Quality Assurance to Prevent Drug-Drug Interactions

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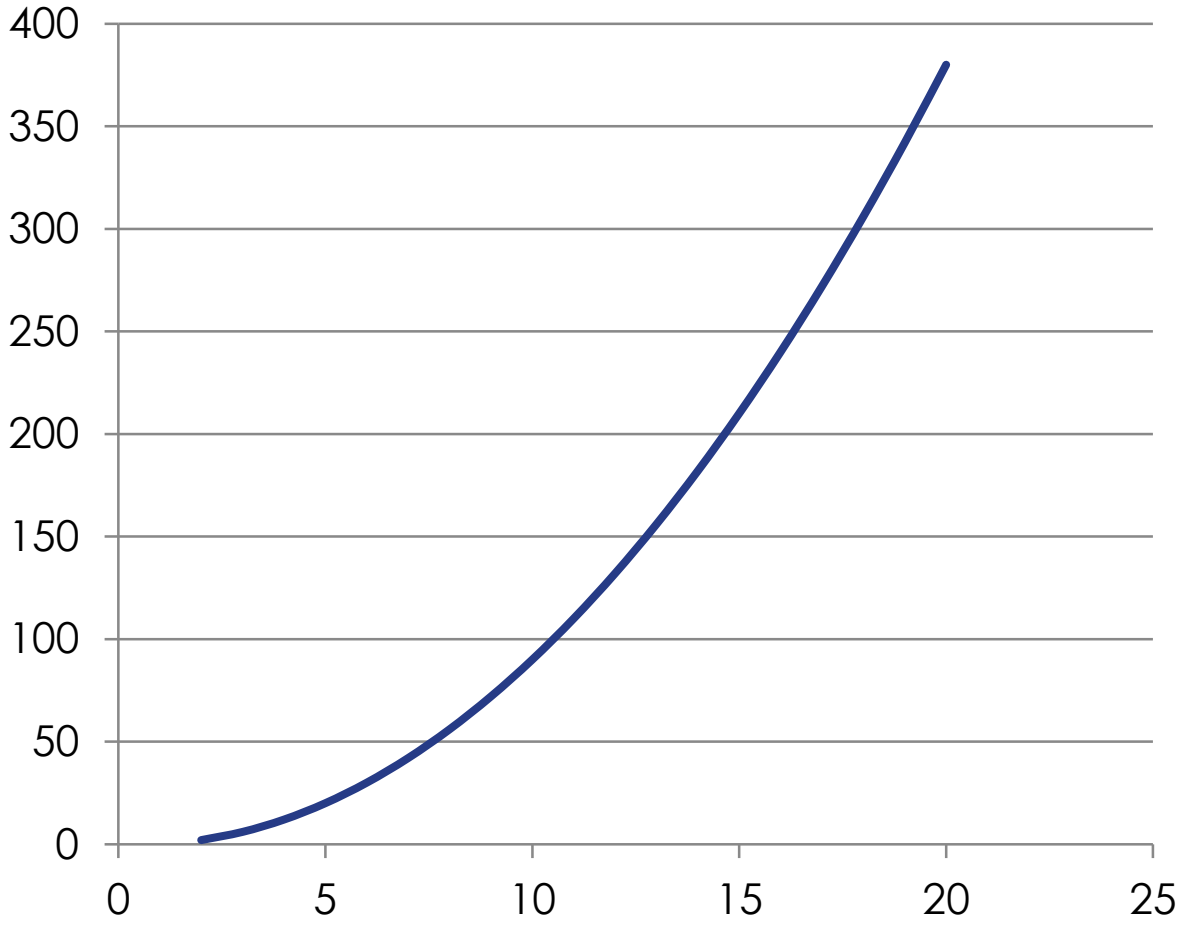
Outline

- The problem
- Pharmacy DDI software evaluation
- Methods for DDI selection
- PQA DDI performance measure

The Problem

Possible Drug Interactions as a Function of Number of Drugs



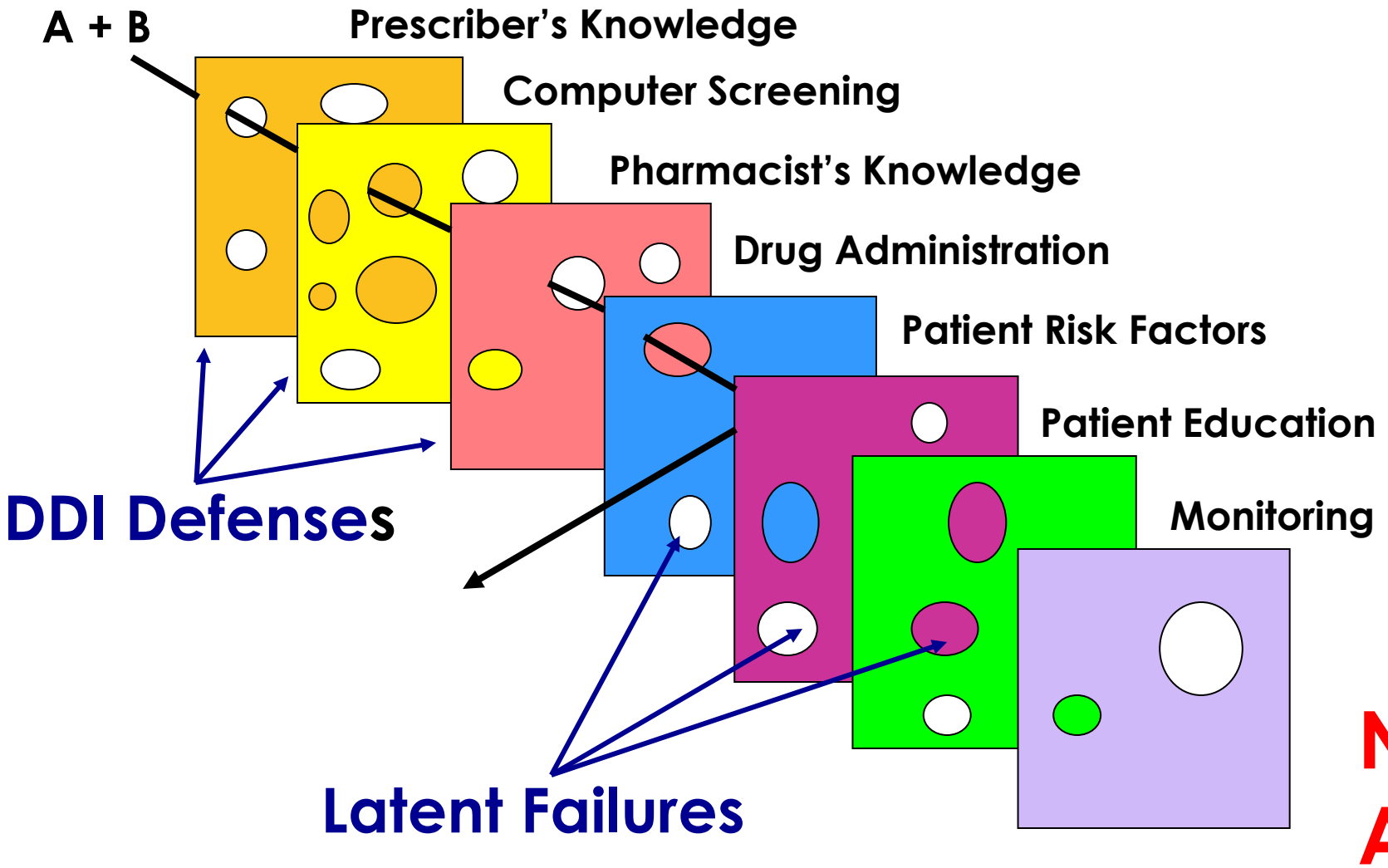
The Problem

- Most DDIs clinically inconsequential…
- BUT harm does occur
  - For example:
    - Hospitalization[1]
    - Gastrointestinal bleeding[2,3]
    - Sudden cardiac death[4]
    - Death from breast caner[5]

- DDIs are *preventable* medication errors
- Why do they still occur?

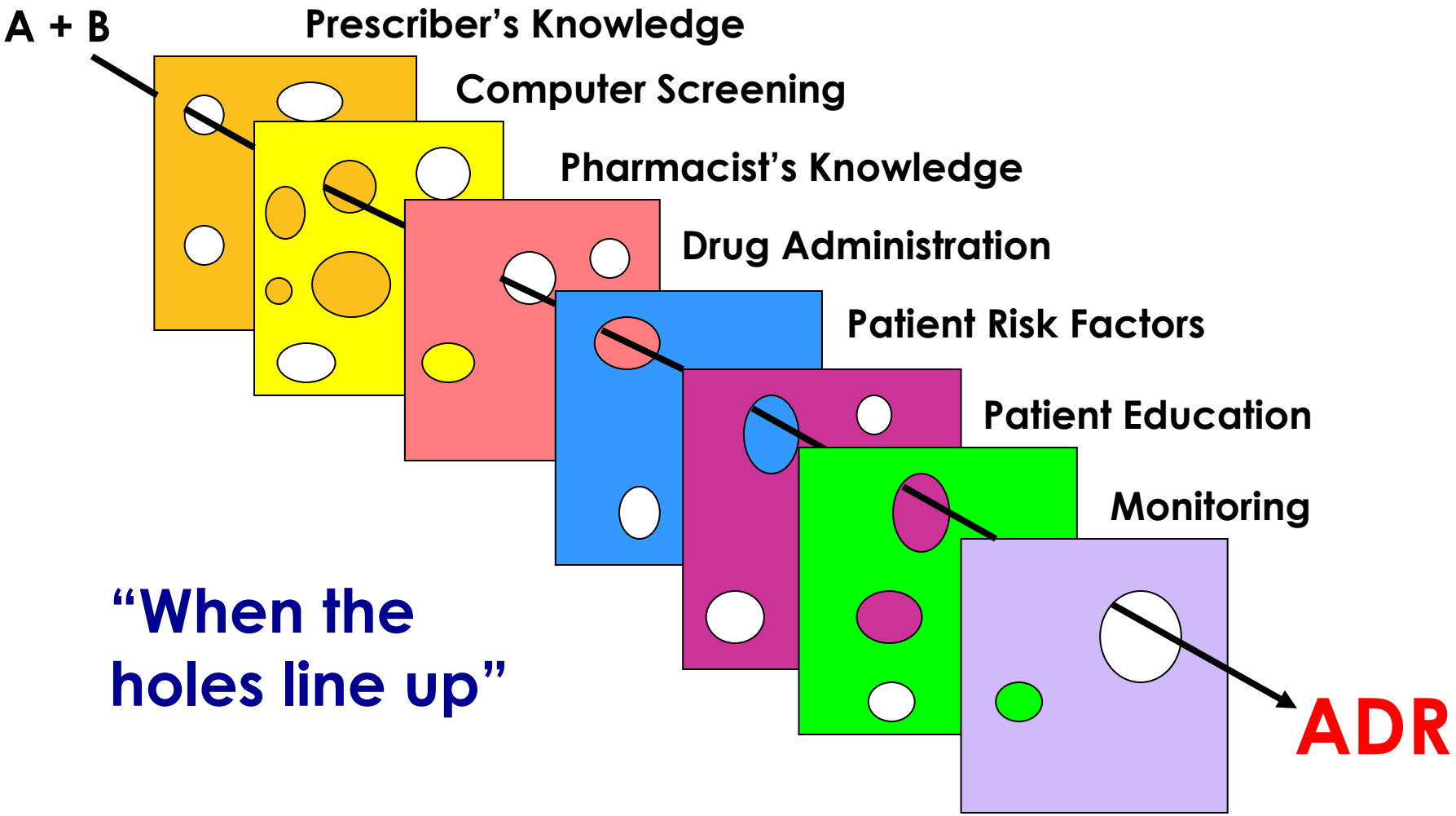
1) Juurlink et al. *JAMA*. 2003;289(13):1652-1658. 2) Schelleman et al. *Clin Pharmacol Ther* 2008;84:581. 3) Fischer et al. Arch Intern Med. 2010;170(7):617-621.
4) Ray et al. *N Engl J Med*. 2004;351(11):1089-1096. 5) Kelly et al. *BMJ*. 2010;340:c693. doi: 10.1136/bmj.c693 2010.

Swiss Cheese Model



Hansten PD, Horn JR. Modified from: James Reason, Human Error, 1990

Swiss Cheese Model



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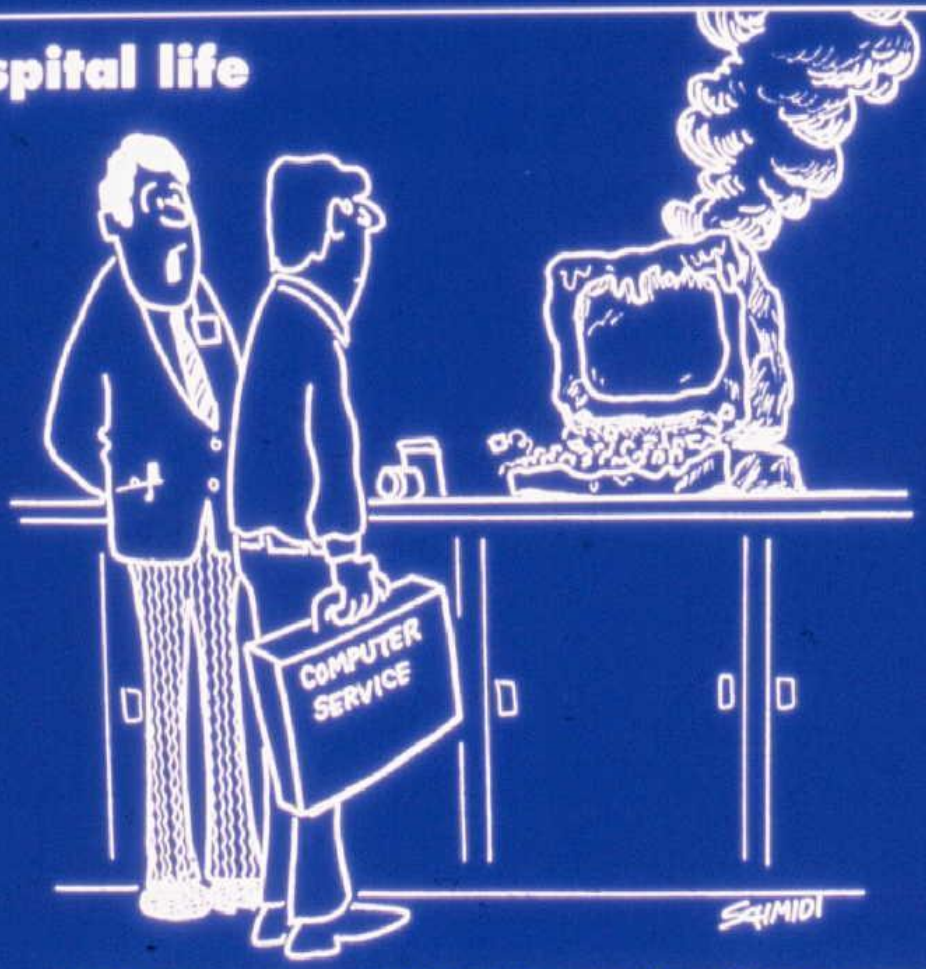
This hospital life



"At first, we thought that it was signaling a very violent drug interaction."

Pharmacy Software Study

- Purpose:
  - Assess performance of pharmacy DDI software
  - Recommend changes for improvement
- Methods:
  - December 2008 to November 2009
  - Pharmacies in Arizona (N=64)
  - On-site visit to evaluate DDI alerts
  - Brief interview of staff about software functionality

Methods

- Fictitious patient profile (18 medications)
- 19 drug pairs & drug-allergy
  - 13 DDIs
  - 6 non-interacting combinations
  - 1 drug-allergy interaction
- Selected DDIs adapted from previous research[1,2]
  - Emphasis on cardiovascular medications
  - Primary and tertiary evidence evaluated

1. Malone et al. *J Am Pharm Assn.* 2004;44(2):142-151.
2. Malone et al. *Am J Health Syst Pharm* 2005;62:1983-1991.

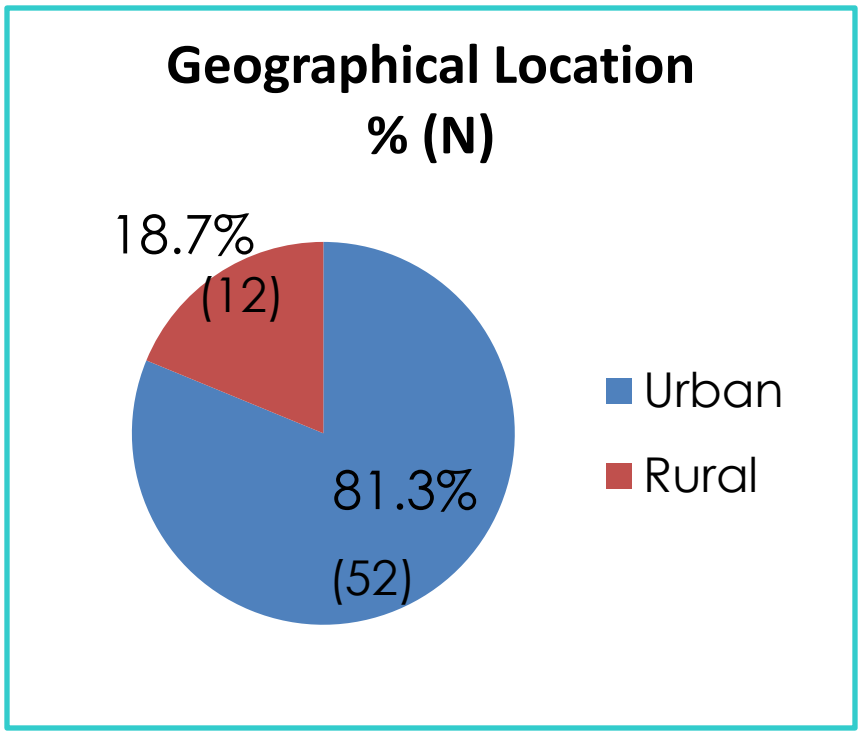
Test Medication Orders
Allergy: Penicillin

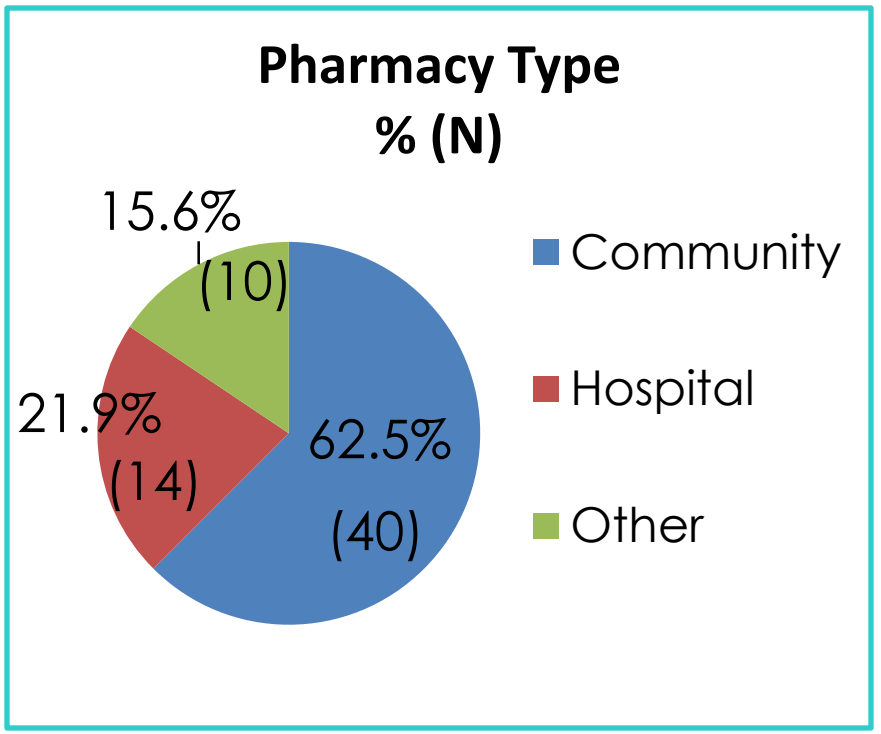
1. Amiodarone 200 mg PO BID #60
2. Amoxicillin 500 mg PO four times a day x 7 days #28
3. APAP/Codeine 300/30 mg (Tylenol #3 with Codeine) TID PRN #30
4. Carbamazepine 400 mg PO BID #30
5. Clarithromycin 250 mg PO BID #14
6. Digoxin 0.125 mg PO QD #30
7. Erythromycin Ophthalmic Ointment 0.5%; Instill ½" (1.25 cm) in both eyes TID x 7 days 1 tube (3.5 g)
8. Fluconazole 200 mg PO QD #30
9. Gemfibrozil 600 mg PO BID #60
10. Itraconazole 100 mg PO QD #30
11. Metformin 1000 mg PO BID #30
12. Naproxen 500 mg PO BID #30
13. Nitroglycerin SL 0.4 mg; 1 tablet SL PRN chest pain, may repeat every 5 minutes as needed #25
14. Pravastatin 40 mg PO QHS #30
15. Sildenafil (Viagra) 25 mg PO, PRN, 1 hour before sexual activity, not to exceed 1 dose per day #30
16. Simvastatin 20 mg PO QHS #30
17. Sulfamethoxazole/trimethoprim 800-160 mg PO BID #14
18. Warfarin 5 mg PO QD #30

Methods

- DDI software analysis
  - Each pharmacy: No. correct responses, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)
  - All pharmacies: median sensitivity, specificity, PPV, NPV, median % correct responses
- Brief interview with pharmacist
  - Responses summarized
- Report with results and recommendations for each

- 64 pharmacies in Arizona





Software Evaluation Results

DDIs	Correct Responses (N=64)* N (%)
Carbamazepine + clarithromycin	57 (89.1)
Digoxin + amiodarone	55 (85.9)
Digoxin + clarithromycin	56 (87.5)
Digoxin + itraconazole	27/60 (45.0)
Nitroglycerin + sildenafil	51/63 (81.0)
Simvastatin + amiodarone	48 (75.0)
Simvastatin + gemfibrozil	54 (84.4)
Simvastatin + itraconazole	54/60 (90.0)
Warfarin + amiodarone	55/63 (87.3)
Warfarin + fluconazole	53 (82.8)
Warfarin + gemfibrozil	51 (79.7)
Warfarin + naproxen	45 (70.3)
Warfarin + sulfamethoxazole/ trimethoprim	48 (75.0)

*Unless otherwise noted.

Software Evaluation Results

	Sensitivity	Specificity	PPV	NPV
Median	0.85	1.00	1.00	0.75
Maximum	1.00	1.00	1.00	1.00
Minimum	0.23	0.83	0.88	0.38

- Median percentage of correct responses was 89.5% (range: 47.4% - 100%)
- Sixty (93.8%) pharmacy software systems correctly detected drug-allergy interaction

Software Evaluation Results

Community Pharmacies (n=40)				
	Sensitivity	Specificity	PPV	NPV
Median	0.92	1.00	1.00	0.86
Maximum	1.00	1.00	1.00	1.00
Minimum	0.31	0.83	0.88	0.40
In-patient Hospital Pharmacies (n=14)				
	Sensitivity	Specificity	PPV	NPV
Median	0.77	1.00	1.00	0.67
Maximum	1.00	1.00	1.00	1.00
Minimum	0.38	0.83	0.93	0.43
Other Pharmacies (n=10)				
	Sensitivity	Specificity	PPV	NPV
Median	0.85	1.00	1.00	0.75
Maximum	1.00	1.00	1.00	1.00
Minimum	0.23	1.00	1.00	0.38

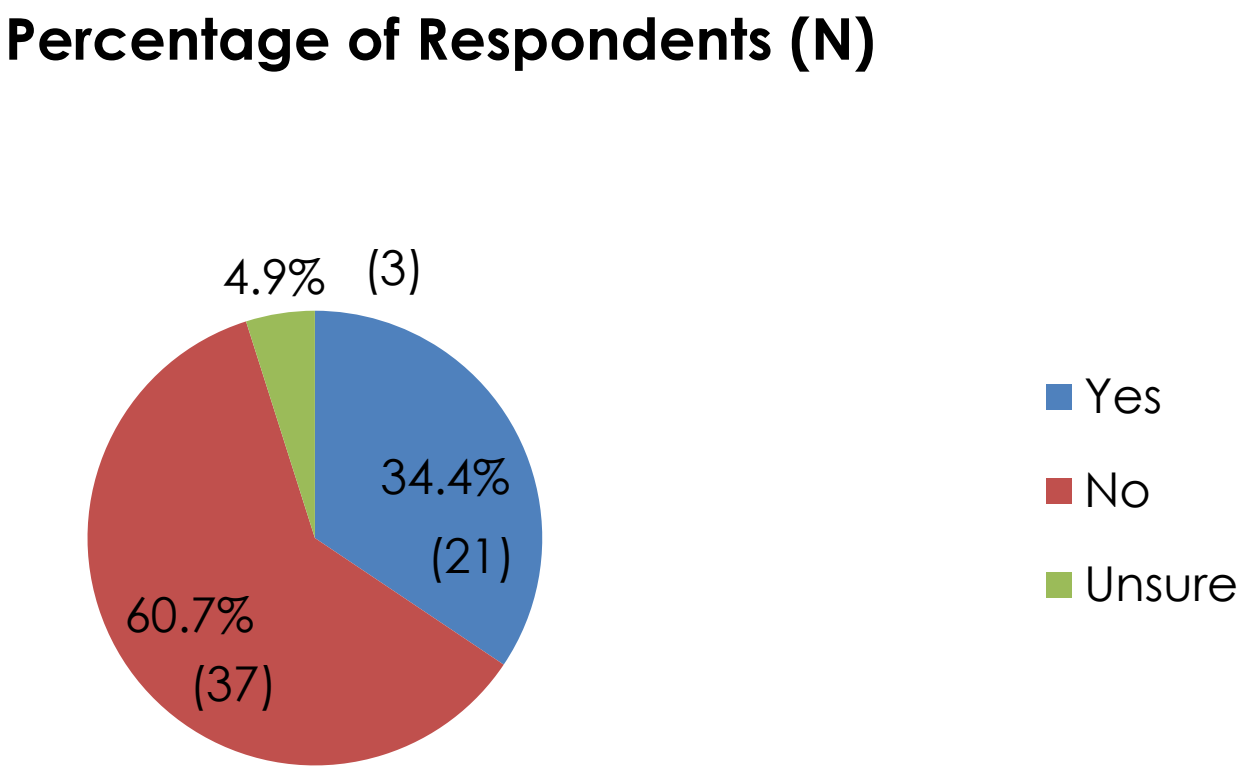
Software Evaluation Results

Non-Interacting Pairs	Correct Responses All Pharmacies (N=64)* N (%)
Acetaminophen/codeine + amoxicillin	64 (100.0)
Carbamazepine + erythromycin ophthalmic	57 (89.1)
Metformin + erythromycin ophthalmic	64 (100.0)
Digoxin + sildenafil	63/63 (100.0)
Warfarin + digoxin	64 (100.0)
Warfarin + pravastatin	62/62 (100.0)

*Unless otherwise noted.

Pharmacist Interview Results

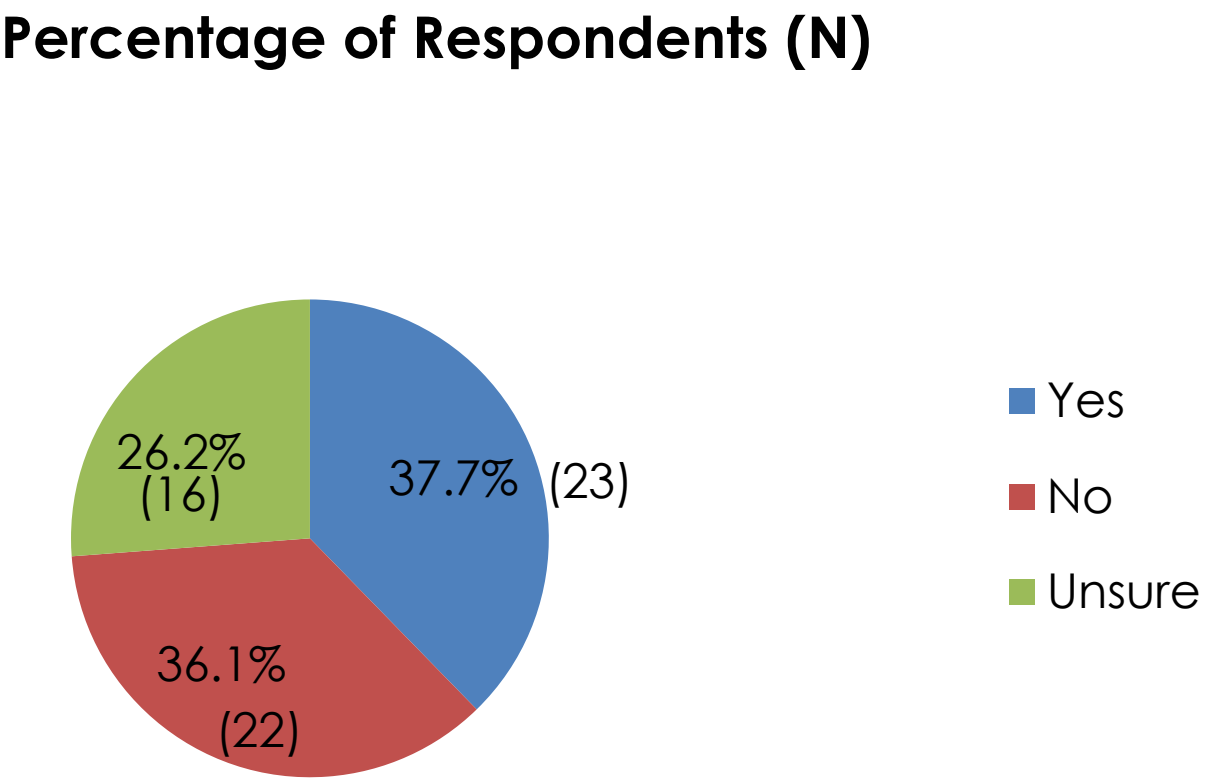
Does the software provide documentation of the DDI categories?



N=61

Pharmacist Interview Results

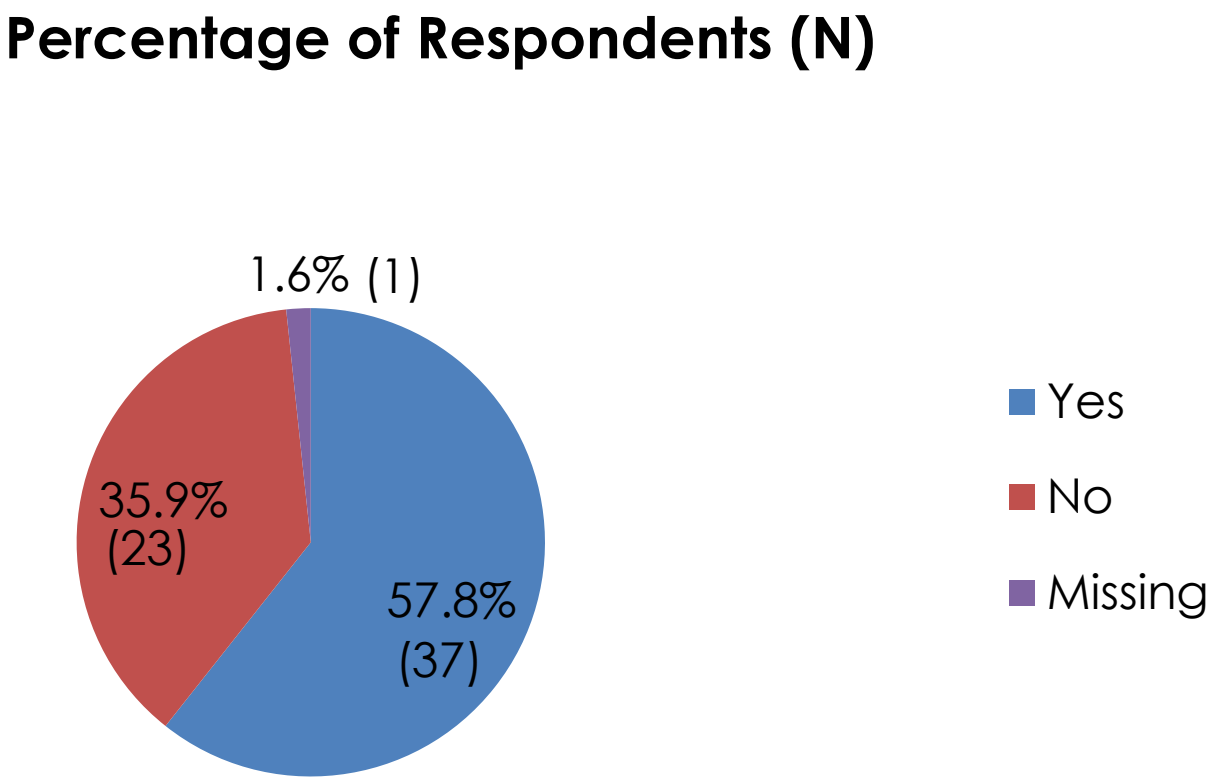
Are certain categories or levels of DDIs suppressed?



N

Pharmacist Interview Results

Are DDI management strategies provided with DDI alerts?

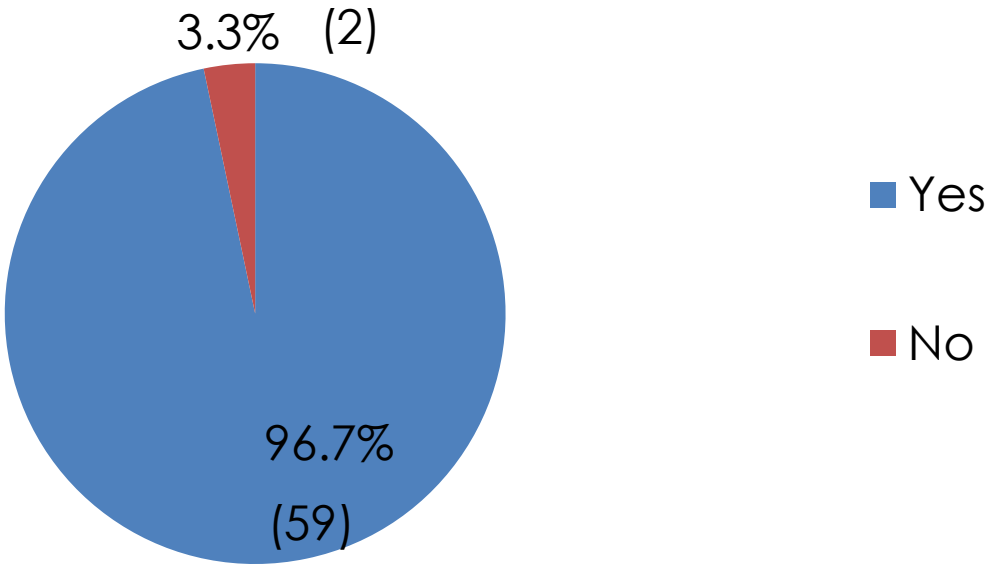


N =

Pharmacist Interview Results

Is a pharmacist required to review DDI alerts?

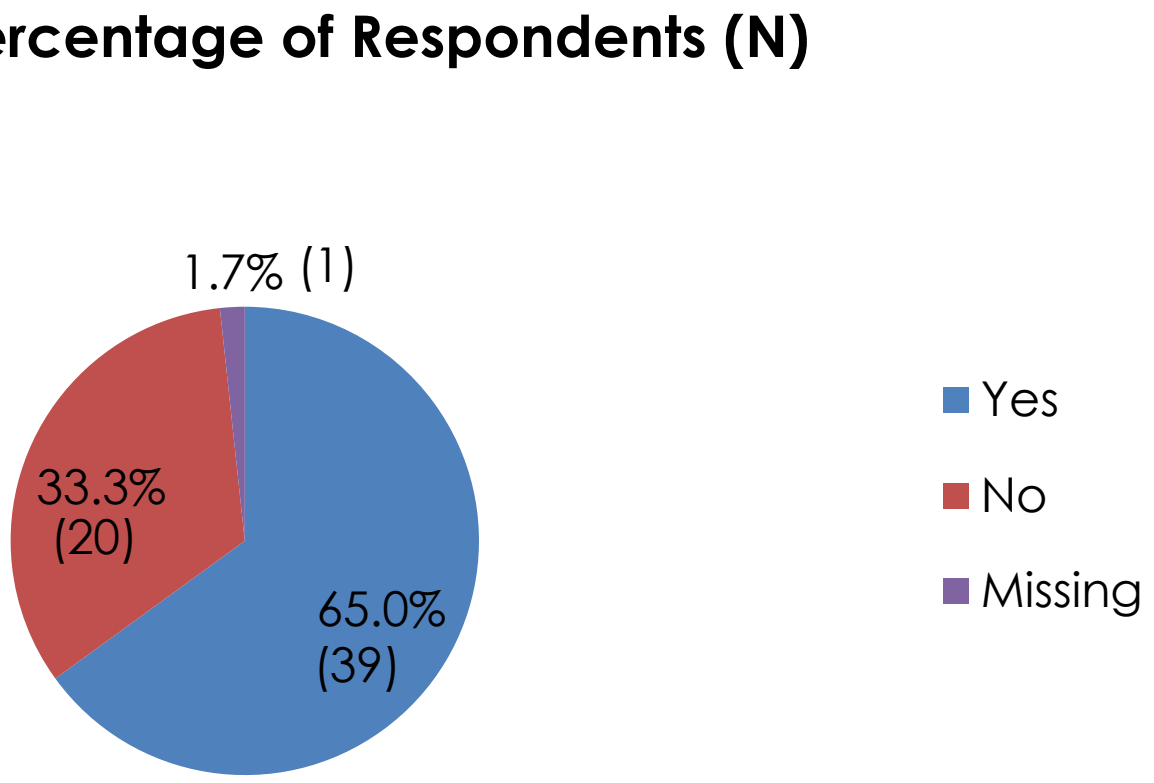
Percentage of Respondents (N)



N=61

Pharmacist Interview Results

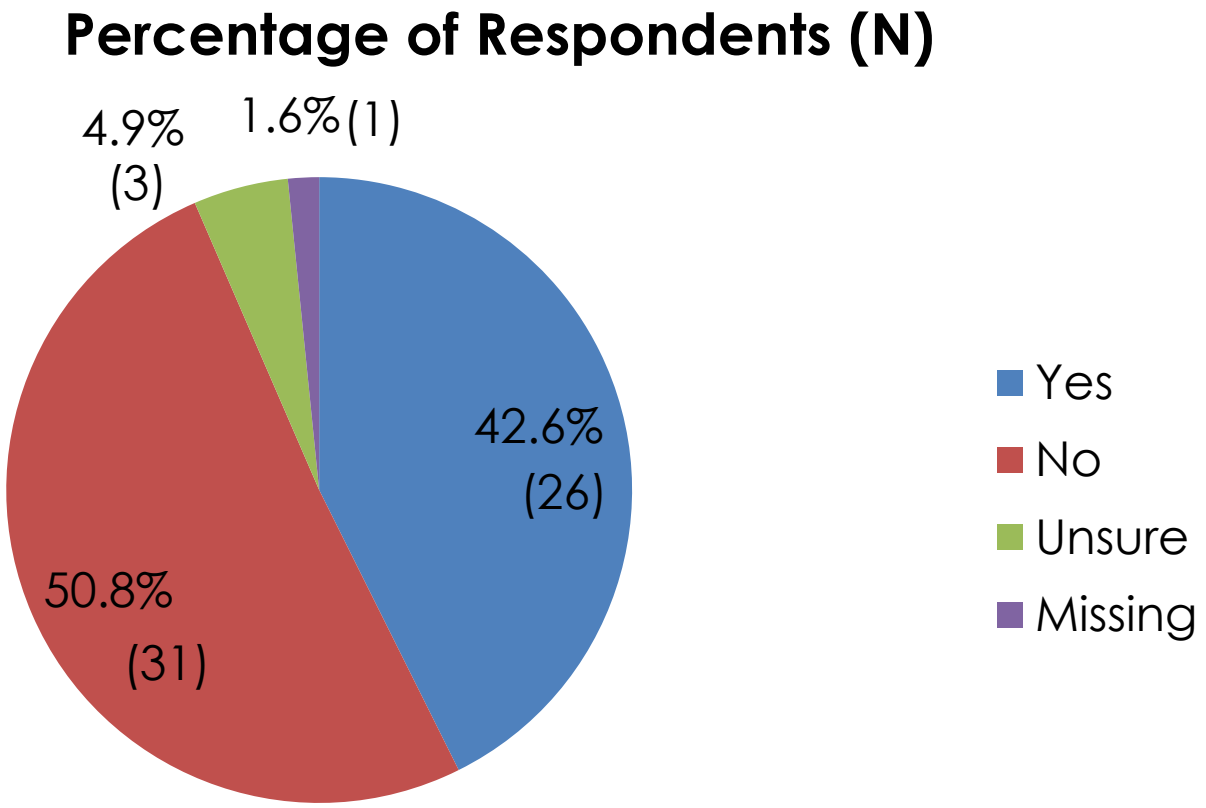
Is it possible to add current medications from other pharmacies and/or OTCs?



N=61

Pharmacist Interview Results

Are drugs entered into the computer system that are not linked to the DDI software?



N=61

Recommendations

- Pharmacists should review all DDI alerts
- Minimize "alert fatigue"
- Pharmacists should familiarize themselves with the pharmacy's CDS system and its capabilities
- Ensure pharmacy is receiving timely and regular software updates
- Pharmacists should also familiarize themselves with the current settings of the pharmacy's CDS

Pharmacy Software Quality Assurance Tool

A Drug Pair		B Correct Response	C Correct Response in Pharmacy Software?	
		Alert/No Alert	Yes	No
INTERACTING DRUG PAIRS				
1.	Carbamazepine + clarithromycin	Alert		
2.	Digoxin + amiodarone	Alert		
3.	Digoxin + clarithromycin	Alert		
4.	Digoxin + itraconazole	Alert		
5.	Isosorbide mononitrate + sildenafil	Alert		
6.	Simvastatin + amiodarone	Alert		
7.	Simvastatin + gemfibrozil	Alert		
8.	Simvastatin + itraconazole	Alert		
9.	Warfarin + amiodarone	Alert		
10.	Warfarin + fluconazole	Alert		
11.	Warfarin + gemfibrozil	Alert		
12.	Warfarin + naproxen	Alert		
13.	Warfarin + sulfamethoxazole/trimethoprim	Alert		
D. Subtotals for interacting drug pairs (items 1-13)			**E.**	**F.**
NON-INTERACTING DRUG PAIRS				
14.	Acetaminophen/codeine + amoxicillin	No Alert		
15.	Carbamazepine + erythromycin ophthalmic	No Alert		
16.	Digoxin + sildenafil	No Alert		
17.	Metformin + erythromycin ophthalmic	No Alert		
18.	Warfarin + digoxin	No Alert		
19.	Warfarin + pravastatin	No Alert		
G. Subtotals of for non-interacting drug pairs (items 14-19)			**H.**	**I.**
J. Total number of correct and incorrect responses (items 1-19)			**K.**	**L.**

E=true positives; F=false negatives (missed DDIs); H=true negatives; I=false positives

Need a benchmark?

- Abarca et al. *JMCP* 2006;12(5):383-89.
- Hazlet et al. *J Am Pharm Assn* 2001; 41:200-204.

Warholak et al. *J Am Pharm Assn* 2010. (in press).

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"25 Clinically Important DDIs"

- Objectives
  - Identify and prioritize DDIs that pose significant clinical risk
  - Identify 10-15 DDIs that are primary candidates for surveillance
- Partnership
  - CDC
  - AdvancePCS (now CVS/Caremark)
  - University of Arizona
  - University of Washington

Methods

- Review compendia for "major" interactions
  - DDI listed in at least 3 compendia
  - Additional criteria:
    - Available in US for human use
    - Likely to be dispensed in community pharmacy
    - Likely to be captured in electronic database
    - Occur upon initiation of therapy
    - DDI not used for therapeutic benefit
- Identify evidence for selected DDIs
  - Compendia citations
  - Medline and IPA (1995 to 2002)
  - Executive summary of supporting literature

Methods

- Expert Panel
  - Members: 2 Physicians, 3 Pharmacists
  - Modified Delphi Technique (3 Rounds)
- First Round:
  - Independent rating of DDIs
  - Survey instrument (16 items)
    - Included:
      - Quality & quantity of evidence
      - Risk of mortality
      - Probability of interaction
      - Risk of adverse event
      - Probability of co-administration

Malone et al. J Am Pharm Assoc 2004; 44:142-151

Methods

- Second Rounds:
  - Compared individual ratings to group means
  - Eliminated DDIs by consensus
  - Added DDIs not initially identified from compendia (n=10)
    - Why? See Abarca et al. *J Am Pharm Assoc* 2004: 44:137-141.
  - Added restrictions on how DDIs should be evaluated
- Third Round
  - DDIs rank-ordered based on clinical significance scores
  - Expert panel selected the 25 most serious and clinically significant interactions

Malone et al. J Am Pharm Assoc 2004; 44:142-151

Agreement Among Compendia

Selected Compendia Severity Rating Scales

Facts & Comparisons EAnswers	Micromedex 1.0	DIAM 2010	Top 100 Drug Interactions 2010
1=Potentially severe or life-threatening	Major	Class 1: Avoid	Class 1: Avoid
2=May cause deterioration of clinical status	Moderate	Class 2: Usually Avoid	Class 2: Usually Avoid
3=May cause minor effects	Minor	Class 3: Minimize Risk	Class 3: Minimize Risk
–	–	Class 4: No Action Needed	Class 4: No Special Precautions
–	–	Class 5: No Interaction	Class 5: Ignore

Agreement Among Compendia

Compendia Ratings for Selected DDIs

	Facts & Comparisons EAnswers	Micromedex 1.0	DIAM 2010	Top 100 2010	Primary Literature
Warfarin + Azithromycin	**1 Major Probable**	**Moderate Good**	**5: No Interaction**	Not listed (isolated cases)	Data inconclusive
Warfarin + Ciprofloxacin	**1 Major Probable**	**Moderate Good**	**3: Minimize Risk**	Not listed (isolated case)	*CPT*. 2008; 84(5):581-8. *Arch Intern Med*. 2010; 12;170(7):617-21.
Warfarin + SMX/TMP	**1 Major Established**	**Major Excellent**	**3: Minimize Risk**	**2: Usually Avoid**	*CPT*. 2008; 84(5):581-8. *Arch Intern Med*. 2010; 12;170(7):617-21.

Clinically Important DDIs

Object	**Precipitant**
Benzodiazepines	Azole antifungal agents
Carbamazepine	Propoxyphene
Cyclosporine	Rifamycins
Dextromethorphan, meperidine, SSRIs	MAO inhibitors
Digoxin	Clarithromycin
Ergot alkaloids	Macrolide antibiotics
Estrogen-progestin products (OCs_)	Rifampin
Ganciclovir	Zidovudine
MAO inhibitors	Anorexiants or sympathomimetics
Methotrexate	Trimethoprim
Nitrates	Sildenafil
Pimozide	Macrolide antibiotics, azole antifungal agents
Theophyllines	Quinolones, fluvoxamine
Thiopurines	Allopurinol
Warfarin	Sulfinpyrazone, NSAIDs, cimetidine, fibrates, barbiturates, thyroid hormone

Malone et al. J Am Pharm Assoc 2004

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PQA DDI Performance Measure

- 2006 measure developed
  - PQA patient safety workgroup
- 2007 measure pilot tested
  - NCQA and Advance Pharmacy Concepts
  - Minor problems - temporarily set aside
- 2009 measure adopted by CMS
  - For inclusion in Part D plan display measure set
  - Problematic pairs excluded
- 2010 measure updated and pilot tested

PQA DDI Performance Measure

- Starting point - List by Malone et al, 2004
- Criteria for DDI selection
  - Evidence to substantiate clinical severity
  - Highest severity level among multiple DDI compendia/software programs
  - Used with sufficient frequency
  - Acceptable non-interacting alternatives available in majority of clinical situations

Proposed DDIs for PQA Measure

Target Drug or Drug Class	Precipitant Drug or Drug Class
Benzodiazepines	Azole antifungal agents
Carbamazepine	Propoxyphene
Cyclosporin	Rifamycins
Digoxin	Erythromycin, clarithromycin, azithromycin, telithromycin
Ergot alkaloids	Erythromycin, clarithromycin, telithromycin
Estrogen/progestin OCPs	Rifamycins
MAO inhibitors	Sympathomimetics, serotonergic agents
Methotrexate	SMX/TMP
Nitrates	Phosphodiesterase inhibitors
* Simvastatin (40 & 80 mg)	Amiodarone
* Tamoxifen	Bupropion, duloxetine, fluoxetine, paroxetine
Theophylline	Ciprofloxacin, fluvoxamine
Mercaptopurine	Allopurinol
Warfarin	Cimetidine, Fibrates, NSAIDs, SMX/TMP

*** NEW**

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Thank you

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THE LAB WHERE
THEY STUDY DRUG INTERACTION