tool Instructions](#) for more information.

## SUMMARY OF CHANGES FROM THE 2025 LEAPFROG HOSPITAL SURVEY

The CPOE Evaluation Tool developers have updated the test medication scenarios to reflect changes to clinical guidelines and to address medications that hospitals frequently reported as not being in their medication formulary.

Due to unforeseen operational challenges, the Test Patients PDF does not include the date of birth for each patient. Hospitals will need to calculate the date of birth based on the age provided. To make this easier for hospitals, Leapfrog has included a Date of Birth Calculator on the [Survey and CPOE Materials webpage](#).

Additionally, patient allergies have not been removed, as the CPOE Test is designed to simulate a real-life environment where allergy information is typically included in patient profiles.

Previously, the Excessive Dosing and Drug Route Order Checking Categories were indicated as scenario-specific clinical decision support, meaning that advice or information presented to the prescriber is related to the Test Order and the Test Patient, which includes specific patient demographics and clinical information. For the 2025 CPOE Test, the Excessive Dosing and Drug Route Order Checking Categories have been updated to indicate that the type of clinical decision support in these Order Checking Categories is medication-specific, meaning that it is specific to the medication and might appear any time the medication is ordered for any patient and is not specifically related to the Test Patient. This change is reflected in the Orders and Observations Sheet.

Lastly, the Sample Test content has been updated to include one Test Order from each of the eight Order Checking Categories to give hospitals a preview of the response options that they will see on the Online Answer Form in the Adult Inpatient Test.

There are no changes to the scoring algorithm for the CPOE Evaluation Tool.

## DESCRIPTION OF THE CPOE EVALUATION TOOL

The CPOE Evaluation Tool was designed by medication safety experts and researchers at Brigham and Women's Hospital and the University of Utah to test the ability of inpatient CPOE systems to alert licensed prescribers to frequent serious medication errors known to cause harm to patients. In addition, the Tool was designed to help hospitals improve their use of clinical decision support to reduce adverse drug events and improve medication safety. The Tool was first included in the Leapfrog Hospital Survey in 2008. The fifth release of the tool (version 5.2) is available for the 2025 Leapfrog Hospital Survey.

The timed Test provides users with a set of Test Patients and corresponding Test Orders, which must be entered into the hospital's CPOE and related clinical systems. The prescriber entering the Test Orders records the advice or information they received, if any, from their hospital's CPOE system onto the Orders and Observation Sheet, and then completes the Online Answer Form. Users receive immediate feedback summarizing the results of the Test. The Tool includes eight Order Checking Categories described in the next section.

## ORDER CHECKING CATEGORIES

Seven of the eight order checking categories included in the CPOE Evaluation Tool represent an area where a serious adverse drug event (ADE) could occur if the CPOE system's clinical decision support fails to alert the prescriber. The eighth order checking category includes Test Orders that, if presented interruptedly, could contribute to over-alerting, which has been shown to contribute to alert fatigue and physician burnout.

The CPOE Evaluation Tool is designed to test two types of clinical decision support:

1. **Scenario-Specific Advice/Information:** Information specific to the Test Patient details, such as demographics (e.g. age), and relevant clinical data (problems/diagnosis, lab values), as well as the Test Order, including the medication dose and frequency.
2. **Medication-Specific Advice/Information:** General information, not specific to the Test Patient details, that applies **any time** the medication is ordered with the specific dose, route and frequency, or **any time** specific medications are ordered.

The table below includes descriptions of each Order Checking Category included in the CPOE Evaluation Tool, as well as examples and the type of clinical decision support (i.e., scenario-specific advice/information or medication-specific advice/information) being tested.

Order Checking Category	Description	Example	Type of Clinical Decision Support
<b>Inappropriate Medication Combinations</b>	Medication combinations to avoid ordering together or ones to use with caution	Using clonazepam and lorazepam together	Medication-specific advice/information
<b>Excessive Dosing</b>	Specified dose of medication or frequency of administration exceeds safe range for single or daily dose.	Tenfold overdose of digoxin	Medication-specific advice/information
<b>Drug Route</b>	Specified route of administration is inappropriate and potentially harmful	Use of hydroxyzine intravenously	Medication --specific advice/information

Order Checking Category	Description	Example	Type of Clinical Decision Support
<b>Drug Diagnosis</b>	Medication is inappropriate/contraindicated based on documented problem/diagnosis	Non-selective beta-blocker in patient with asthma	Scenario-specific advice/information
<b>Drug Age</b>	Medication dose inappropriate/contraindicated based on patient age	Prescribing diazepam for a patient over 65 years old	Scenario-specific advice/information
<b>Drug Laboratory</b>	Medication dose inappropriate/contraindicated based on documented laboratory test results (includes renal status)	Use of nitrofurantoin in patient with severe renal failure or ordering digoxin for a patient with hypokalemia	Scenario-specific advice/information
<b>Drug Monitoring</b>	Medication for which the standard of care includes subsequent monitoring of the drug level or lab value including baseline labs to avoid harm	Prompt to monitor drug levels when ordering aminoglycosides or INR/PT when ordering warfarin or checking baseline LFTs when starting a statin	Medication-specification advice/information
<b>Excessive Alerts</b>	Low-priority medication combinations, such as drug interactions or therapeutic duplications, that should not trigger decision support warnings.	Concurrent use of hydrochlorothiazide and captopril	Medication-specific advice/information

If a prescriber reported receiving advice/information for the Test Orders in the Excessive Alerts category or reports not receiving advice/information for the Test Orders that are fatal, these Test Orders are listed in the CPOE Results.

The Adult Inpatient Test also includes a “Potentially Inaccurate Test Results” test category, which checks for “false positives” (e.g., hospitals reporting advice/information for Test Orders that should not generate any warning in the hospital’s CPOE system). Hospitals that score “Potentially Inaccurate Test Results” are scored and publicly reported as “Incomplete Evaluation” and will not be able to retake an Adult Inpatient Test for 120 days.

## GENERAL GUIDANCE

### HARD STOPS VS. DISRUPTIVE ALERTS

Both hard stops and disruptive alerts can be effective in preventing potentially unsafe orders from reaching the patient.

The CPOE Evaluation Tool developers recommend a “hard stop” when a medication order is absolutely contraindicated because a “hard stop” prevents the licensed prescriber from entering the unsafe order and prevents manual overrides. However, “hard stops” should be used judiciously and infrequently as there are very few contraindications that warrant a hard stop. Some examples include:

- Inappropriate Medication Combinations where there is no benefit of the drug combination that outweighs the risk (i.e., Monoamine Oxidase Inhibitors and Sumatriptan).
- Drug Route combinations where there has been documented harm or death (i.e., Vincristine given intrathecally).

Other Inappropriate Medication Combinations might not warrant a hard stop. For example, Bactrim and warfarin should trigger an alert but would not warrant a hard stop.

## GUIDANCE FOR SPECIFIC ORDER CHECKING CATEGORIES

### INAPPROPRIATE MEDICATION COMBINATIONS<sup>1-5, 7-8</sup>

Inappropriate Medication Combination alerts should appear when prescribers order medications that should not be ordered together, or when prescribers order medications together that require caution. The CPOE Evaluation Tool tests for two specific types of inappropriate medication combination alerts: Drug-Drug Interactions and Therapeutic Duplication.

#### Drug Interactions

Level 1 Drug Interactions are drug combinations that are contraindicated for concurrent use. These Drug Interactions have a high potential for patient harm where the risk outweighs the benefit.

Examples of Level 1 Drug Interactions include:

- Concurrent use of simvastatin and itraconazole, which may result in increased exposure to Simvastatin and an increased risk of myopathy or rhabdomyolysis.
- Concurrent use of tizanidine and ciprofloxacin, which may result in increased Tizanidine plasma concentrations resulting in increased hypotensive and sedative effects.
- Concurrent use of monoamine oxidase inhibitors and sumatriptan, which may result in increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, and mental status changes).

Level 2 Drug Interactions have a high potential for patient harm if action is not taken by a licensed prescriber. These actions may include monitoring drug levels and/or making dose adjustments as needed.

Examples of Level 2 Drug Interactions<sup>7</sup> include:

- Concurrent use of levofloxacin and warfarin
  - Concomitant use has been associated with increases in INR or prothrombin time and clinical episodes of bleeding. If concomitant use is required, early and more frequent monitoring of the patient's INR is recommended.
- Bactrim DS (sulfamethoxazole 800 mg and trimethoprim 160 mg) and warfarin sodium

- Concurrent use of Bactrim and warfarin may result in increased warfarin exposure. If co-administration is required, monitor prothrombin time and INR early and closely, especially during initiation. Preemptive warfarin dose reductions may be considered to prevent INR prolongation during co-administration. The physician may also consider changing the antibiotic that is more appropriate for this patient.
- Drugs that both cause QT prolongation (see <http://www.torsades.org> for list of known risk drugs)
  - haloperidol and amiodarone<sup>8</sup>
    - Concurrent use of either of these drug combinations may result in prolonged QTC interval or torsades de pointes. It is recommended to avoid concurrent use, however if co-therapy is warranted, monitoring QTc closely is recommended.
  - levofloxacin and amiodarone
    - Concurrent use may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
  - citalopram and omeprazole
    - Concurrent use may result in increased citalopram exposure and risk of QT interval prolongation. If co-administration of citalopram with omeprazole is required, do not exceed citalopram doses of 20 mg/day and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds.

### Therapeutic Duplication

Therapeutic Duplication are drug combinations that overlap therapeutically (same agent or same class).

Examples of Therapeutic Duplication include:

- 2 Ace Inhibitors – captopril and lisinopril
- 2 Statins – atorvastatin and simvastatin
- 2 NSAIDs – ibuprofen and naproxen
- 2 Benzodiazepines – diazepam and alprazolam
- ibuprofen and Motrin (generic and brand name of the same drug)

### DRUG DIAGNOSIS<sup>9</sup>

Drug Diagnosis alerts should occur when the medication that is ordered is contraindicated based on a patient's documented problem or diagnosis.

Examples of Drug Diagnosis contraindications include:

- ketorolac and patients with GI Bleeds
  - Black Box warning: Contraindicated in active or history of peptic ulcer disease, recent gastrointestinal bleeding or perforation, or history of gastrointestinal bleeding
- prasugrel and stroke patients
  - Black Box warning: prasugrel can cause significant and sometimes fatal bleeding. Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke
- propranolol and carvedilol and asthma patients
  - Non-cardio selective beta-blockers were associated with a significantly increased risk of moderate asthma exacerbations when initiated at low to moderate doses and both moderate and severe exacerbations when prescribed chronically at high dose.<sup>9</sup>
- Hepatotoxic drugs and patients with liver disease

## DRUG AGE<sup>10-13</sup>

Drug Age alerts should occur when the medication should be avoided based on a patient's age. The CPOE Evaluation Tool focuses on medications that should be avoided for geriatric patients. There are two resources that provide important examples of drug-age contraindications.

- 2023 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.<sup>10</sup> Hospitals should focus on those recommendations where the quality of evidence is high and strength of the recommendation is strong, which includes the following:
  - dronedarone – Avoid in individuals with permanent atrial fibrillation or severe or recently decompensated heart failure
  - nifedipine, immediate release – Avoid
  - Antidepressants with strong anticholinergic activity (alone or in combination (amitriptyline, amoxapine, clomipramine, desipramine, doxepin >6 mg/d, imipramine, nortriptyline, paroxetine, protriptyline, trimipramine) – Avoid
  - Barbiturates (amobarbital, butobarbital, butalbital, mephobarbital, pentobarbital, phenobarbital, secobarbital) – Avoid
  - Ergoloid mesylates (dehydrogenated ergot alkaloids, Isoxsuprine) – Avoid
  - Sulfonylureas, long-duration (chlorpropamide) – Avoid
- Screening Tool of Older Persons' Prescriptions (STOPP) version 2.<sup>11</sup> Potentially inappropriate medications listed in STOPP criteria, like some of those listed in Beers criteria, are significantly associated with avoidable ADEs in older people that cause or contribute to urgent hospitalization.<sup>12</sup>
  - Use of benzodiazepines, opiates or neuroleptics that lead to falls
  - Use of NSAID that lead to gastritis /peptic ulcer disease
  - Use of diuretics that lead to acute kidney injury and symptomatic orthostasis

Hospitals should also focus on drugs that are known to induce a patient's risk of falling such as: Antihypertensive agents, diuretics, sedatives and hypnotics, neuroleptics and antipsychotics, benzodiazepines, and narcotics.<sup>13</sup>

STOPP criteria and BEERS criteria have several areas of overlap. Both sets of criteria emphasize the higher risk of adverse drug reactions and events in older people with use of long-acting benzodiazepines, tricyclic antidepressants, anticholinergic drugs, and non-cyclooxygenase 2-selective nonsteroidal anti-inflammatory drugs.<sup>12</sup>

## DRUG LABORATORY AND DRUG MONITORING<sup>14-16</sup>

Drug Laboratory alerts should occur when a drug is contraindicated based on documented laboratory test results, which includes renal status.

Examples of drug lab contraindications include:

- Ordering potassium chloride (KCl) or a potassium sparing diuretic (spironolactone) in a patient with a high potassium level
- Ordering digoxin in a patient with a high digoxin level
- Ordering nephrotoxic and/or renally cleared medications in a patient with a high Creatinine level

Drug Monitoring alerts should occur for drugs where the standard of care includes subsequent monitoring of the drug level or lab value including baseline labs to avoid harm. Hospitals should focus on drugs with a narrow therapeutic range, such as aminoglycosides, digoxin, lithium, phenytoin, and warfarin.





Hospitals should ensure that when ordering these medications, their systems directly alert the licensed prescriber at the point of ordering or provide a laboratory order to monitor the patient's labs that are needed for that medication. Examples of these include potassium levels, LFTs, creatinine level, INR, and therapeutic drug levels.<sup>14</sup>

Hospitals implementing protocolized pharmacist-driven drug monitoring to always monitor inpatient drug administration of certain drugs, such as anticoagulants and nephrotoxic antibiotics, are now provided a dedicated response option in the CPOE Evaluation Tool. Studies have shown that pharmacist-driven drug monitoring has significantly improved drug monitoring and medication safety.<sup>15-16</sup>

## EXCESSIVE DOSING

Excessive drug dose alerts should occur when the specified dose or frequency of administration for a medication exceeds the safe range for a single dose or daily dose.

Hospitals should focus on drugs with a narrow therapeutic range, such as digoxin, as well as drugs that can cause serious or immediate toxicity if given in excessive amounts, such as narcotics and benzos. Hospitals should consult the [Institute for Safe Medication Practices High-Alert Medications](#) to ensure their clinical decision support alerts their prescribers to drugs that are known to cause harm if given in excessive doses, including:

- Hypoglycemic agents
- Anticoagulants
- Neuromuscular blockers
- Narcotics / Opioids

## EXCESSIVE ALERTS<sup>6</sup>

Medication orders in the Excessive Alerts category include low-priority medication combinations that should not trigger decision support warnings. By presenting these orders uninterruptedly, the number of alerts prescribers see is reduced, which can help reduce alert fatigue.

Examples of these inconsequential medication combinations include, but not limited to<sup>6</sup>:

- omeprazole and benzodiazepines
- NSAIDs and thiazide-type diuretics

## CLINICAL DECISION SUPPORT REFERENCES

Hospitals without the appropriate clinical decision support in place for one of more of the Order Checking Categories included in the CPOE Evaluation Tool can reference the citations below for tips on improving the efficacy of their system.

Order Checking Category	Reference Title	Section of Reference to Focus On	Reference Link
Inappropriate Drug Combinations	High-priority drug-drug interactions for use in electronic health records	Table 2 - focus on the drug pairs where alerts should be triggered	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3422823/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3422823/</a>
Drug Route	Wrong-Route Errors	This document focuses on ways to prevent wrong route errors	<a href="http://www.macoalition.org/documents/SafetyFirst1.pdf">http://www.macoalition.org/documents/SafetyFirst1.pdf</a>
Drug Diagnosis (Pregnancy)	Drugs contraindicated in pregnancy	Focus on drugs that are contraindicated in all stages of pregnancy or commonly prescribed	<a href="https://www.sciencedirect.com/science/article/pii/S0002914924005794">https://www.sciencedirect.com/science/article/pii/S0002914924005794</a>  <a href="https://www.empr.com/charts/drugs-contraindicated-in-pregnancy/">https://www.empr.com/charts/drugs-contraindicated-in-pregnancy/</a>
Drug Diagnosis	Successful deployment of drug-disease interaction clinical decision support across multiple Kaiser Permanente regions	Focus on the Supplementary Data Appendix A: Three Hundred Record Sample of Final, Scored Drug-Disease Subset.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7647201/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7647201/</a>
Drug Age (geriatric)	American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults	Table 2 - focus on medications where there is a strong recommendation to avoid	<a href="https://agsjournals.onlinelibrary.wiley.com/doi/epdf/10.1111/jgs.18372">https://agsjournals.onlinelibrary.wiley.com/doi/epdf/10.1111/jgs.18372</a>
Drug Monitoring and Drug Laboratory	Selection of drug–laboratory result pairs for an inpatient asynchronous alert program: Results of a Delphi survey	Table 3- focus on the Final Consensus List of 24 Drug–Laboratory Pairs	<a href="https://www.researchgate.net/publication/49845070_Selection_of_drug_laboratory_result_pairs_for_an_inpatient_asynchronous_alert_program_Results_of_a_Delphi_survey">https://www.researchgate.net/publication/49845070_Selection_of_drug_laboratory_result_pairs_for_an_inpatient_asynchronous_alert_program_Results_of_a_Delphi_survey</a>



Order Checking Category	Reference Title	Section of Reference to Focus On	Reference Link
Excessive Alerts	Drug–drug interactions that should be non interruptive in order to reduce alert fatigue in electronic health records	Table 1 - focus on the low priority DDI that should not trigger alerts	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628052/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628052/</a>

## REFERENCES

1. Hug BL, Witkowski DJ, Sox CM, et al. Adverse Drug Event Rates in Six Community Hospitals and the Potential Impact of Computerized Physician Order Entry for Prevention. *J Gen Intern Med.* 2010;25(1):31-38. doi:10.1007/s11606-009-1141-3
2. Phansalkar S, Desai AA, Bell D, et al. High-priority drug–drug interactions for use in electronic health records. *J Am Med Informatics Assoc.* 2012;19(5):735-743. doi:10.1136/amiajnl-2011-000612
3. Payne TH, Hines LE, Chan RC, et al. Recommendations to improve the usability of drug-drug interaction clinical decision support alerts. *J Am Med Informatics Assoc.* 2015;22(6):1243-1250. doi:10.1093/jamia/ocv011
4. Tilson H, Hines LE, McEvoy G, et al. Recommendations for selecting drug–drug interactions for clinical decision support. *Am J Heal Pharm.* 2016;73(8):576-585. doi:10.2146/ajhp150565
5. McEvoy DS, Sittig DF, Hickman T-T, et al. Variation in high-priority drug-drug interaction alerts across institutions and electronic health records. *J Am Med Inform Assoc.* 2017;24(2):331-338. doi:10.1093/jamia/ocw114
6. Phansalkar S, van der Sijs H, Tucker AD, et al. Drug—drug interactions that should be non-interruptive in order to reduce alert fatigue in electronic health records. *J Am Med Informatics Assoc.* 2013;20(3):489-493. doi:10.1136/amiajnl-2012-001089
7. Classen DC, Phansalkar S, Bates DW. Critical Drug-Drug Interactions for Use in Electronic Health Records Systems With Computerized Physician Order Entry. *J Patient Saf.* 2011;7(2):61-65. doi:10.1097/PTS.0b013e31821d6f6e
8. Tisdale J. Tisdale Risk Score for QT Prolongation. MDCalc. Accessed March 26, 2023. <https://www.mdcalc.com/calc/10293/tisdale-risk-score-qt-prolongation>
9. Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. *BMC Med.* 2017;15(1). doi:10.1186/S12916-017-0781-0
10. By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023 Jul;71(7):2052-2081. doi: 10.1111/jgs.18372. Epub 2023 May 4. PMID: 37139824.
11. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing.* 2014;44(2):213-218. doi:10.1093/ageing/afu145
12. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially Inappropriate Medications Defined by STOPP Criteria and the Risk of Adverse Drug Events in Older Hospitalized Patients. *Arch Intern Med.* 2011;171(11):1013-1019. doi:10.1001/archinternmed.2011.215
13. de Jong MR, Van der Elst M, Hartholt KA. Drug-related falls in older patients: implicated drugs, consequences, and possible prevention strategies. *Ther Adv Drug Saf.* 2013;4(4):147-154. doi:10.1177/2042098613486829
14. Yu S, Galanter WL, DiDomenico RJ, Borkowsky S, Schiff GD, Lambert BL. Selection of drug-laboratory result pairs for an inpatient asynchronous alert program: results of a Delphi survey. *Am J Health Syst Pharm.* 2011 Mar 1;68(5):407-14. doi: 10.2146/ajhp100215. PMID: 21330682.
15. Schillig J, Kaatz S, Hudson M, Krol GD, Szandzik EG, Kalus JS. Clinical and safety impact of an inpatient pharmacist-directed anticoagulation service. *J Hosp Med.* 2011 Jul-Aug;6(6):322-8.
16. Joseph K, Ramireddy K, Madison G, Turco T, Lui M. Outcomes of a pharmacist-driven vancomycin monitoring initiative in a community hospital. *J Clin Pharm Ther.* 2021 Aug;46(4):1103-1108.