Drug-Drug Interaction (DDI) Screening for Oncology Clinical Trial Enrollment

Dan Hertz, PharmD, PhD

4/25/18

Oishi Symposium

SWOG Spring 2019

Outline

- PK and PD Drug-drug Interactions
- DDI Screening
- SWOG DDI Screening Initiative

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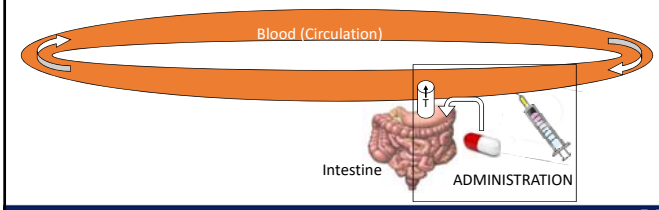
Pharmacokinetics (PK) and Pharmacodynamics (PD)

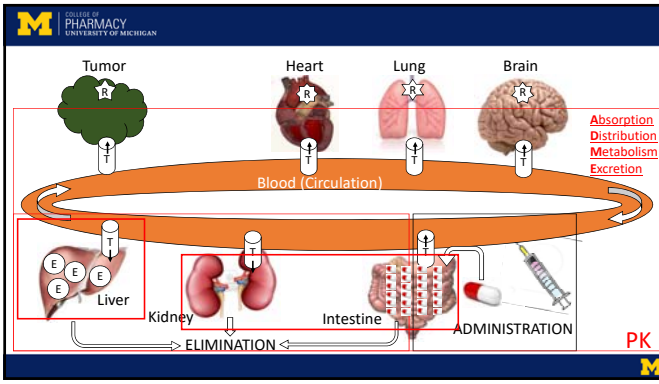
Pharmacokinetics (PK)

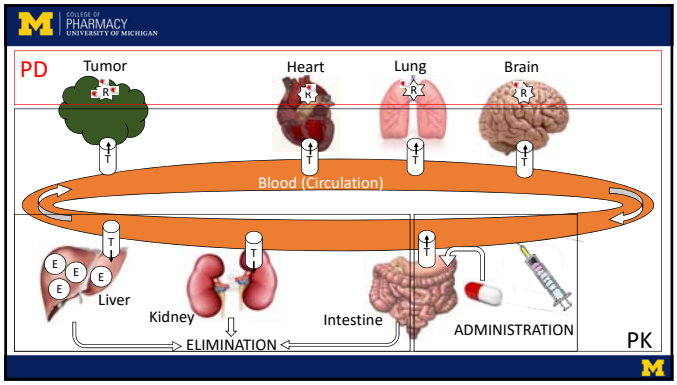
- PK: amount of drug in the body
  - "what the body does to the drug"
- PK determined by ADME processes
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**xcretion

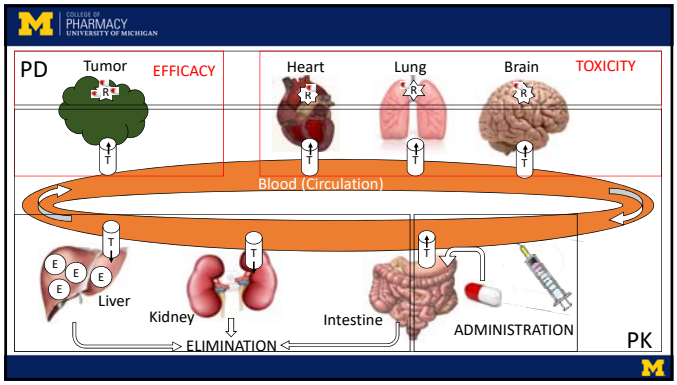
Pharmacodynamics (PD)

- PD: bodies response to drug
  - "what the drug does to the body"
- PD determined by interaction of drug with targets (receptors)
  - On-target effects: efficacy
  - Off-target effects: toxicity









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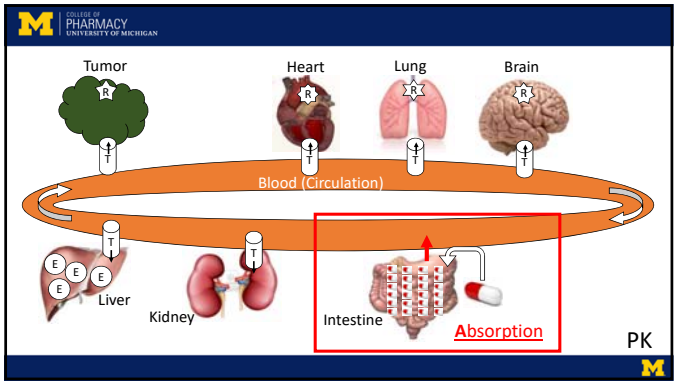
Drug Interactions

- Drug interactions:
  - "A situation in which a substance affects the activity of a drug when both are administered together"
  - Focus on drug-drug interactions (DDI) but others exist:
    - Drug-food interactions
    - Drug-gene interactions (pharmacogenetics)
- DDI influence the relationship between dose and response
  - Pharmacokinetic (PK) relationship: amount of drug in body
  - Pharmacodynamic (PD) relationship: body response to drug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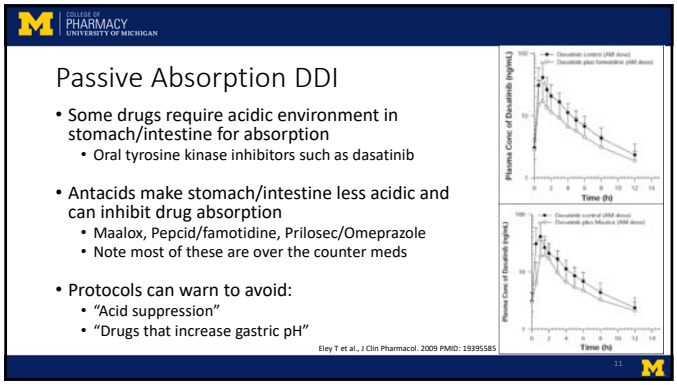
Tumor
Heart
Lung
Brain
Blood (Circulation)
Liver
Kidney
Intestine
Absorption
PK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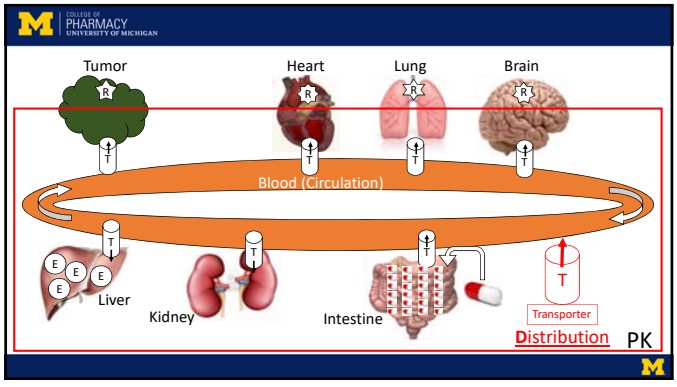
Passive Absorption DDI
• Some drugs require acidic environment in stomach/intestine for absorption
• Oral tyrosine kinase inhibitors such as dasatinib
• Antacids make stomach/intestine less acidic and can inhibit drug absorption
• Maalox, Pepcid/famotidine, Prilosec/Omeprazole
• Note most of these are over the counter meds
• Protocols can warn to avoid:
• "Acid suppression"
• "Drugs that increase gastric pH"
Eley T et al., J Clin Pharmacol. 2009 PMID: 19395585
Time (h)
Time (h)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Tumor
Heart
Lung
Brain
Blood (Circulation)
Liver
Kidney
Intestine
T
Transporter
Distribution
PK

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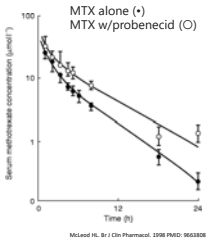
Active Absorption/Distribution DDI

- Most drugs are actively absorbed and distributed around the body via drug **transporters**
  - P-gp, ABCB/ABCC, MDR, OAT/OCT, SLCO
- Some drugs inhibit or induce transporters
  - Inhibitors DECREASE transport
  - Inducers INCREASE transport
- Protocols may recommend avoiding:
  - "Inhibitors of p-glycoprotein (P-gp)"
  - "Inducers of OATP1B3"
- We have limited knowledge of transporters and their DDI, relative to enzymes



McLeod HL. Br J Clin Pharmacol. 1998 PMID: 9663808

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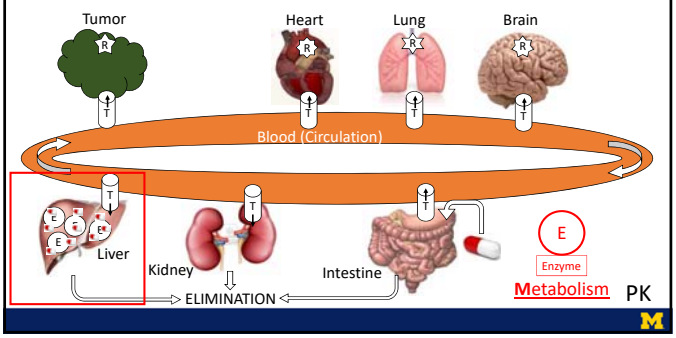

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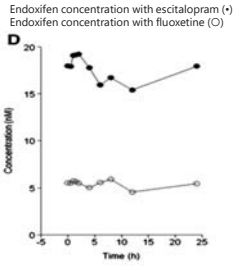
Metabolism DDI

- Most drugs are metabolized by **enzymes**
  - This drug is referred o as a "substrates" of that enzyme
  - i.e., CYP3A4, CYP2D6, UGT1A1, SULT1A1
- Many drugs inhibit or induce enzymes
  - Inhibitors DECREASE metabolism
  - Inducers INCREASE metabolism
- Protocols may recommend avoiding:
  - "CYP3A4 substrates"
  - "CYP2D6 inducers"
  - "UGT1A1 inhibitors"
- We have extensive knowledge of enzymes and their DDI



Binkhorst L et al. Clin Pharmacokinet. 2016 PMID: 26446141

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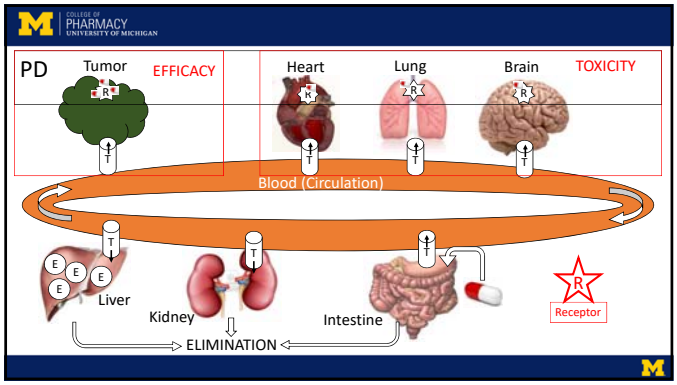

PD DDI

- PD: The body response to the drug
- PD DDI occur when drugs taken together have effects that are similar (additive) or opposing (antagonistic)
  - Similar effects enhance efficacy or toxicity
  - Opposing effects offset efficacy or toxicity
- Most often concerned about additive toxicity
  - i.e., additive sedation (sleepiness), QT prolongation (heart arrhythmia)
  - "Avoid drugs that cause QT prolongation"
- We could also be concerned about opposing efficacy

Outline

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DDI Severity and Relevance

Severity (in general, no single scale)

- Contraindicated
  - Drugs should never be co-administered
  - Confirmation of likely severe harm
- Major
  - Drugs should not be co-administered
  - Strong likelihood of severe harm
- Moderate
  - Co-administration should be avoided if possible
  - Possibility of harm
- Minor
  - Co-administration likely ok
  - Theoretical risk considered not to be clinically relevant

Relevance to SWOG

- Trial Subject Safety
  - Increase toxicity
  - Decrease efficacy
- Clinical Trial Data
  - Inaccurate estimates of efficacy and/or toxicity from trials

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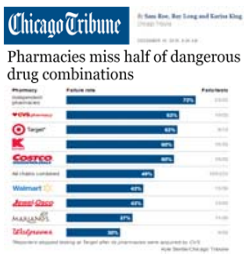
DDI Screening

- Standard practice in clinical care
  - Often pharmacists' responsibility
  - Built into electronic medical systems
    - Prescription systems at pharmacy
    - Electronic medical records at hospital
- DDI in Oncology Patients
  - Study of Dutch oncology patients (n=278)
    - 161 patients (58%) had at least one DDI
    - 348 total DDI detected
      - 34% major, 60% moderate
      - 40% involved anticancer drug


Chicago Tribune

Pharmacies miss half of dangerous drug combinations

van Leeuwen RW, Ann Oncol. 2011 PMID: 21343376

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Nurses Role and Confidence in DDI Screening

- Surveys of nurses suggest :
  - Nurses often encounter DI
    - 25% in last year
  - Nurses often responsible for teaching patients about DI
    - 45%-50%
  - Nurses lack confidence in their DDI knowledge
    - 23%


Table 2

Nurses' practices for drug interactions

Practices	n (%)
Encountered drug interactions	
Yes	46 (40.0)
No	69 (60.0)
Encountered drug interactions in last year	
Yes	26 (22.6)
No	89 (77.4)
Teaching to patients about drug interaction	
Always	53 (46.1)
Sometimes	56 (48.7)
Never	6 (5.2)

Karahan A, Asia Pac J Oncol Nurs. 2015

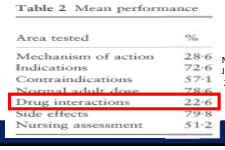
Table 2 Mean performance

Area tested	%
Mechanism of action	28·6
Indications	72·6
Contraindications	57·1
Normal adult dose	78·6
Drug interactions	22·6
Side effects	79·8
Nursing assessment	51·2

Ndosi ME. J Clin Nurs. 2009

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DDI Screening Tools

- Flockhart Table of CYP enzyme substrates/inhibitors/inducers
  - https://drug-interactions.medicine.iu.edu/main-table.aspx
- Subscription Tools
  - Lexicomp
  - Micromedex
- Free Tools
  - Drugs.com
  - WebMD
- Our study of screening 145 Oncology DDIs with 9 tools
  - Lexicomp had best information
  - **Drugs.com** is free and performed similar to Lexicomp

Marcath LA et al. J Oncol Pract. 2018 PMID: 29787332

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DDI Screening for Oncology Trials

- Recent editorial: all oncology clinical trial subjects need to be screened for DDI by a pharmacist during enrollment
  - McGahey KE et al. Am J Health-Syst Pharm 2017 PMID: 28389457
- Screening should be conducted:
  - At enrollment to screen current medications
  - At each evaluation or at the time of any medication changes
- Screening should be based off information in protocol
  - Responsibility of PI (and SWOG Pharmaceutical Sciences Committee) to ensure that information in protocol is accurate and complete

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DDI Information in Clinical Trial Protocols

- Lack of uniformity in location of information, terms used etc.
  - Even within protocols sections can disagree
- Protocol sections that include DDI Information
  - Drug Information (Sec 3): Potential Drug Interactions
    - Discusses mechanism and data
  - Exclusion criteria (Sec 5)
    - Drugs, classes, or PK/PD mechanisms (i.e. 3A4 inducers, QT prolongation)
  - Treatment Plan (Sec 7): Concomitant Medications
    - Recommendations for exclude, avoid, use with caution
  - Prohibited Medications List
    - Usually table of substrates, inhibitors and/or inducers, like Flockhart Table

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DDI Survey of SWOG Head CRAs

- 78 Responses (~160 Invited)
  - 55% Community hospital/outpatient
  - 29% Academic teaching hospital
  - 4% Non-academic hospital
  - 4% VA hospital
  - 1% Private practice infusion center
  - 8% Other (Military, HMO, NCORP office)

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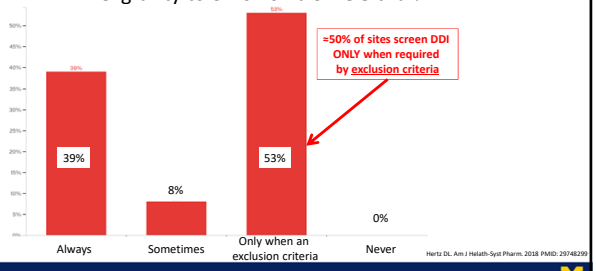
How often are DDI screened for potential subjects to assess their eligibility to enroll on a SWOG trial?



Hertz DL. Am J Helath-Syst Pharm. 2018 PMID: 29748299

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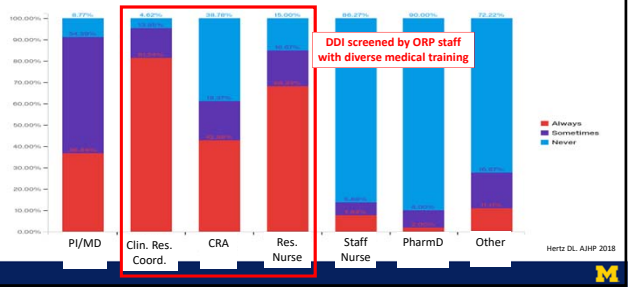
Who Screens DDI during SWOG Eligibility Assessment?



Hertz DL. AJHP 2018

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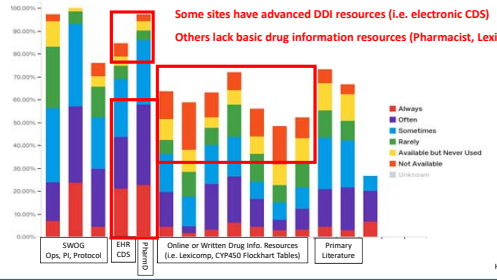
How often are the following resources used for DDI screening?



Hertz DL. AJHP 2018

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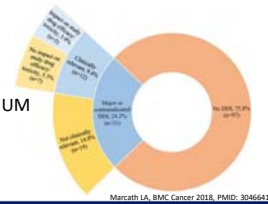
DDI In Oncology Clinical Trial Subjects

- 291 patients prospectively screened for 4 NCI phase I trials
  - 3.2% (n=7) excluded due to DDI
  - 74 patient enrolled
    - 69% (n=51) had at least 1 DDI
    - 93 total DDI identified and managed
      - Medication stopped (41%) or changed (44%)
- 128 Patients enrolled on NCTN studies at UM
  - 31 (24.2%) had major DDI
  - 12 (9.4%) had clinically relevant DDI

Wisinski KB, Am J Health Syst Pharm, 2015, PMID: 25987691



Marcath LA, BMC Cancer 2018, PMID: 30466416

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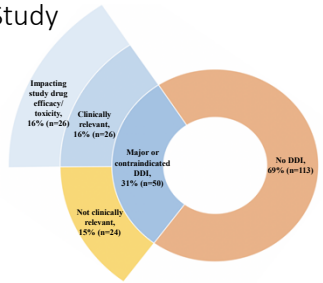
SWOG Retrospective Study

- Repeat pilot using SWOG data
  - S0711 (dasatinib)
  - S0528 (lapatinib)
- N=163 patients enrolled
  - 31% (n=50) 1+ major DDI identified by Lexicomp
  - 16% (n=26) 1+ clinically relevant DDI assessed by pharmacist
    - All affected study agent
- DDI rates similar to UM pilot



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Summary of Background

- High prevalence of DDI in oncology clinical trial subjects
  - Concern for patient safety
  - Concern for SWOG trial data accuracy
- Processes for DDI screening are inconsistent and ineffective
  - DDI screening conducted by various staff, when conducted at all
  - Pharmacist-led screening may be ideal, but is impractical
- Critical need to equip all SWOG sites with user-friendly tool for efficient, appropriate, and uniform DDI screening

Outline

- PK and PD Drug-drug Interactions
- DDI Screening
- SWOG DDI Screening Initiative

SWOG DDI Screening Initiative

Overall goal

- Reduce DDI in patients enrolling on oncology clinical trials to enhance efficacy, prevent toxicity, and ensure integrity of clinical trial data

Project Objectives

1. Develop oncology clinical trial-specific tool to aid in screening DDI
2. Assess user satisfaction with tool in implementation pilot
3. Demonstrate benefit of tool in system-wide implementation study

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SWOG-PEPID DDI Screening Tool

- Web-based tool for DDI screening
  - PEPID.com/SWOG
- Can be made accessible to all SWOG ORP
- Specific functionalities for oncology trial DDI screening

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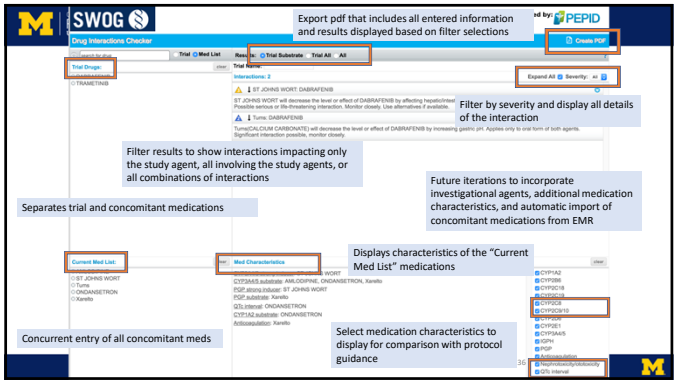

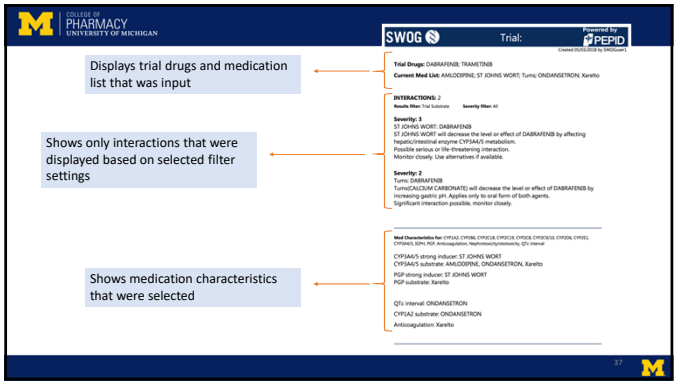
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SWOG
Trial:
Powered by PEPID
Trial Drugs: DABRAFENIB; TRAMETINIB
Current Med List: AMLODIPINE; ST JOHNS WORT; Tums; ONDANSETRON; Xarelto
INTERACTIONS: 2
Severity: 3
ST JOHNS WORT: DABRAFENIB
Severity: 2
Tums: DABRAFENIB
Displays trial drugs and medication list that was input
Shows only interactions that were displayed based on selected filter settings
Shows medication characteristics that were selected
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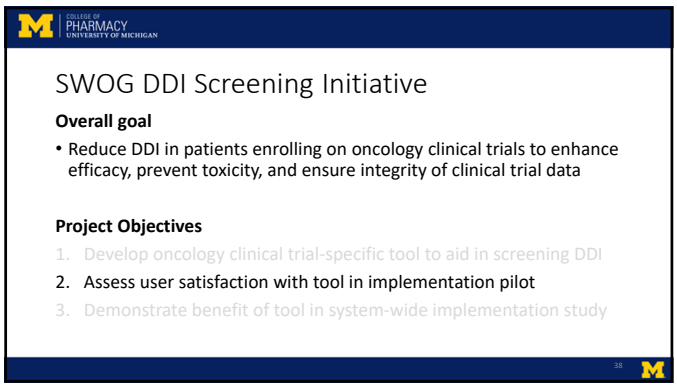
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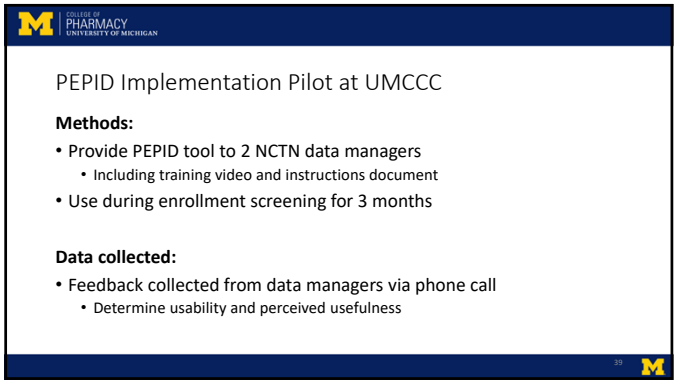
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PEPID Implementation Pilot at UMCCC
Methods:
• Provide PEPID tool to 2 NCTN data managers
• Including training video and instructions document
• Use during enrollment screening for 3 months
Data collected:
• Feedback collected from data managers via phone call
• Determine usability and perceived usefulness
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Pilot Implementation Data Manager Feedback

Strengths	Weaknesses	Approach to Resolve Weakness
Easy to use	Missing some pharmacodynamic interactions (i.e. antiarrhythmic agents)	• Add additional pharmacodynamic interactions to the Medication Characteristics panel
Increased screening efficiency (1hr -> 10 min)	Provider confusion about interpreting PDF report	• Filter PDF report and tool for level 3+ interactions • Move Medication Characteristics summary to top of report
Great for screening CYP450 interactions	Not all herbal supplements included	• None: limited data on DI of many herbal supplements
PDF export useful to convey information		

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PEPID Implementation Expansion Study

- Objective
  - Test PEPID implementation at ~10 diverse SWOG sites
    - Different institutional settings, workflows, staff roles
- Methods
  - Identify sites that are interested in using tool
  - Provide training video, instructions, and PEPID login information
  - ORP staff use tool for ~ 3 months
  - Collect feedback from ORP staff via survey and brief telephone interview

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Sites Interested in Participating in Pilot

- Looking for 10 diverse sites
  - Community cancer centers
  - Academic teaching hospitals
  - Non-academic hospitals
  - VA hospitals
  - Private practice offices
  - NCORP Sites
- If you are interested in participating contact me!!!!
  - Come talk to me at ORP Open Forum (today 12-2:30, PMB table)
  - Daniel L Hertz, University of Michigan, DLHertz@umich.edu
    - Include what type of site you represent

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SWOG DDI Screening Initiative

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Test Case for PEPID-SWOG Tool: S1913

- S1913: A Randomized Double-Blind Phase II trial to improve sexual desire in women with cancer
  - Study agent is flibanserin
- Flibanserin has multiple black box warnings
  - Highest level of warning in drug labeling
- Contraindication with alcohol
  - Additive hypotension and fainting risk
- Contraindication with moderate/strong CYP3A4 inhibitors
  - Increased hypotension and fainting risk
- Study proposal includes use of PEPID-SWOG Tool for enrollment screening

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PEPID Implementation Trial within SWOG

- Multi-site implementation trial of PEPID within SWOG
  - Developed within Cancer Care Delivery Committee
- Select n=(50?) SWOG sites across diverse practice settings
  - Use within all trials? Subset of trials with DDI?
  - Cluster-randomized design?
  - Compare DDI screening pre-/post- implementation?
- Study goal is to demonstrate improvement in DDI screening:
  - Less time spent screening DDI during enrollment
  - Fewer DDI in patients enrolled on trials
  - Reduced DDI-related adverse events (?)

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SWOG DDI Screening Initiative Summary

- 1st Generation PEPID-SWOG DDI Screening Tool Created
- Single-center implementation pilot completed
  - High user satisfaction
  - Feedback used to make further improvements
- Looking for sites for multi-center expansion pilot (DLHertz@umich.edu)
- Prospective implementation studies anticipated to confirm usefulness
- We want feedback from ORP regarding this overall project, our tool, how this tool fits into their workflow, and anything else!

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Questions?

Dan Hertz, PharmD, PhD
DLHertz@med.umich.edu

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Comparison of DDI Tools

- Examined 145 drug pairs (with oral oncolytics) chosen based on:
  - Common adjunct therapy for side effects
  - Package insert
  - Anecdotal experience
  - Case studies
- Collect severity information from each tool
  - Reclassify as none, minor, moderate, and major for each tool
- Compare with clinician judgement and Stockley's as gold standard
  - Estimate positive and negative predictive values, sensitivity and specificity

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Comparison of PEPID with DDI Tools

	PEPID	Other Subscription tools			Free tools				
	Grade 3+	Facts & Comparisons	Lexicomp	Micromedex	Drugs.com	Epocrates Free	Medscape	RxList	WebMD
Sensitivity (±SE)	0.72	0.67 (0.044)	0.96 (0.019)	0.86 (0.062)	0.93 (0.024)	0.73 (0.041)	0.79 (0.038)	0.65 (0.044)	0.79 (0.038)
Specificity (±SE)	0.87	0.93 (0.046)	0.80 (0.073)	0.87 (0.062)	0.73 (0.081)	0.83 (0.068)	0.73 (0.081)	0.83 (0.068)	0.77 (0.077)
Positive Predictive Value (±SE)	0.95	0.97 (0.018)	0.95 (0.021)	0.96 (0.075)	0.93 (0.024)	0.94 (0.024)	0.92 (0.027)	0.94 (0.027)	0.93 (0.026)
Negative Predictive Value (±SE)	0.45	0.42 (0.061)	0.83 (0.070)	0.62 (0.075)	0.73 (0.081)	0.45 (0.066)	0.48 (0.074)	0.38 (0.060)	0.49 (0.073)

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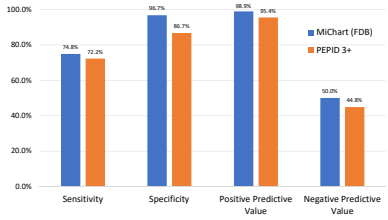
PEPID 3+ compared to FirstDatabank (UM EMR)



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