COLLEGE OF PHARMACY UNIVERSITY OF MICHIGAN

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

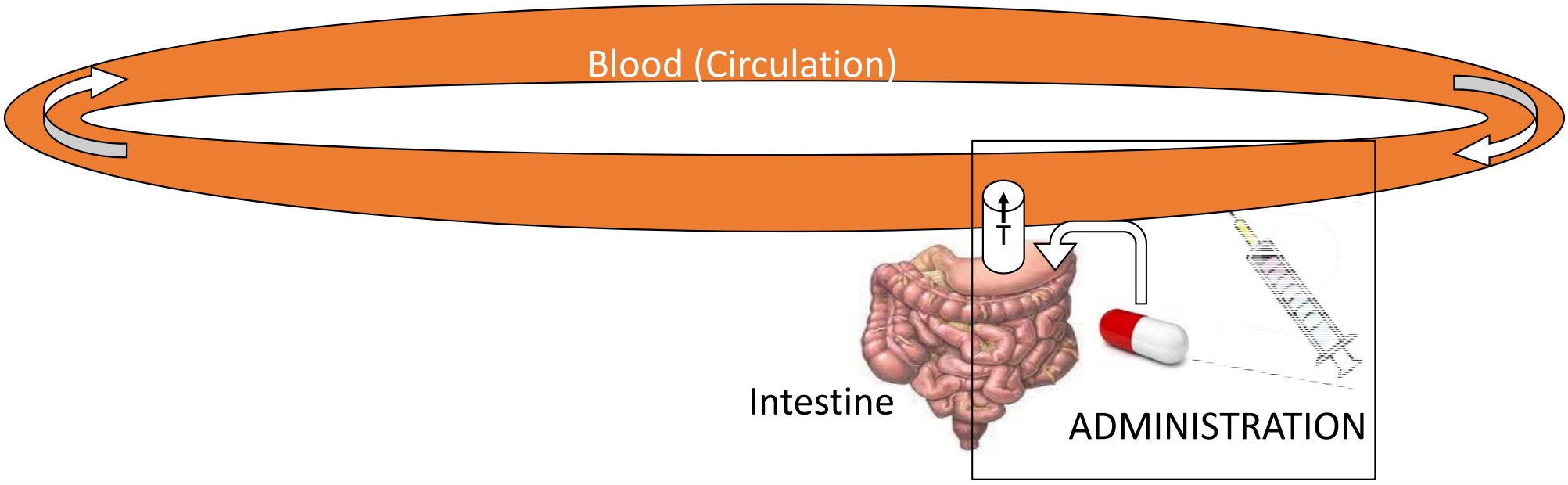
Pharmacokinetics (PK) and Pharmacodynamics (PD)

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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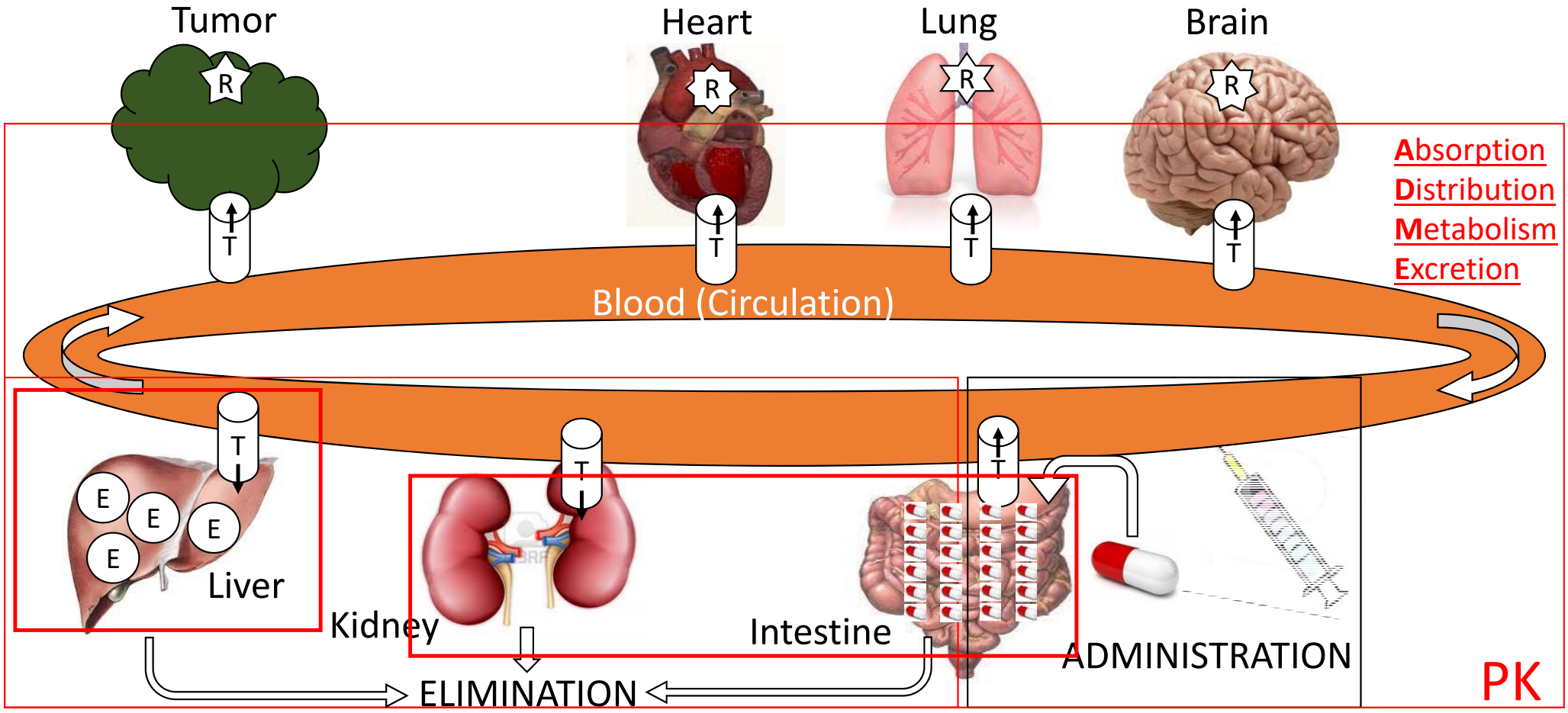
ADMINISTRATION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Metabolism
Excretion
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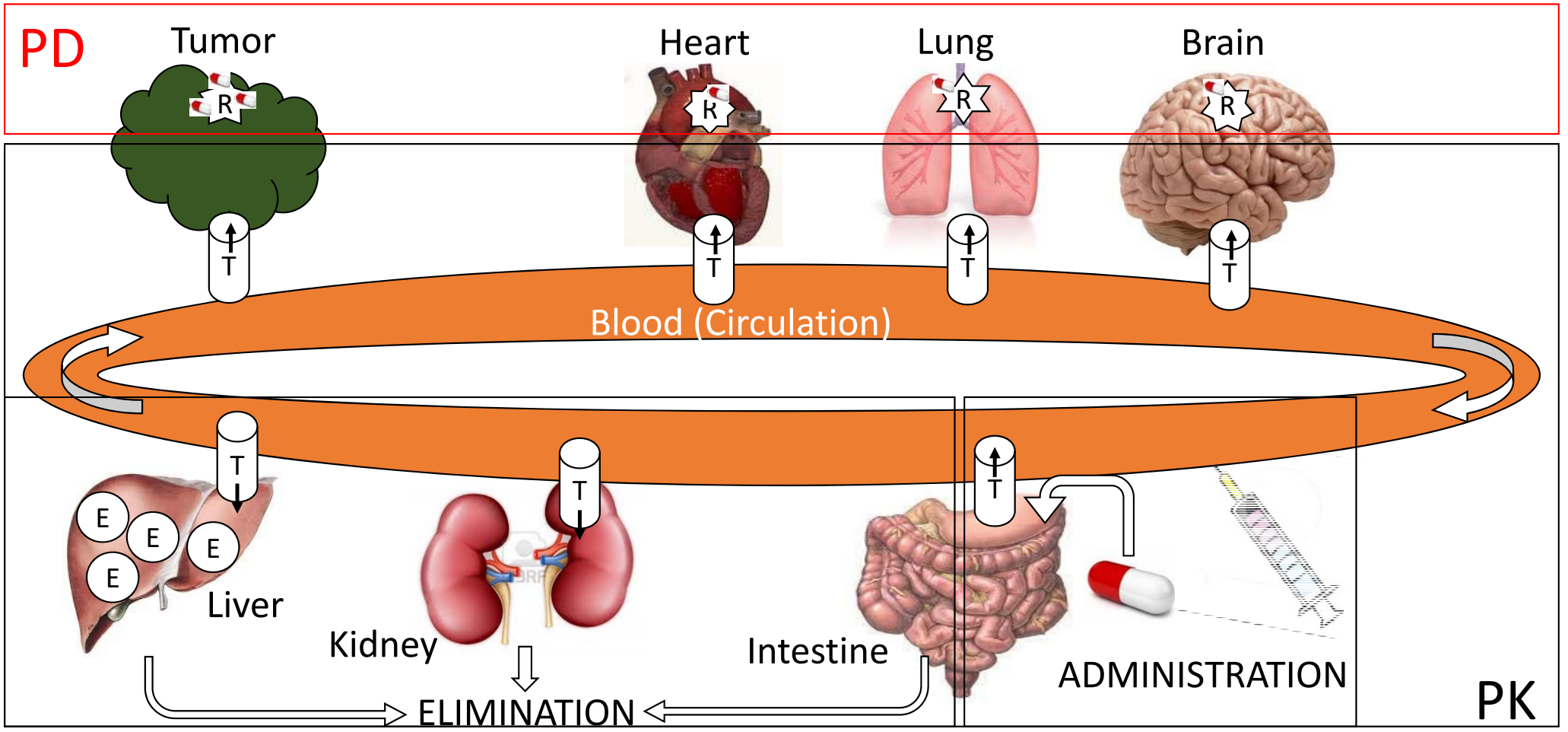
ADMINISTRATION
ELIMINATION
PK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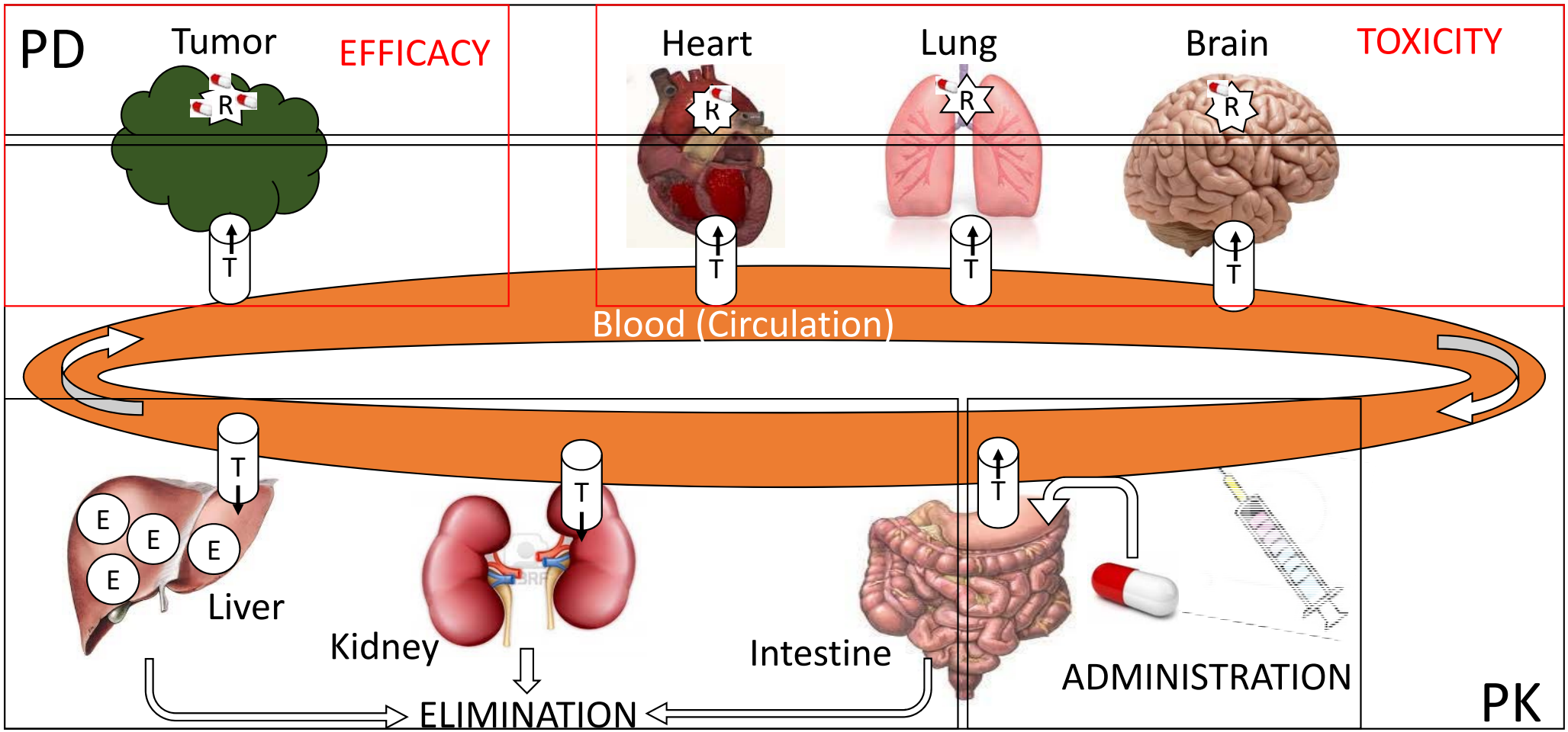
ELIMINATION
ADMINISTRATION
PK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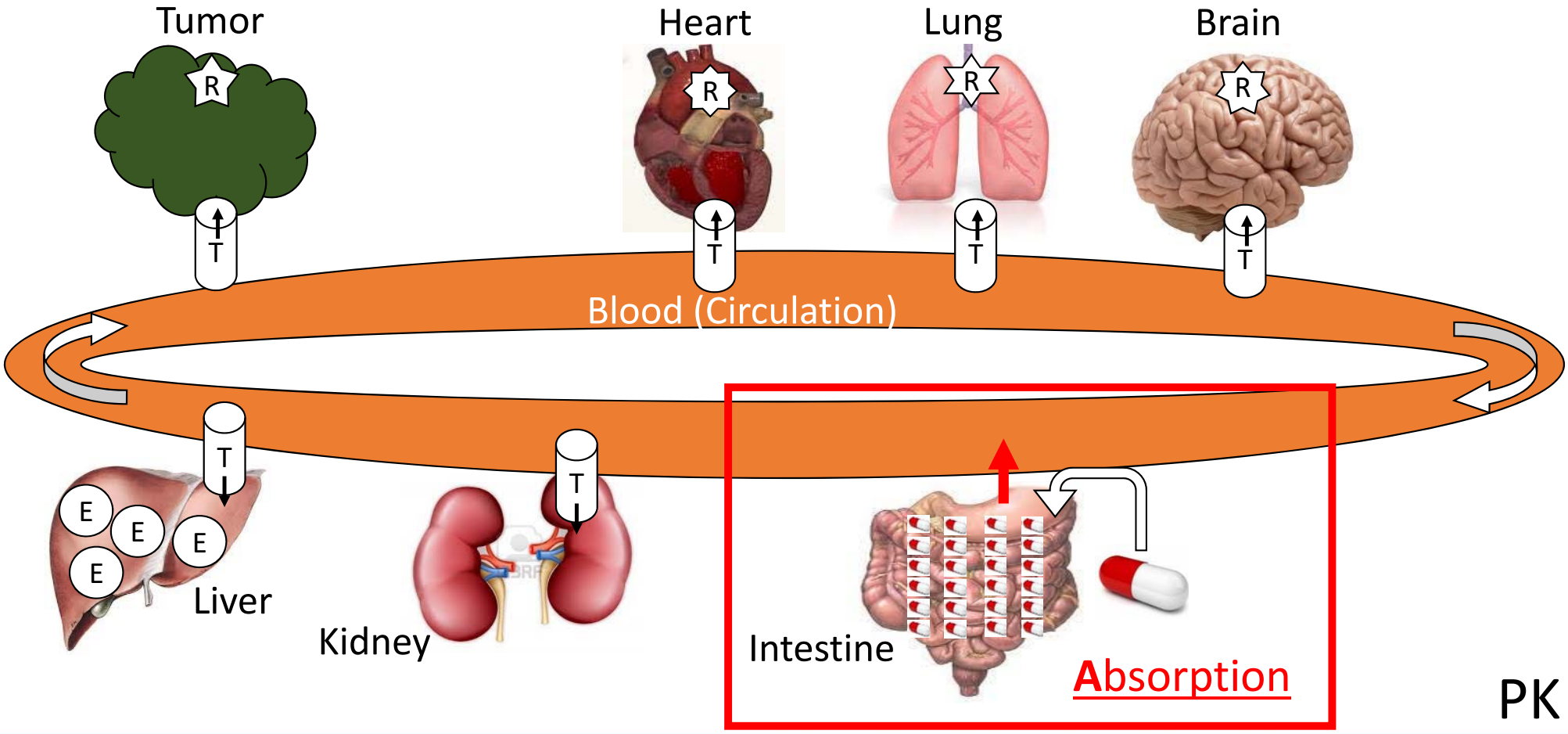
Intestine
ADMINISTRATION
ELIMINATION
PK

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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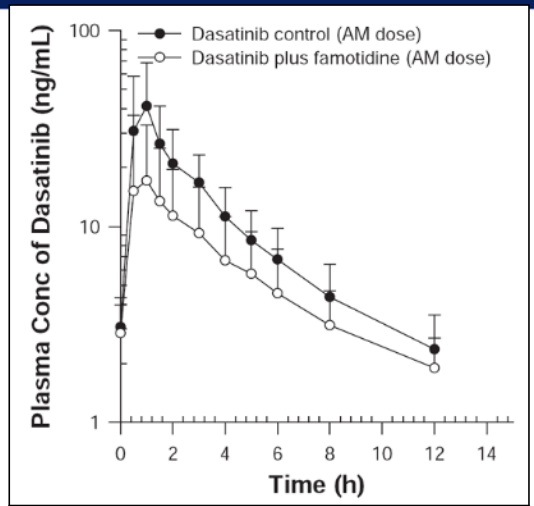
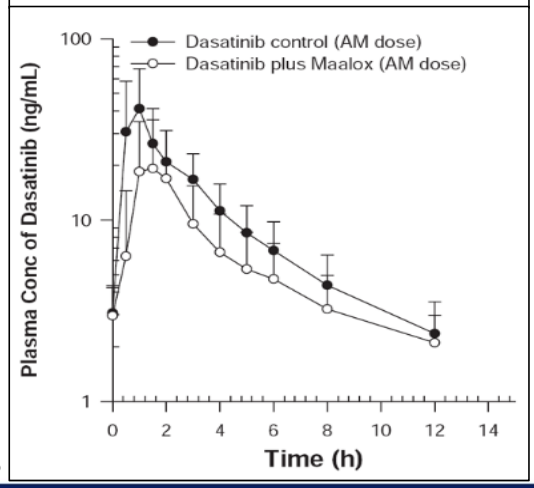
Intestine
Absorption

PK

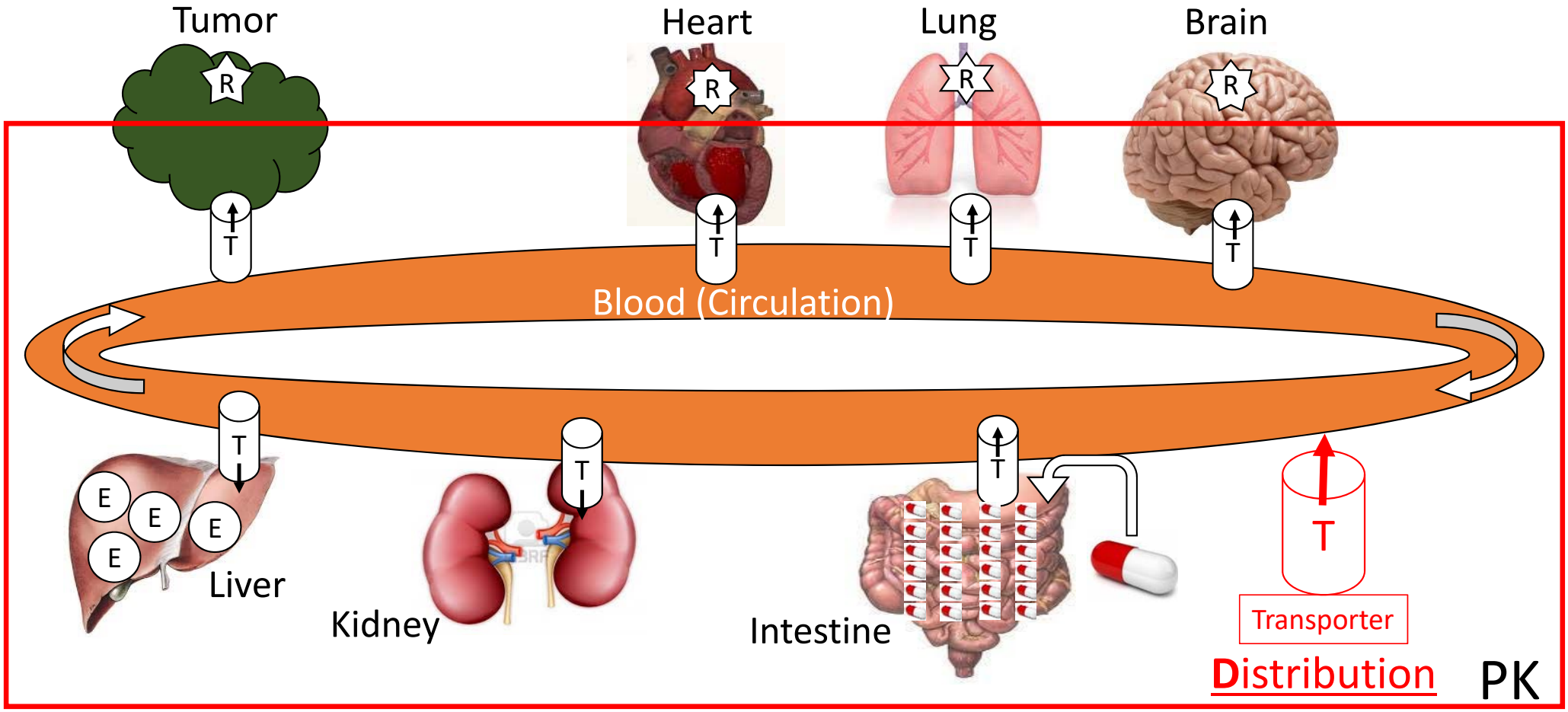
Passive Absorption DDI

- 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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Blood (Circulation)
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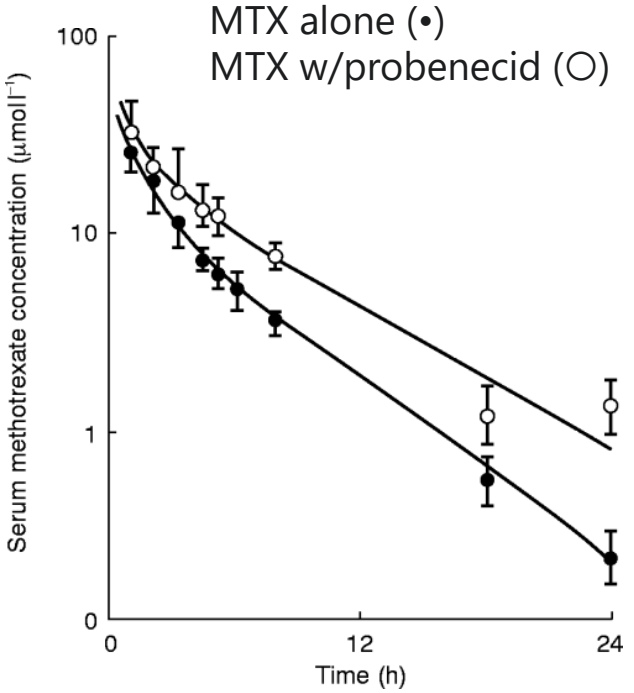
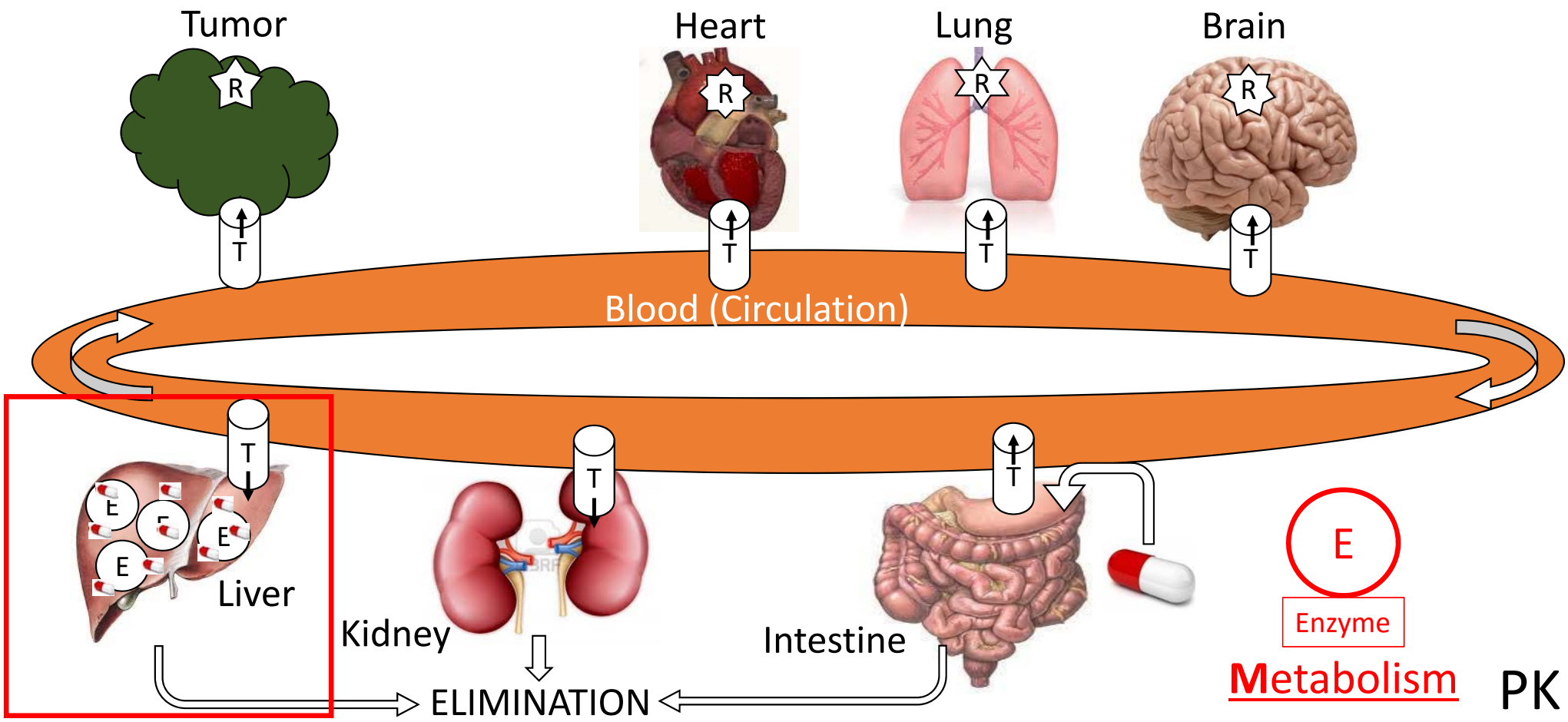
Liver
Kidney
Intestine
Transporter
Distribution
PK

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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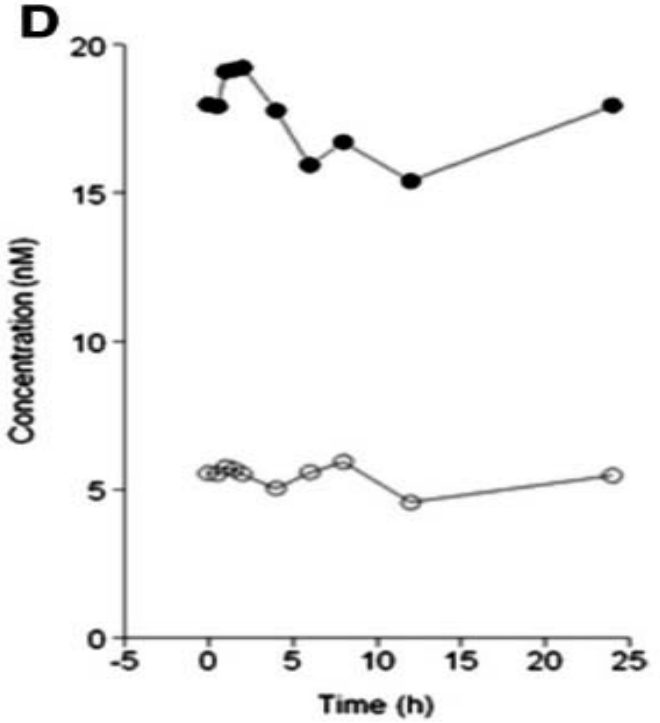
Intestine
ELIMINATION
E
Enzyme
Metabolism
PK

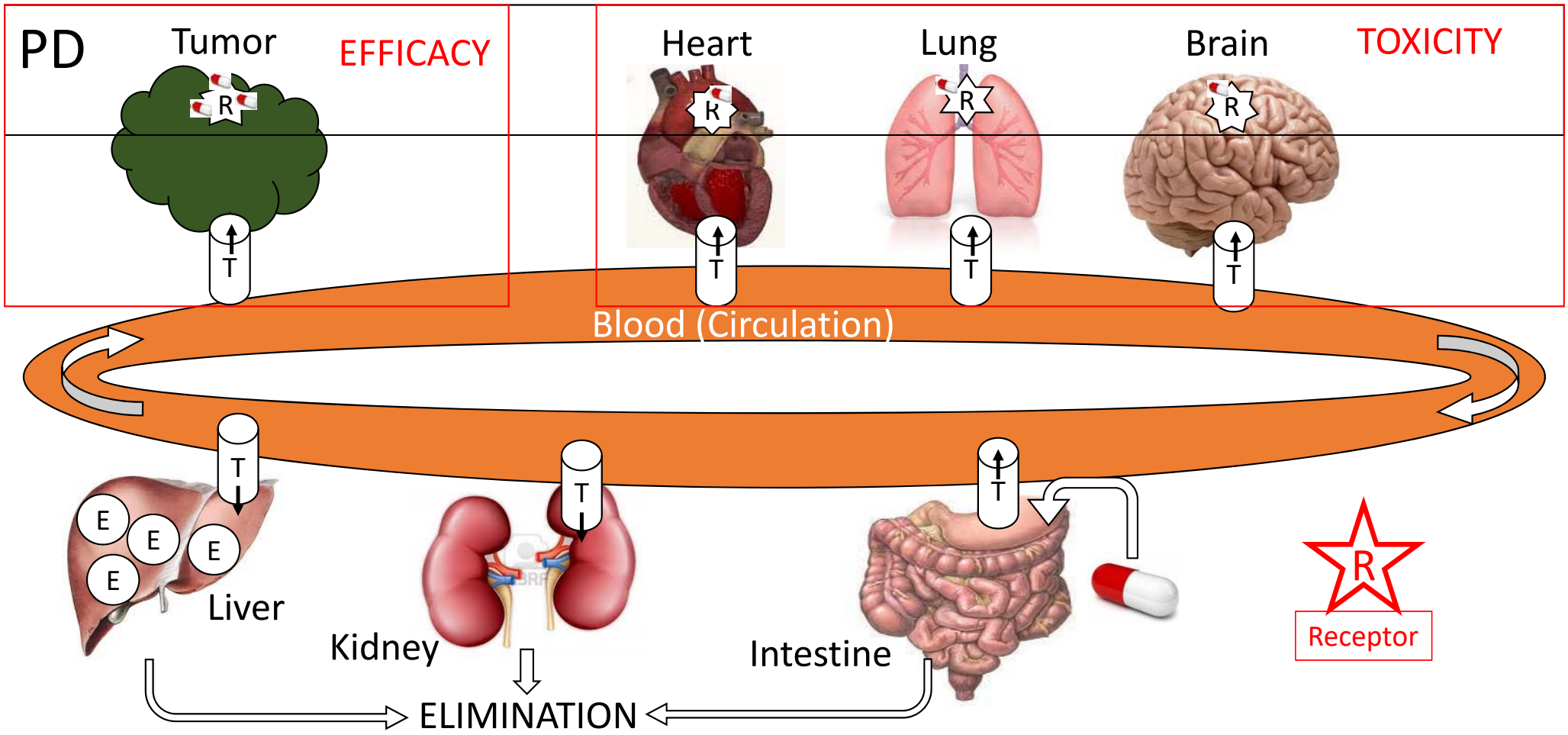
Metabolism DDI

- Most drugs are metabolized by **enzymes**
  - Drug referred to as a "substrate" 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

Endoxifen concentration with escitalopram (•)
Endoxifen concentration with fluoxetine (○)



Binkhorst L et al. Clin Pharmacokinet. 2016 PMID: 26446141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Intestine
ELIMINATION
Receptor

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) or QT prolongation (heart arrhythmia)
  - “Avoid drugs that cause QT prolongation”
- We could also be concerned about opposing efficacy

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- PK and PD Drug-drug Interactions
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DDI Severity and Relevance to SWOG ORP

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

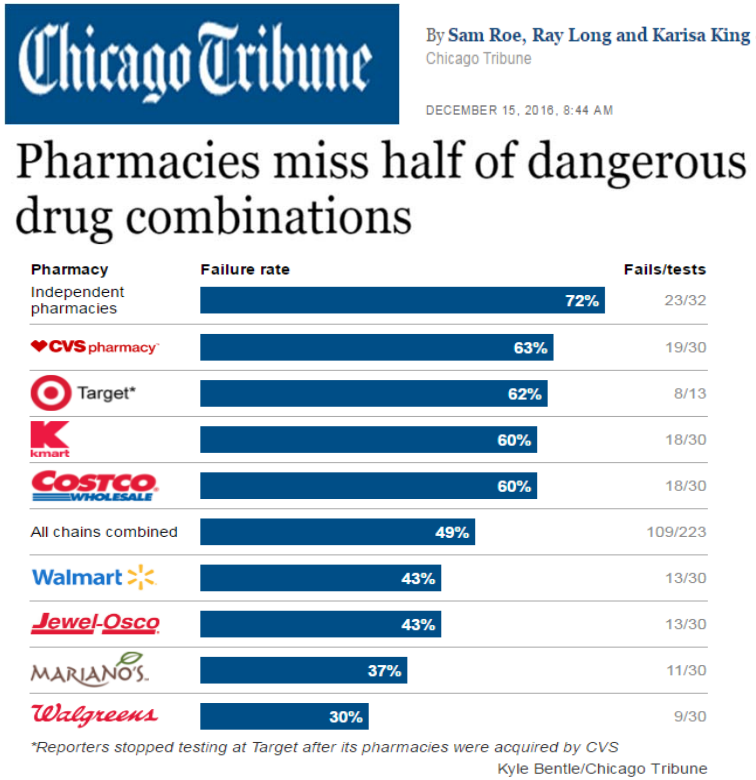
Relevance to SWOG

- SWOG Study Subjects
  - Increased toxicity
  - Decreased efficacy
- SWOG Trial Data
  - Inaccurate estimates of efficacy and/or toxicity from trials

DDI Screening

- Standard practice in medical 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



van Leeuwen RW, Ann Oncol. 2011 PMID: 21343376

Nurse's Role and Confidence in DDI Screening

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

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 (6.2)

Karahan A, Asia Pac J Oncol Nurs. 2015

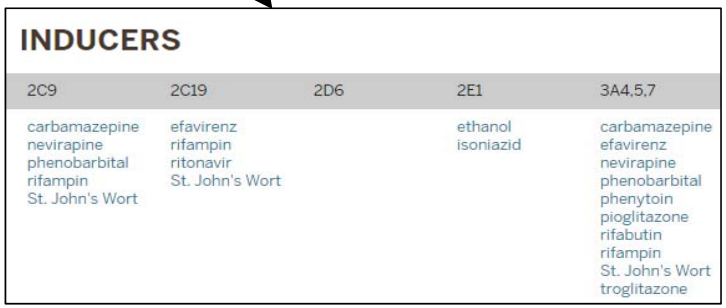
Table 2 Mean performance

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

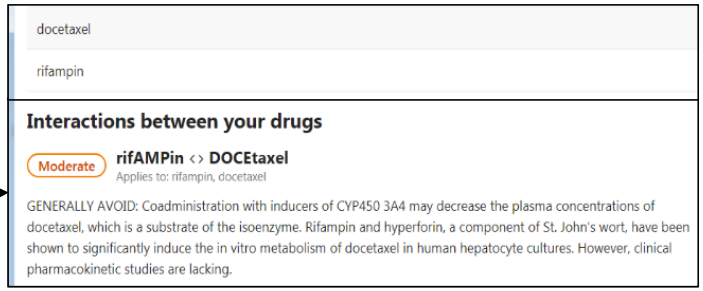
DDI Screening Tools

- 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



INDUCERS

2C9	2C19	2D6	2E1	3A4,5,7
carbamazepine nevirapine phenobarbital rifampin St. John's Wort	efavirenz rifampin ritonavir St. John's Wort		ethanol isoniazid	carbamazepine efavirenz nevirapine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's Wort troglitazone



docetaxel

rifampin

Interactions between your drugs

Moderate **rifAMPin ‹› DOCEtaxel**

Applies to: rifampin, docetaxel

GENERALLY AVOID: Coadministration with inducers of CYP450 3A4 may decrease the plasma concentrations of docetaxel, which is a substrate of the isoenzyme. Rifampin and hyperforin, a component of St. John's wort, have been shown to significantly induce the in vitro metabolism of docetaxel in human hepatocyte cultures. However, clinical pharmacokinetic studies are lacking.

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

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 DDI information in protocol is accurate and complete

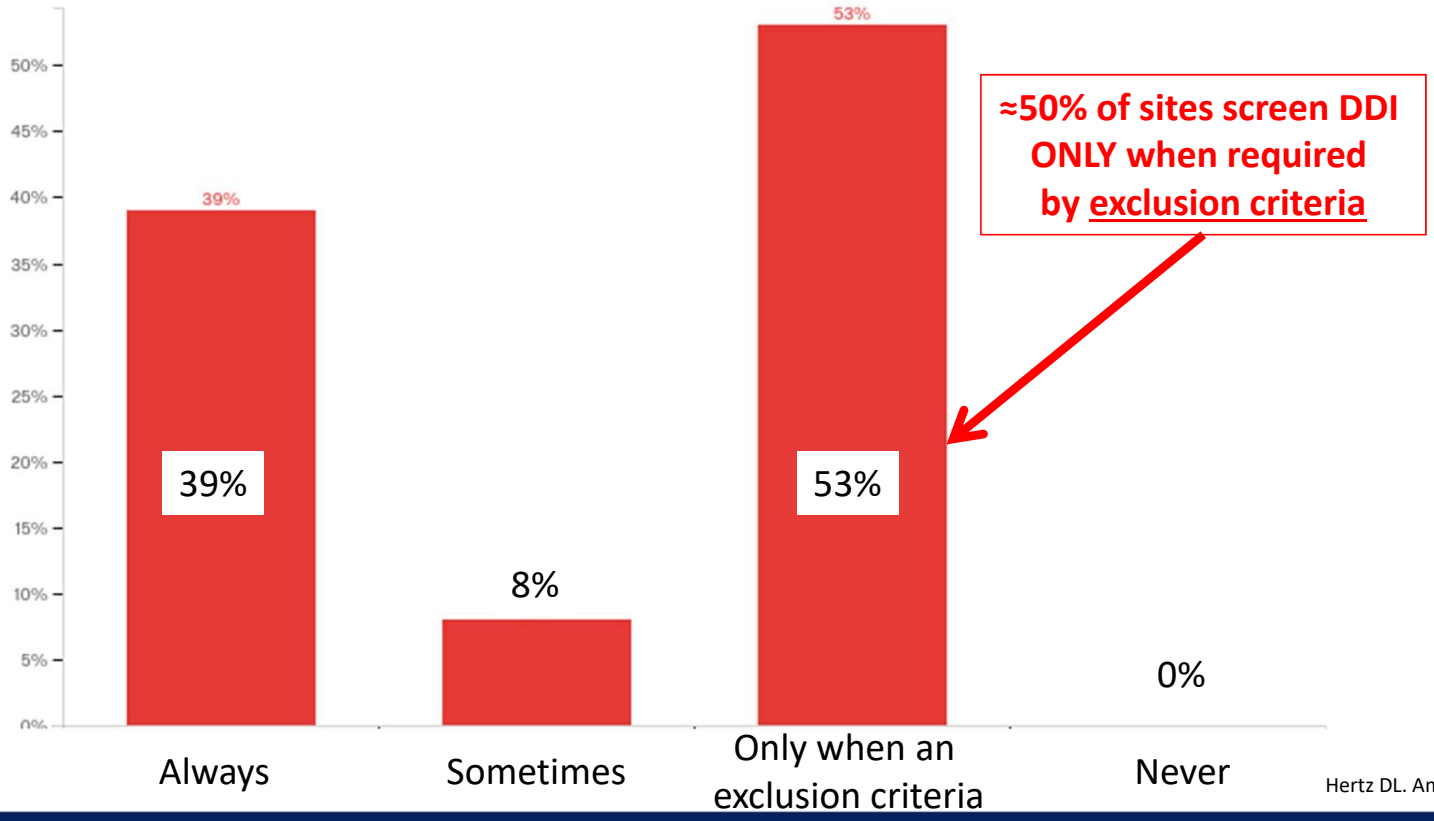
DDI Information in Clinical Trial Protocols

- Lack of uniformity in location of information, terms used etc.
  - Information can conflict within sections of a single protocol
- 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

DDI Survey of SWOG Head CRAs

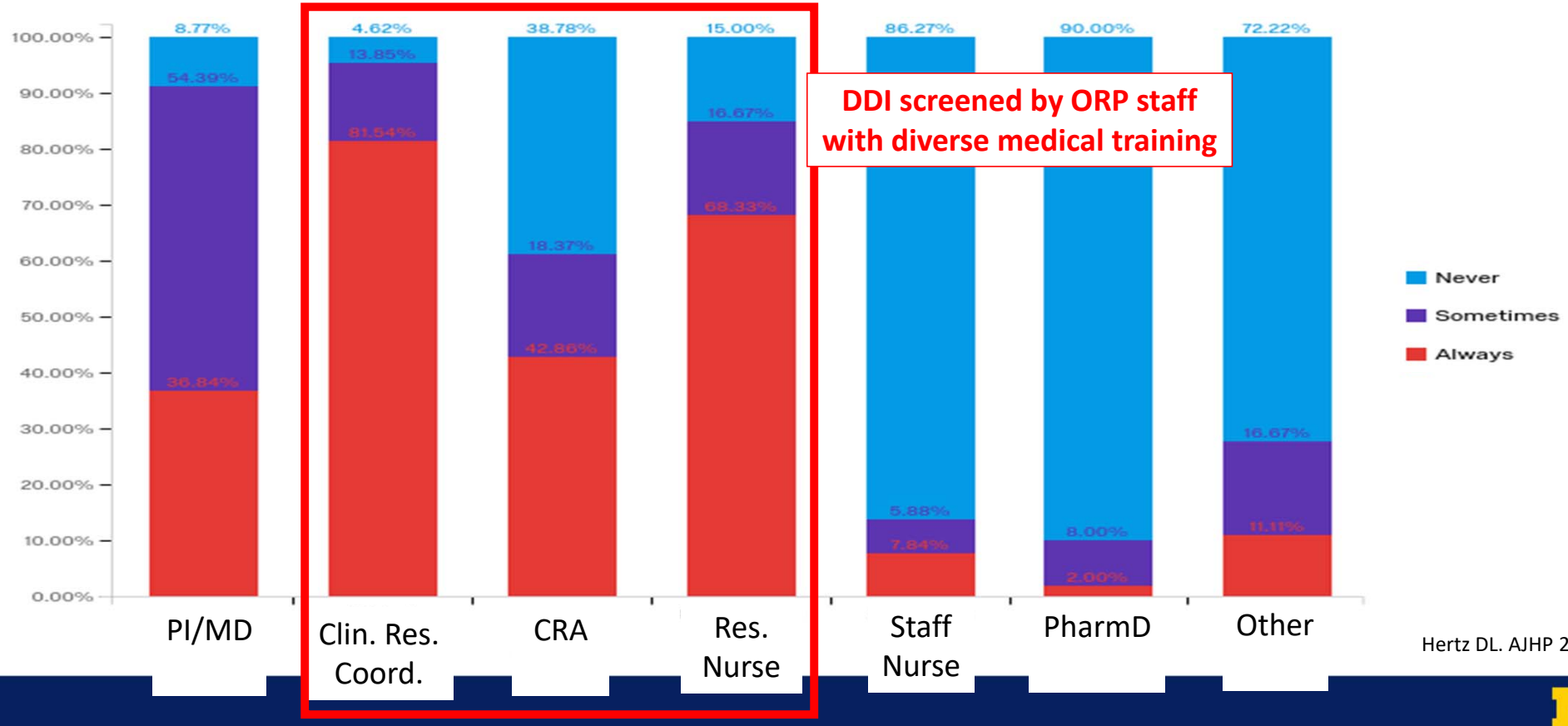
- 78 Responses (~160 Invited)
  - 55% Community hospital/outpatient
  - 29% Academic teaching hospital
  - 4% Non-academic hospital
  - 4% VA hospital
  - 1% Private practice infusion center
  - 8% Other (Military, HMO, NCORP office)

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



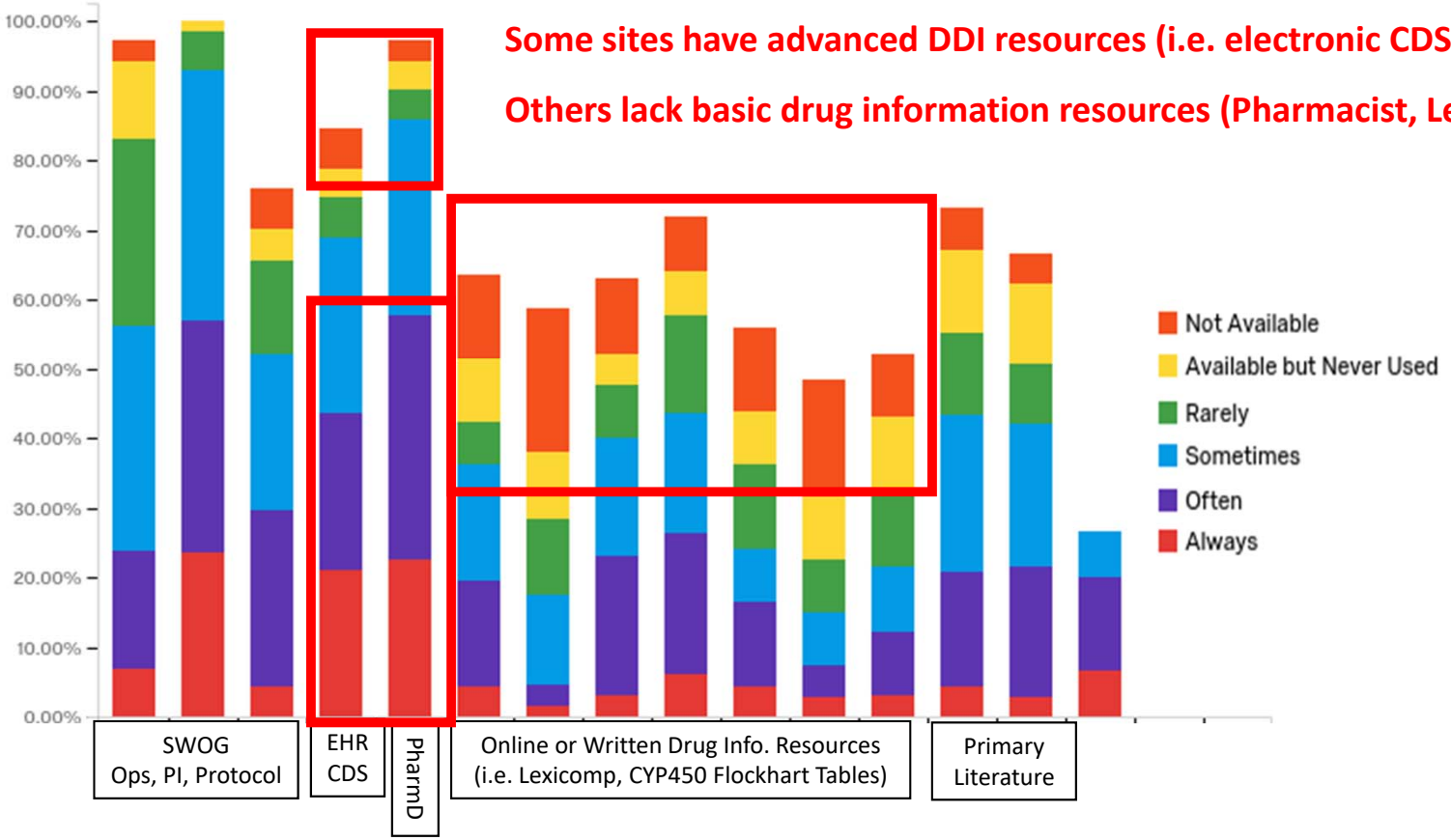
Hertz DL. Am J Helath-Syst Pharm. 2018 PMID: 29748299

Who Screens DDI during SWOG Eligibility Assessment?



Hertz DL. AJHP 2018

How often are the following resources used for DDI screening?



Some sites have advanced DDI resources (i.e. electronic CDS)

Others lack basic drug information resources (Pharmacist, Lexicomp)

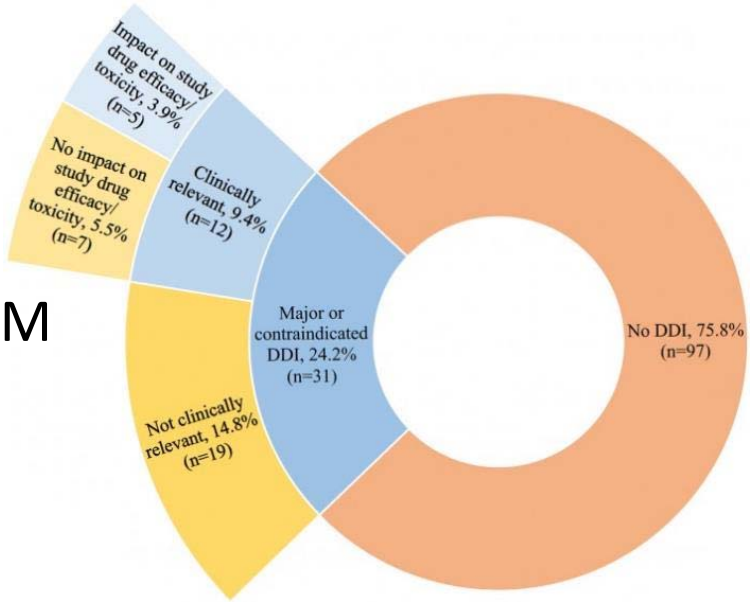
Hertz DL. AJHP 2018

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 subjects enrolled
    - 69% (n=51) had ≥1 DDI identified and managed
    - 93 total DDI managed:
      - Medication stopped (41%) or changed (44%)

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

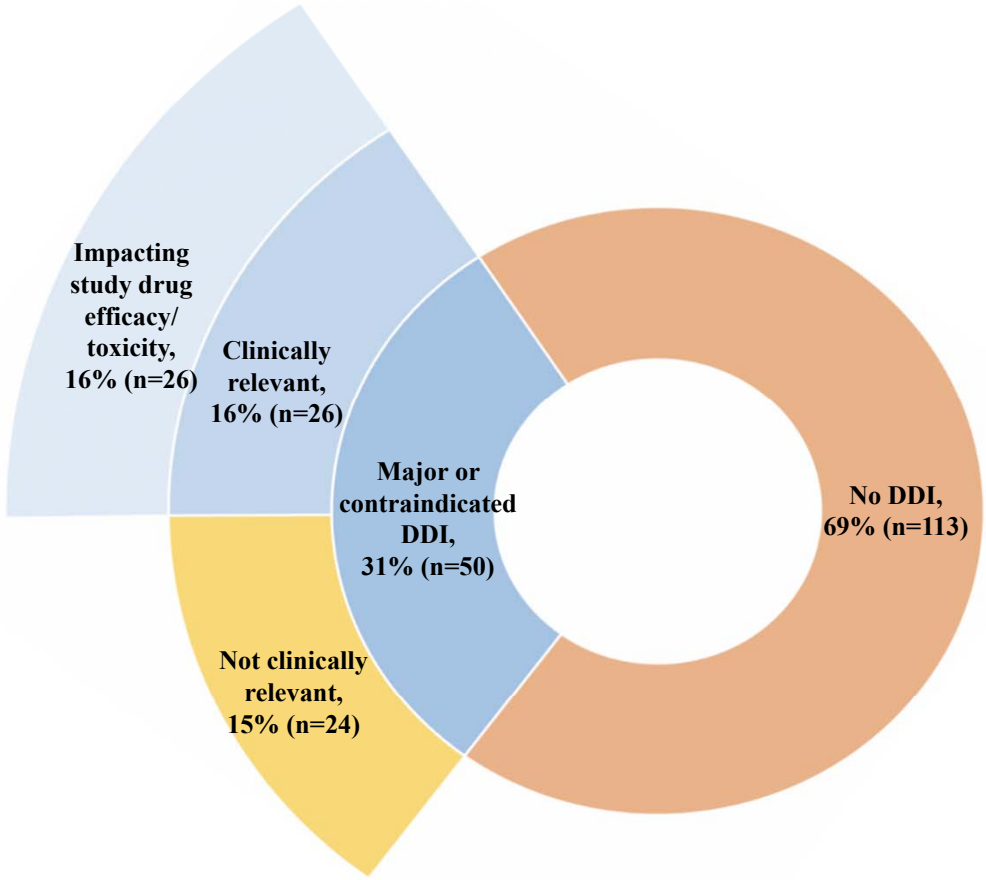
- 128 Patients enrolled on NCTN studies at UM
  - 24% had major DDI w/study drug
  - 9% had clinically relevant DDI w/study drug



Marcath LA, BMC Cancer 2018, PMID: 30466416

DDI in SWOG Subjects

- SWOG trials of agents w/DDI and concomitant med info
  - S0711 (dasatinib)
  - S0528 (lapatinib)
- N=163 patients enrolled
  - 31% had ≥1 major DDI
  - 16% had ≥1 clinically relevant DDI
    - All affected study agent
- DDI rates similar to UM pilot



Summary of DDI Background

- High prevalence of DDI in oncology patients and clinical trial subjects
  - Concerning for patient safety and SWOG clinical 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 accuracy of clinical trial data

Project Objectives

1. Develop clinical trial DDI screening tool
2. Assess user satisfaction during implementation pilot
3. Demonstrate benefit in implementation study

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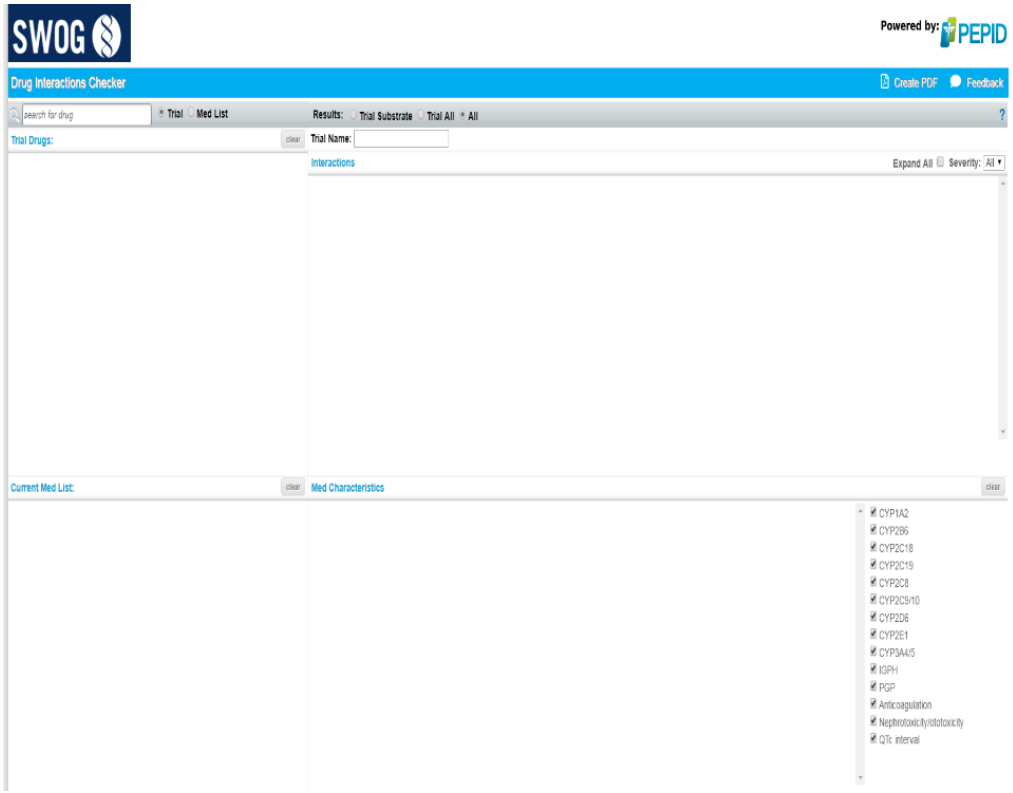
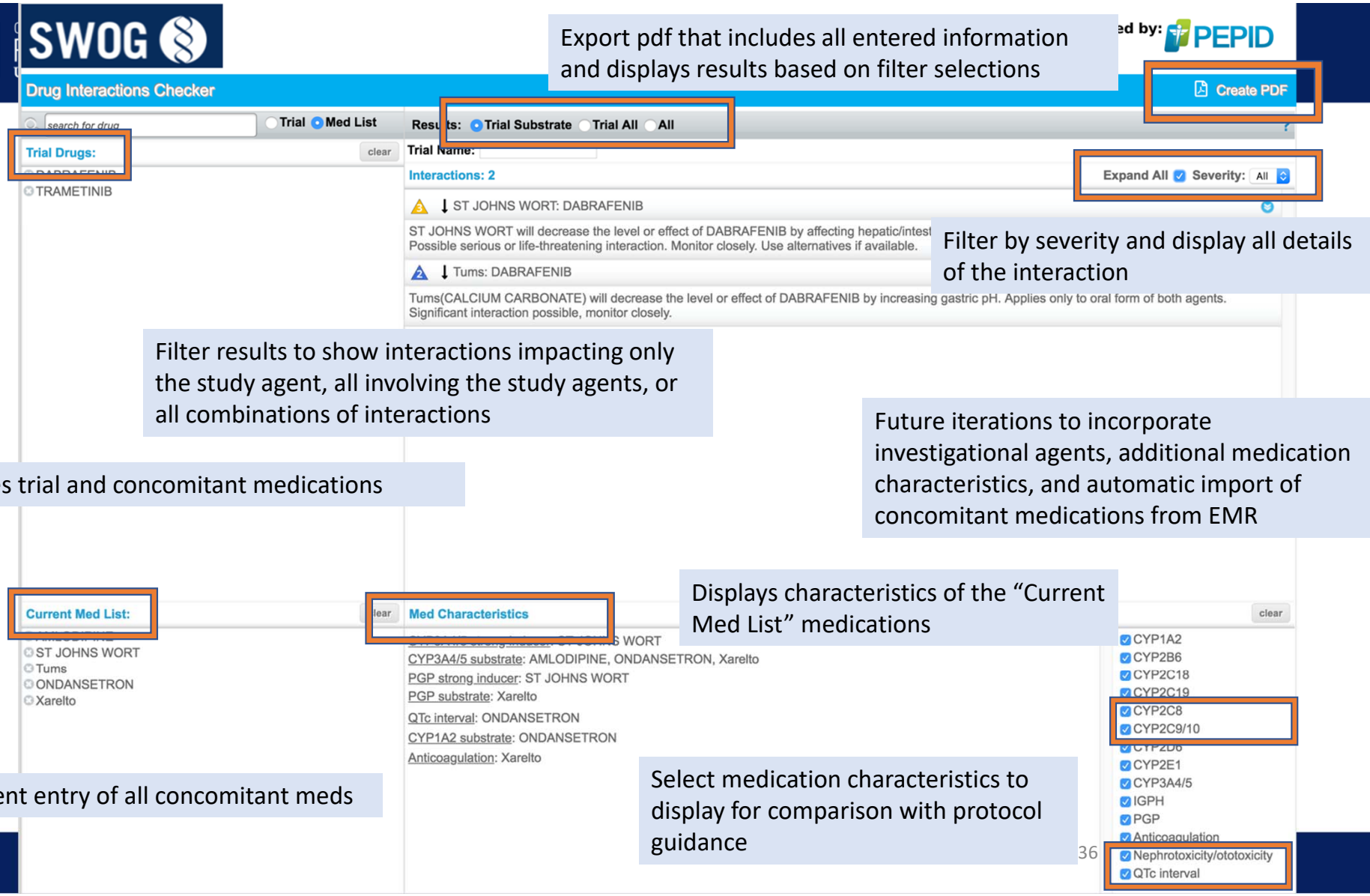
SWOG-PEPID DDI Screening Tool

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





Export pdf that includes all entered information and displays results based on filter selections

Filter by severity and display all details of the interaction

Filter results to show interactions impacting only the study agent, all involving the study agents, or all combinations of interactions

Separates trial and concomitant medications

Future iterations to incorporate investigational agents, additional medication characteristics, and automatic import of concomitant medications from EMR

Displays characteristics of the “Current Med List” medications

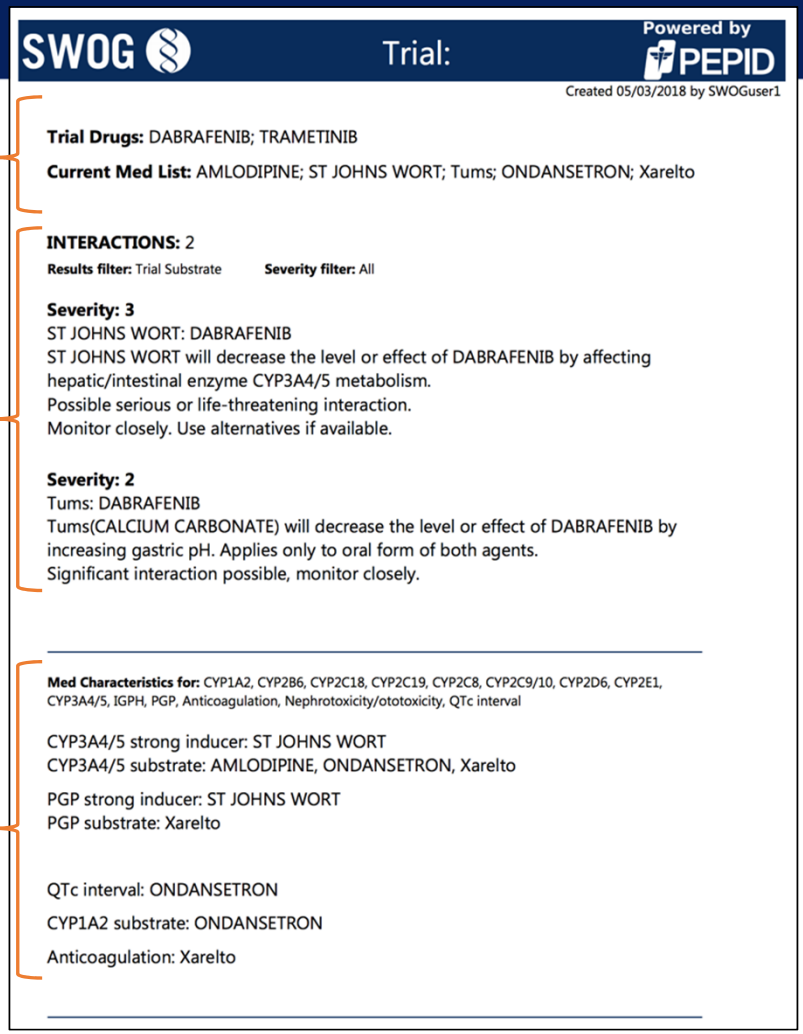
Concurrent entry of all concomitant meds

Select medication characteristics to display for comparison with protocol guidance

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



SWOG Trial: Powered by PEPID

Created 05/03/2018 by SWOGuser1

Trial Drugs: DABRAFENIB; TRAMETINIB

Current Med List: AMLODIPINE; ST JOHNS WORT; Tums; ONDANSETRON; Xarelto

INTERACTIONS: 2

Results filter: Trial Substrate **Severity filter:** All

Severity: 3
ST JOHNS WORT: DABRAFENIB
ST JOHNS WORT will decrease the level or effect of DABRAFENIB by affecting hepatic/intestinal enzyme CYP3A4/5 metabolism.
Possible serious or life-threatening interaction.
Monitor closely. Use alternatives if available.

Severity: 2
Tums: DABRAFENIB
Tums(CALCIUM CARBONATE) will decrease the level or effect of DABRAFENIB by increasing gastric pH. Applies only to oral form of both agents.
Significant interaction possible, monitor closely.

Med Characteristics for: CYP1A2, CYP2B6, CYP2C18, CYP2C19, CYP2C8, CYP2C9/10, CYP2D6, CYP2E1, CYP3A4/5, IGPH, PGP, Anticoagulation, Nephrotoxicity/ototoxicity, QTc interval

CYP3A4/5 strong inducer: ST JOHNS WORT
CYP3A4/5 substrate: AMLODIPINE, ONDANSETRON, Xarelto

PGP strong inducer: ST JOHNS WORT
PGP substrate: Xarelto

QTc interval: ONDANSETRON

CYP1A2 substrate: ONDANSETRON

Anticoagulation: Xarelto

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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
- Feedback collected from data managers via phone call
  - Determine usability and perceived usefulness

Pilot Implementation Data Manager Feedback

Strengths
Easy to use
Increased screening efficiency (1hr -> 10 min)
Great for screening CYP450 interactions
PDF export useful to convey information

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 (TODAY!)
  - 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

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)
    - Can watch instructional video and test tool
  - E-mail me: Daniel L Hertz, University of Michigan, DLHertz@umich.edu
    - Include type of SWOG site you represent

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PEPID Implementation Trial within SWOG

- Multi-site implementation trial of PEPID within SWOG
  - To be developed within Cancer Care Delivery Committee
- Select (n=50?) SWOG sites across diverse practice settings
  - Use tool within SWOG trials
  - Compare DDI screening pre-/post- implementation
- Study objective: 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 (?)

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 contraindications:
  - Moderate/strong CYP3A4 inhibitors (PK DDI)
    - Increased hypotension and fainting risk
  - Alcohol (PD DDI)
    - Additive hypotension and fainting risk

- Protocol in development includes PEPID Tool for enrollment DDI screening

SWOG DDI Screening Initiative Summary

- 1st Generation PEPID-SWOG DDI Screening Tool Created
- Single-center implementation pilot completed
  - High user satisfaction
- Looking for sites for multi-center expansion pilot (DLHertz@umich.edu)
  - Feedback critical for improvements and to determine next steps
- Prospective implementation studies anticipated to confirm usefulness
- We would greatly appreciate ORP feedback regarding the project, PEPID tool, how the tool fits into your workflow, and anything else!

Questions?

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