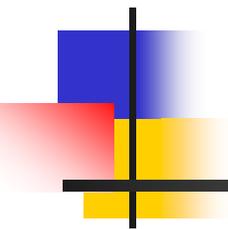


Lessons Learned from Drug-Drug Interactions: Implications for Risk Management



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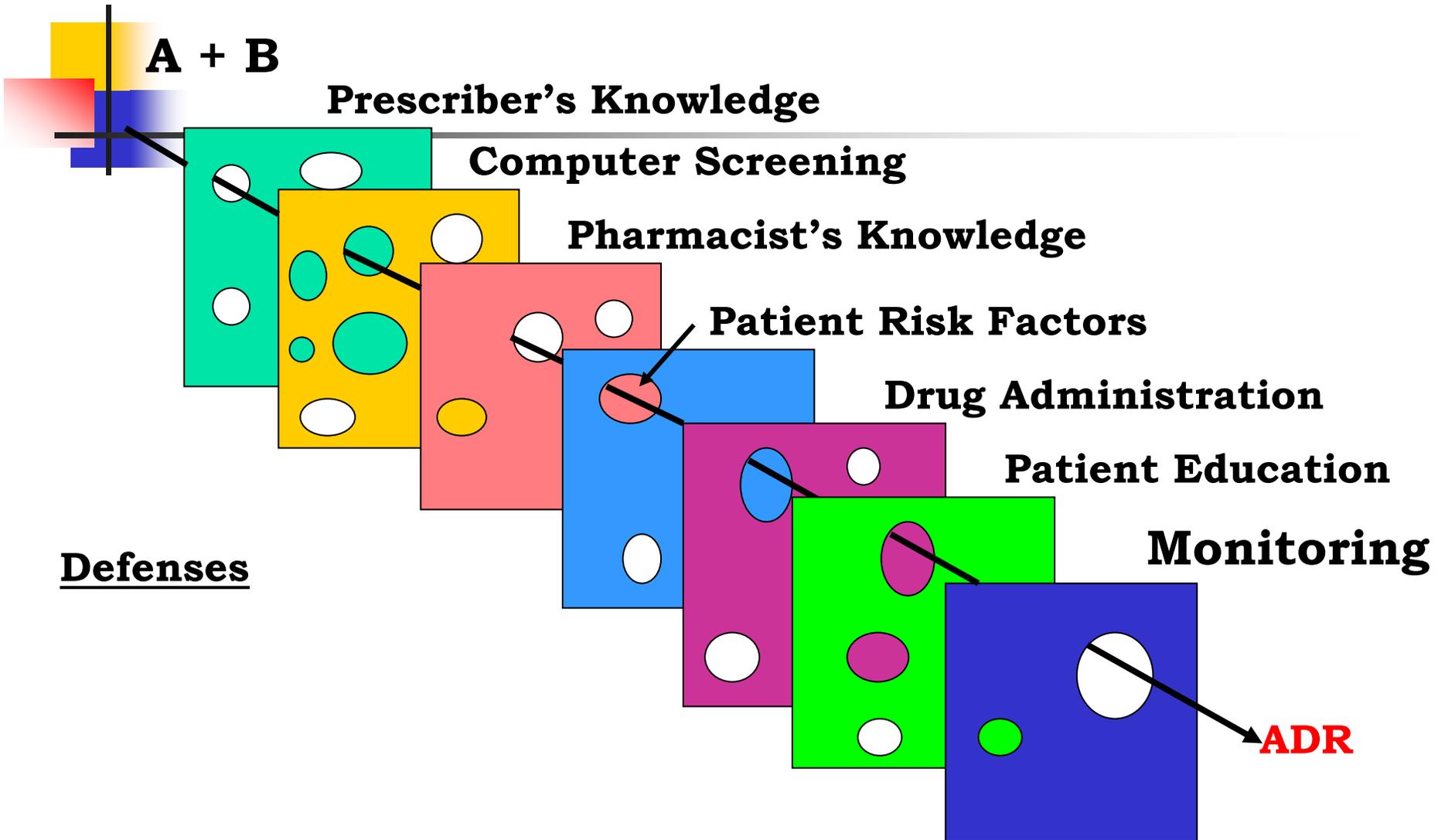


Risk and Pharmaceuticals

- Restatement of Torts (Second)
 - Strict Liability
 - Comment k
 - Pharmaceuticals considered exempt from strict liability
 - Unavoidably unsafe
 - Benefit to society outweighs inherent risks
 - Continuum of Risk
 - From over-the counter to restricted distribution

Drug Interactions

“When the Holes Line Up”

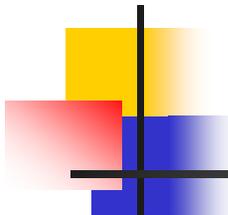


Hansten PD, Horn JR. Modified from: James Reason, Human Error, 1990



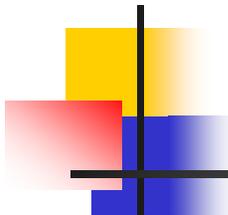
Computerization of Potential Drug-Drug Interactions

- Pharmacy Computer Systems
 - Perform routine check of medications on the patient's profile for potential interactions
 - Alerts provided to the pharmacy staff
 - Numerous methods to classify interaction severity



Rating Systems for Drug-Drug Interactions

Reference	Levels
Evaluation of Drug Interactions	1: highly clinically significant; 2: moderate; 3: minimally; 4: not
Drug Interaction Facts	Severity: Major; moderate; minor Documentation: Established, probable, suspected, possible, unlikely
Drug Interactions: Analysis and Management	1: contraindicated; 2: usually avoid; 3: conditional; 4: minimal risk; 5: no interaction
DRUG-REAX®	Major; moderate; minor

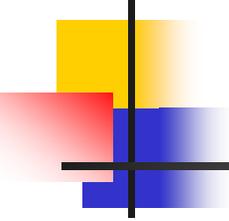


Problems with Identifying Drug-Drug Interactions

“Major” Drug Interactions (at ***Medication Class Level***) by Compendium

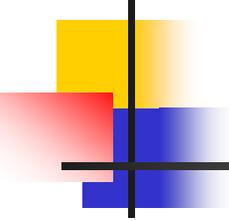
Compendium	No.
MicroMedex <i>DRUG-REAX</i> ®	275
<i>Evaluation of Drug Interactions</i>	64
<i>Drug Interactions: Analysis and Management</i>	94
<i>Drug Interaction Facts</i>	141
Total	406*

* Sum of column exceeds total due to duplicate interactions.



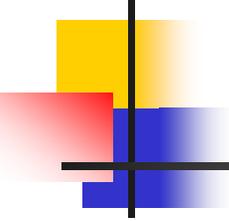
Concordance of "Major" Drug Interaction Classifications by Compendia

Number of compendia listing interaction	Micro-Medex	Evaluation of Drug Interactions	Drug Interactions: Analysis and Management	Drug Interaction Facts	Total Cumulative Total
Four	9	9	9	9	9 (2.2%)
Three	3	3	3		
	7	7		7	
	20		20	20	
		5	5	5	35 (8.6%)



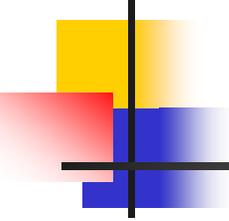
In-store Pharmacy Software to Detect Drug-Drug Interactions

	<u>Sensitivity</u>	<u>Specificity</u>	<u>PPV</u>	<u>NPV</u>
Overall	0.71	0.89	0.83	0.80
Best	0.88	1.00	1.00	0.90
Median	0.69	0.90	0.83	0.79
Worst	0.44	0.71	0.67	0.69



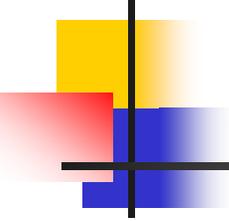
In-store Community Pharmacy Software to Detect Drug-Drug Interactions – An Update

	<u>Sensitivity</u>	<u>Specificity</u>	<u>PPV</u>	<u>NPV</u>
Overall	0.88	0.89	0.86	0.90
Best	0.94	1.00	1.00	0.95
Worst	0.81	0.67	0.68	0.87



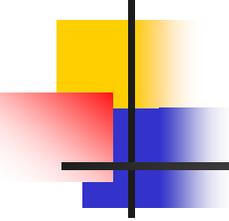
Hospital Pharmacy Software to Detect Drug-Drug Interactions – “Warning”

	<u>Sensitivity</u>	<u>Specificity</u>	<u>PPV</u>	<u>NPV</u>
Overall Median	0.44	0.95	0.83	0.67
Best	0.94	0.95	0.94	0.95
Worst	0.15	0.95	0.67	0.65



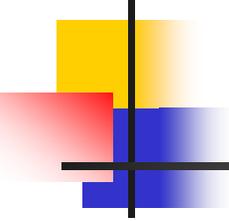
Why the “poor” performance of pharmacy systems to “catch” interactions

- Poor definitions of what “significant” means
 - The risk/benefit formula is determined in subjective manner
 - Few studies to support interactions
 - Those studies are evaluated by a few persons operating in different environments than the end users
- Ability to enter new drug products into the pharmacy system – not linked to the underlying databases
 - Most clinical support systems use NDC codes - opportunity for error or work a rounds.



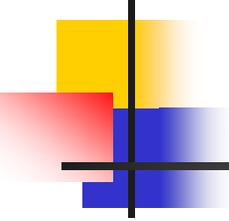
Computerization of Potential Drug-Drug Interactions

- Pharmacy Computer Systems
 - Perform routine check of medications on the patient's profile for potential interactions
 - Alerts provided to the pharmacy staff
 - Numerous methods to classify interaction severity
- Pharmacy Benefit Managers
 - Provide real-time checking for drug-drug interactions



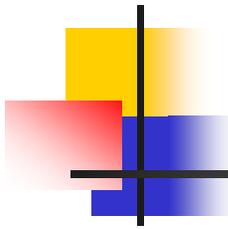
Pharmacy – PBM Communications

- Pharmacy claims processing
 - Types of verifications/information
 - Pharmacy eligibility
 - Patient eligibility
 - Medication eligibility
 - Utilization review
 - Dose considerations
 - Refill history
 - Interactions
 - 2 seconds per transaction
 - Warning messages sent to pharmacy



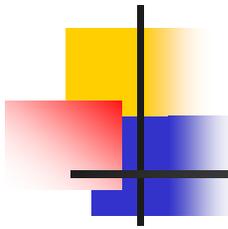
Alert "Fatigue"

- Pharmacists commonly see 2 alert messages for each potential interaction
 - Pharmacy software
 - PBM
- Many alerts are for refills, low risk of ADEs
- Failure to incorporate time element
- Most alerts ignored by pharmacists
 - Chui and Rupp (JMCP 2000)
 - Murphy et al (Am J. Health-Sys Pharm 2004)



Pharmacists Workload and Dispensing of Potential Drug-Drug Interactions

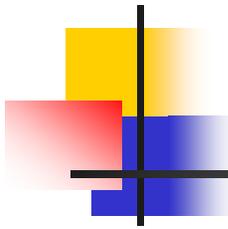
- Merged pharmacy store data with prescription claims from 4 PBMs
- Examined pharmacy characteristics and work volume and rate of dispensed potential DDIs
- Significant factors affecting rate of potential DDIs:
 - Pharmacist workload
 - Pharmacy staff workload



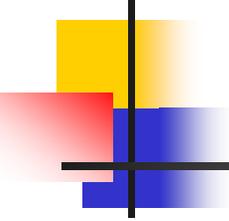
Prescribing Safety During Pregnancy

- Randomized trial of a computerized alert to pharmacist when pregnant women prescribed a “D” or “X” medication
- Results
 - Main findings (receiving an inappropriate drug)
 - 2.9% (intervention)
 - 5.5% (usual care)
 - Study stopped due to false positive alerts
 - Misidentification of contraindicated medications by pharmacy computer system
 - Misidentification of women who were not pregnant

Raebel MR et al. J Am Med Inform Assoc (in press)

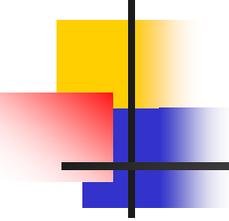


Computerized Physician Order Entry



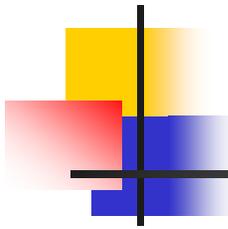
Reasons Provided by Prescribers When Overriding Drug-Drug Interaction Alerts

- Objective:
 - Determine why prescribers override drug-drug interaction (DDI) alerts
 - Evaluate whether reasons provided were helpful to pharmacists
- Study Design:
 - Observational, retrospective database analysis using override reasons from 6 Veterans Affairs Medical Centers



VA Drug-Drug Interaction Alert System

- VA specific methods that classifies interactions into “Critical” and “Significant”
- Alert specification set at a national level
- Individual VAMCs can add new interactions or upgrade a significant interaction to critical
- Prescribers required to response to critical interactions
 - Some VAMCs may require response to significant

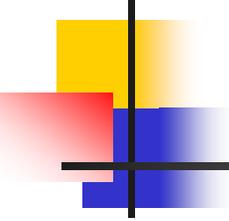


Analysis by Severity of DDIs

- Critical DDIs (72% of sample)
 - Reason provided 47%
 - Rated useful 20%
 - Rated not useful 80%
 - No reason provided 53%

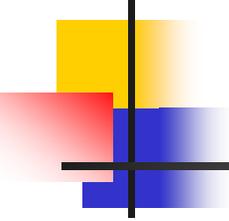
- Significant DDIs (28% of sample)
 - Reason provided 4%
 - Rated useful 2%
 - Rated not useful 98%

 - No reason provided 96%



Issues Relevant to RiskMAPs

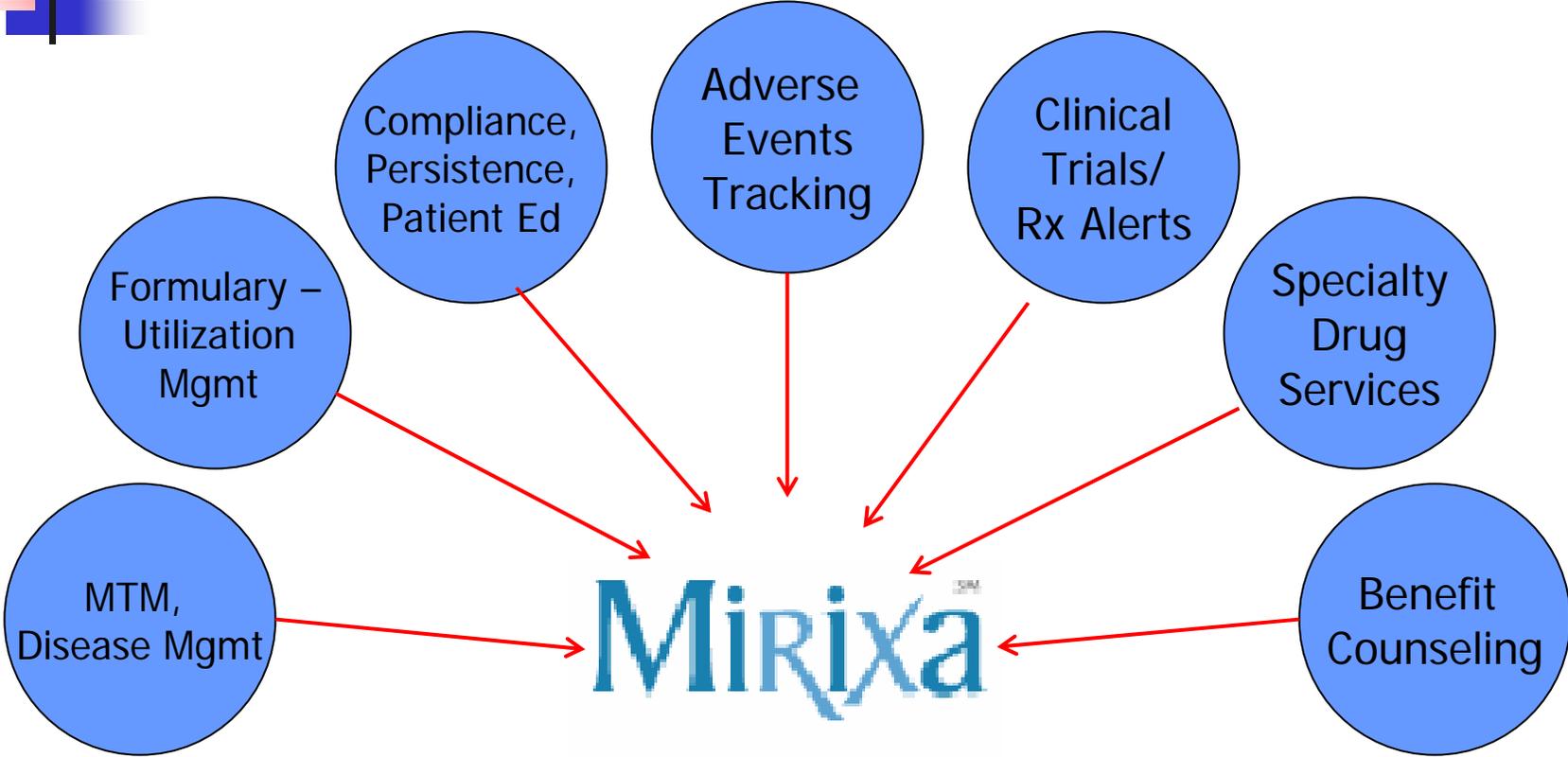
- Poor specification of risk
- One size does not fit all
 - Multiple vendors/multiple systems
 - Setting risk levels
 - Non-staff model MCOs creating own RiskMAP – likely to create confusion among providers/pharmacists
 - New models constantly being developed

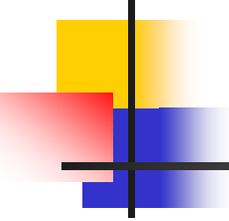


Evolving Systems for RiskMAPs: The Mirixa Corporation

- MirixaPro: Web-based delivery system for ANY pharmacist services programs (including MTM, Adverse Events Tracking, Clinical Trials, etc.)
- Platform configured to meet Program Sponsor design needs
- A solution for creating a **network** of patient care programs
- Network of 41,000 pharmacies

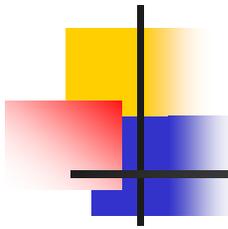
Mirixa Programs





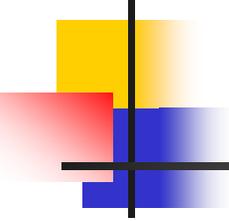
Issues Relevant to RiskMAPs

- Ability to verify/document 24/7 @ 365
 - Patients show up at the pharmacy in the middle of the night
 - Many clinical decision support systems not “real time” – even in the best environments



Issues Relevant to RiskMAPs

- Don't assume that linking to the NDC will be successful
 - New drugs often entered manually
 - Re-labelers result in a new NDC
- Pharmacists are extremely busy - difficult to change the dispensing process
- Silo computer software packages abound – even within the same institution/system



Consequences of Computerization/Automation

- Thinking ceases
- “asdf” is a four letter response to a “required” action
- Implementing hard edits can have adverse consequences
 - People often act like water
 - Seek the lowest point
 - Exploit every “crack” to get there
- Details are “everything” to get buy-in