UNC
INSTITUTE FOR
PHARMACOGENOMICS AND
INDIVIDUALIZED THERAPY

Pharmacogenomics as a proof of principal for genomic medicine: emphasis on 'real' endpoints
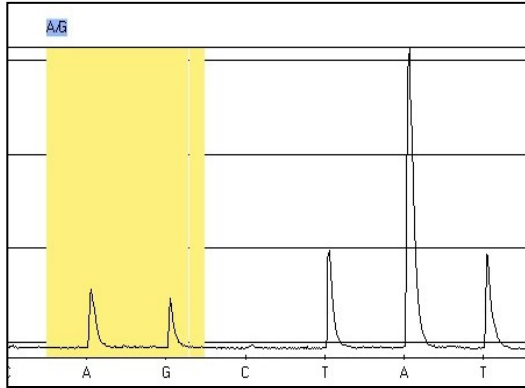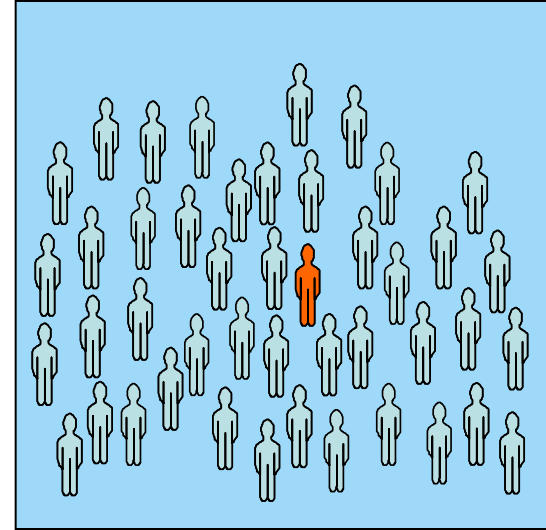
December 5, 2011

Dr Howard L. McLeod
Eshelman Distinguished Professor and Director
Institute for Pharmacogenomics and Individualized Therapy (IPIT)
University of North Carolina – Chapel Hill, NC

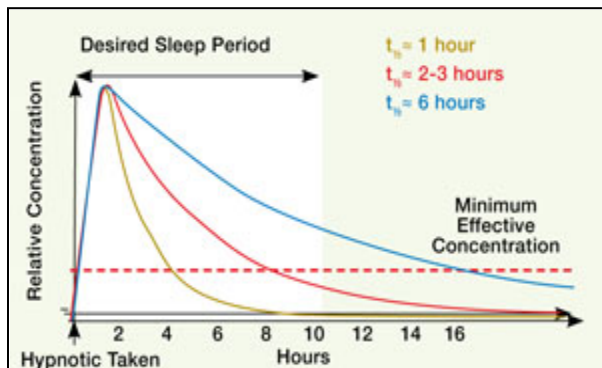# Pharmacogenetics: what is your intent?
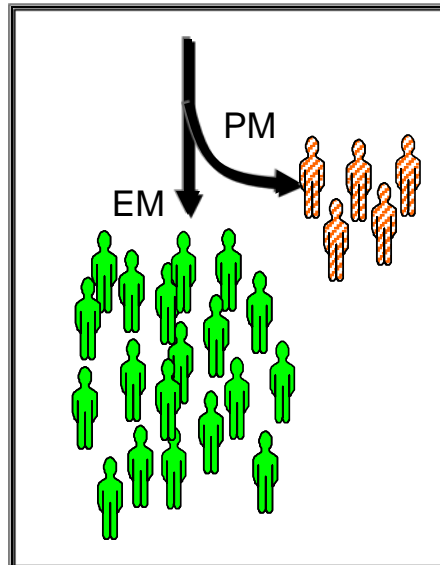
Human genetic discovery

Drug Safety

Explain variation in phenotype


Clinical trial inclusion/exclusion

Clinical practice

Why is IPIT succeeding?

Marker Discovery

Marker Validation

Routine Clinical Use

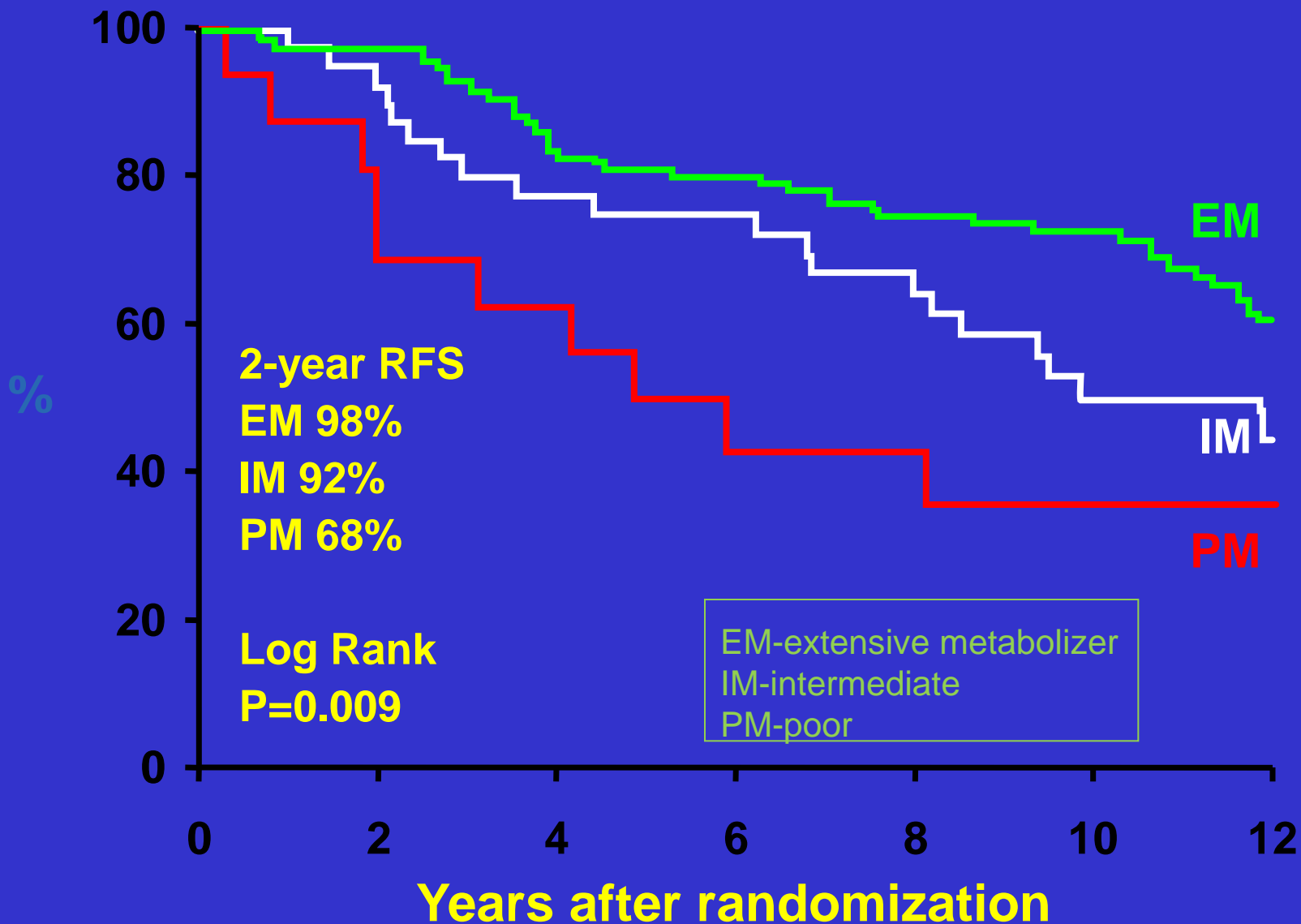Integration into Practice

Germline Pharmacogenomic examples-2011

- Thiopurine S-methyltransferase—mercaptopurine and azathioprine*
- IL28B-interferon
- UGT1A1-irinotecan**
- CYP2C9/VKORC1-warfarin*
- HLA-B*5701-abacavir *
- HLA-B*1502-carbamazepine *
- CYP2C19-clopidogrel
- Cytochrome P-450 (CYP) 2D6—5-HT3 receptor antagonists, antidepressants, ADHD drugs, pimizide, and codeine derivatives, tamoxifen*

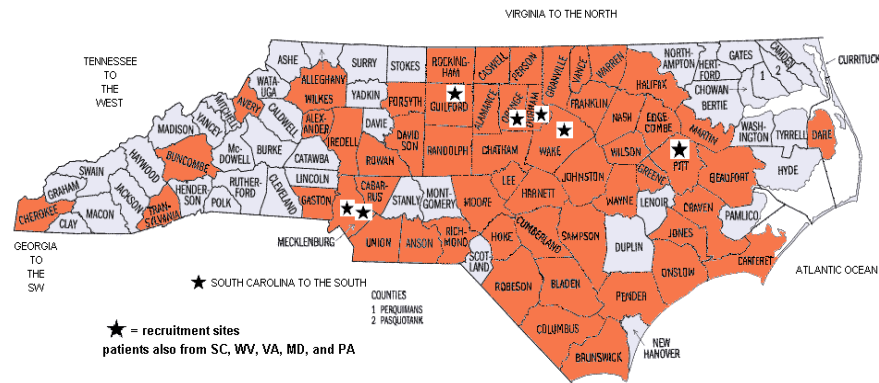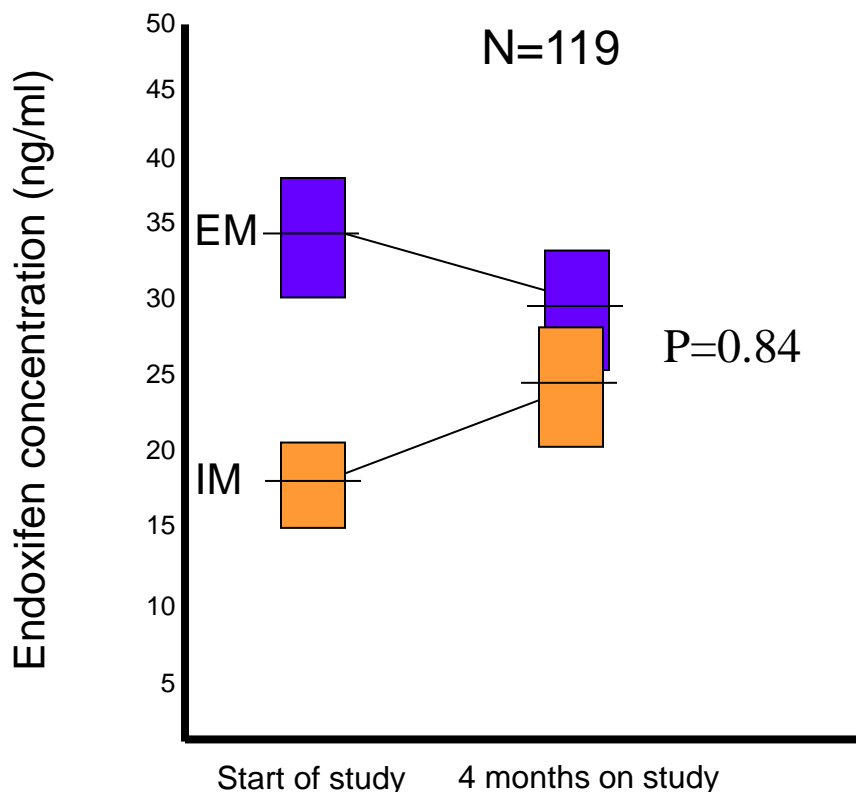# Relapse-free Survival

2-year RFS
EM 98%
IM 92%
PM 68%

Log Rank
P=0.009

EM-extensive metabolizer
IM-intermediate
PM-poor

EM

IM

PM

%

Years after randomization

Goetz et al. Breast Cancer Res Treat. 2007

CP1229323-16

Genotype-Guided Tamoxifen Dosing Increases Active
Metabolite Exposure in Women With Reduced CYP2D6
Metabolism: A Multicenter Study

William J. Irvin Jr, Christine M. Walko, Karen E. Weck, Joseph G. Ibrahim, Wing K. Chiu, E. Claire Dees,
Susan G. Moore, Oludamilola A. Olajide, Mark L. Graham, Sean T. Canale, Rachel E. Raab, Steven W. Corso,
Jeffrey M. Peppercorn, Steven M. Anderson, Kenneth J. Friedman, Evan T. Ogburn, Zeruesenay Desta,
David A. Flockhart, Howard L. McLeod, James P. Evans, and Lisa A. Carey

William J. Irvin Jr, Christine M. Walko, Karen E. Weck, Joseph G. Ibrahim, Wing K. Chiu, E. Claire Dees, Howard L. McLeod, James P. Evans, Lisa A. Carey, University of North Carolina at Chapel Hill, Chapel Hill; Susan G. Moore, Oludamilola A. Olajide, Rex Hematology/Oncology Associates; Sean T. Canale, Carolina Breast Care Specialists, Raleigh; Mark L. Graham.

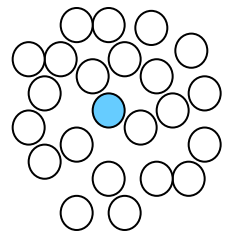## CYP2D6-guided tamoxifen dosing normalizes endoxifen levels

Study of 500 patients across NC is completed, with oversampling of African American and Hispanic patient
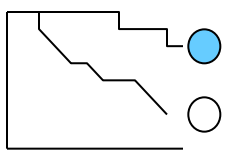
Germline Pharmacogenomic examples-2011

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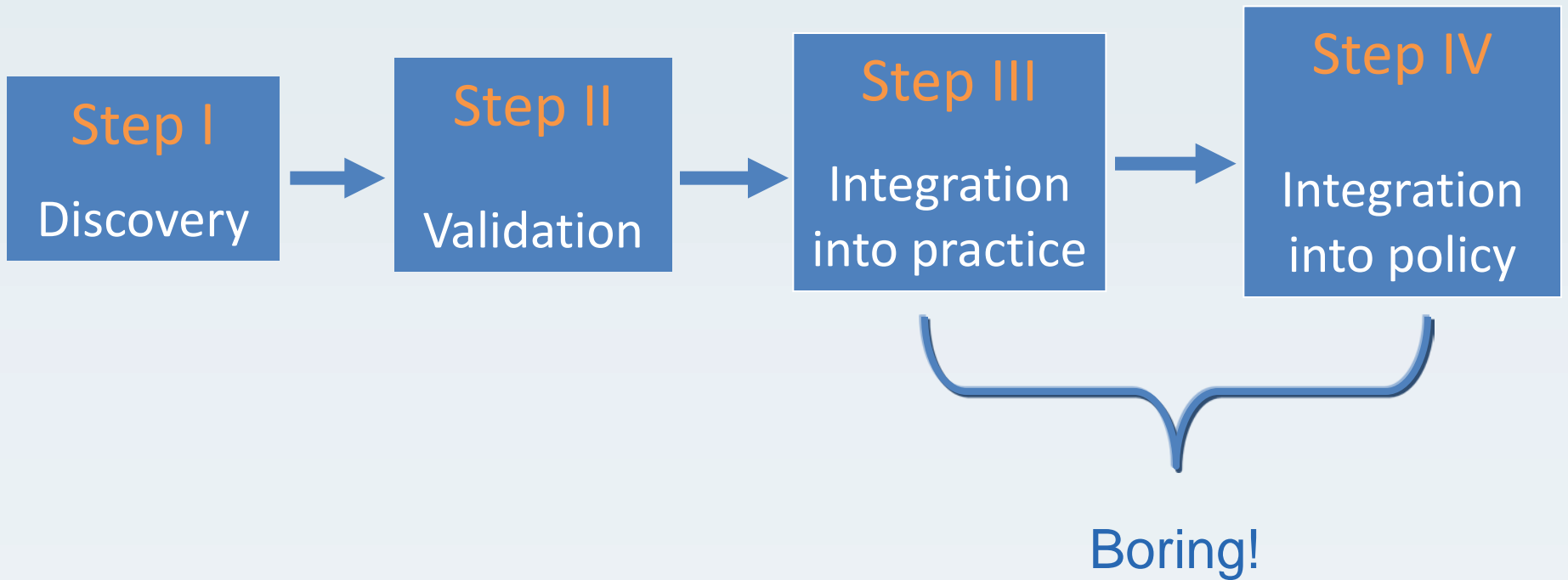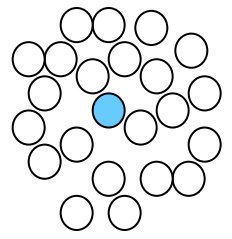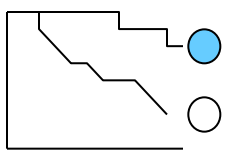
Marker
Discovery

Marker
Validation

Translational science: The steps to success

Step I — Discovery

Step II — Validation

Step III — Integration into practice

Step IV — Integration into policy

Boring!

PGENI

Treating the Population.
Impacting the World.
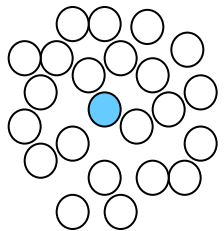
Marker
Discovery
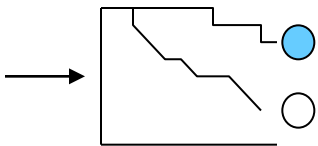
Marker
Validation

Health Economics

○ $$$ ● $$

Health system integration

? !

Marker Discovery

Marker Validation
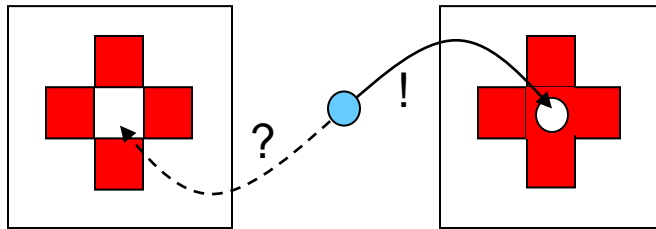
Medical informatics

IF

THEN
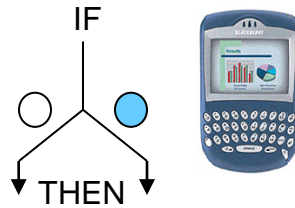
Research assay to Clinical assay
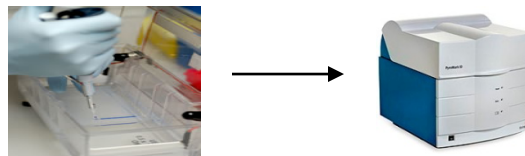
changing old habits

Routine Clinical Use

Family Physician Medical Group Inc.

PATIENT NAME: THOMAS BOOE   DOB: 12/01/1976
ADDRESS: DATE: 03/22/2004

R

po BID

John Doe MD , MD

LABEL   DO NOT SUBSTITUTE
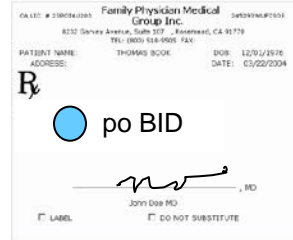
We now have new audiences

- Past
  - Ourself
  - Editors/reviewers
  - Study section

- Now
  - Clinic administrators
  - Payers
  - Patients

We now have new (additional) endpoints

- Past
  - survival
  - Stent thrombosis
  - Severe adverse drug reaction

- Now
  - Selection from amongst 'equal' therapies
  - Return on investment for medical home
  - Quality measures
  - Patient satisfaction

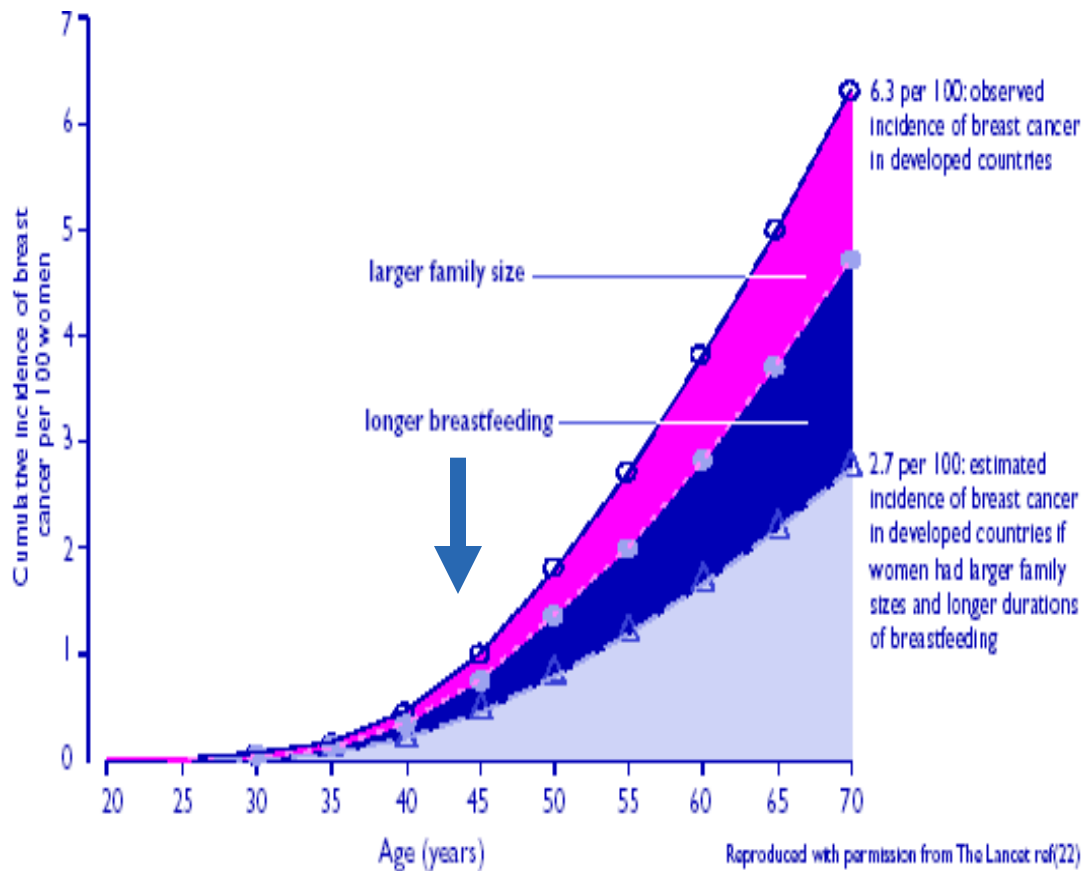# Preemptive action is a clinical major weapon

- Renal dysfunction
- Age
- Drug interactions
- vaccination

- We already know factors associated with ADR
- Comorbidity
- Polypharmacy

- Certain medical conditions
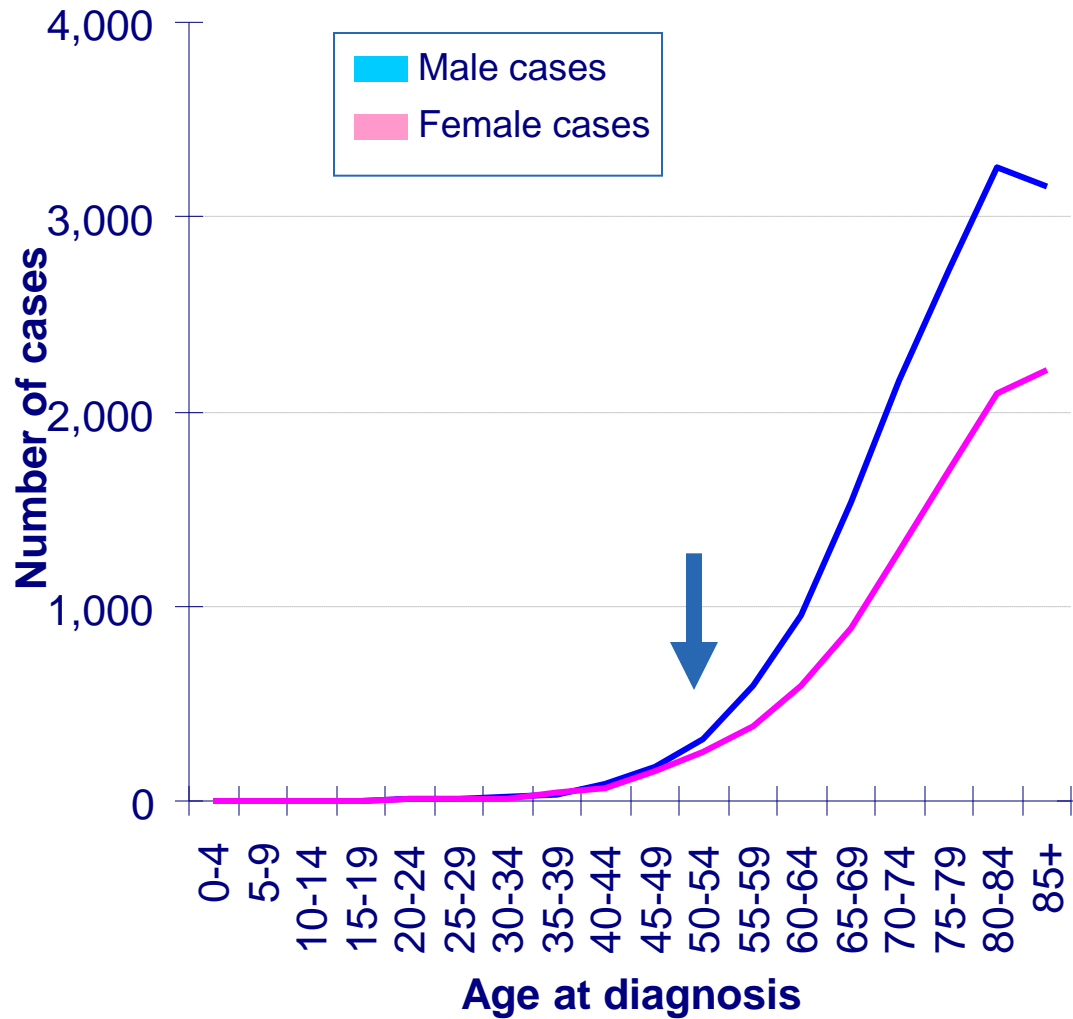- Certain types of medication

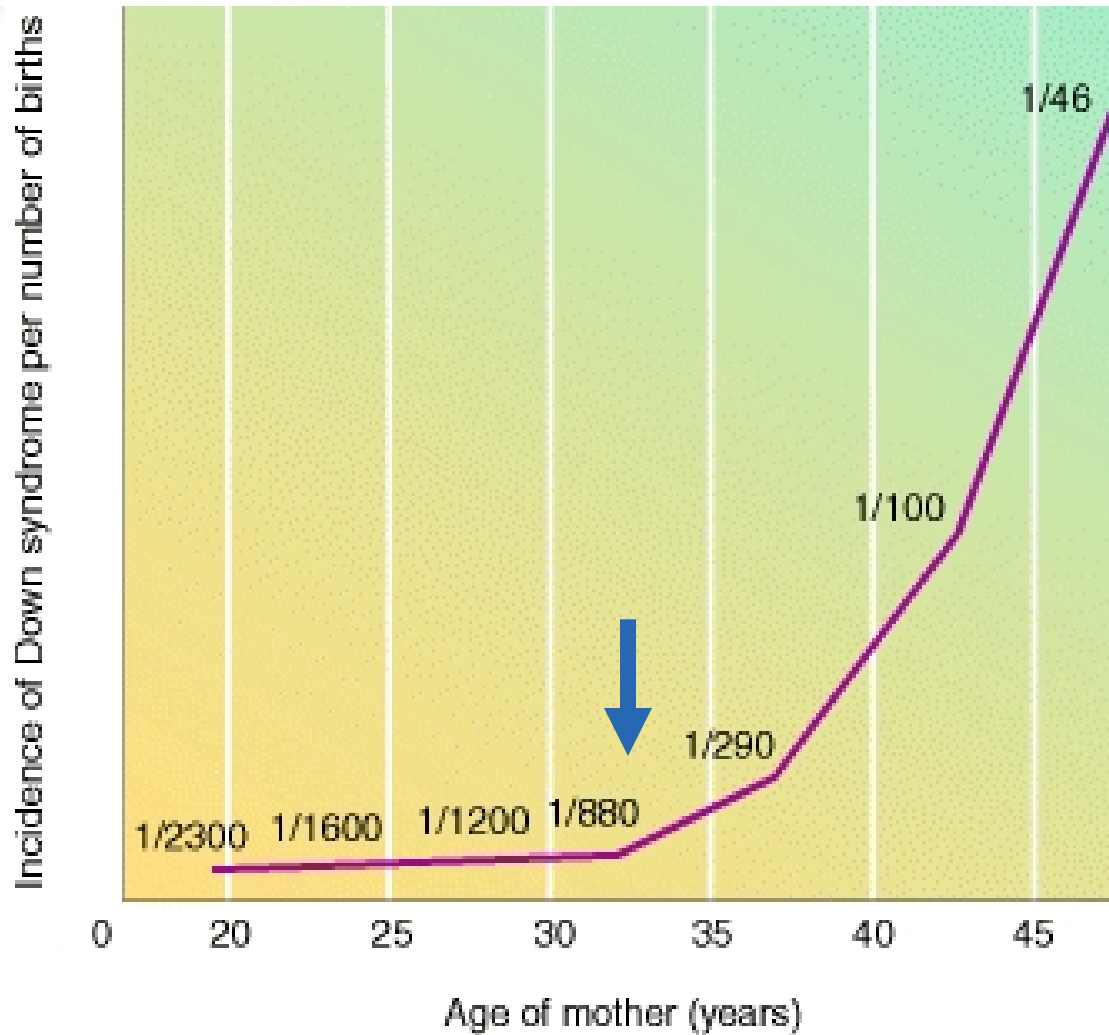# Increase risk = intervention Breast cancer screening

Increase risk = intervention Colon cancer screening

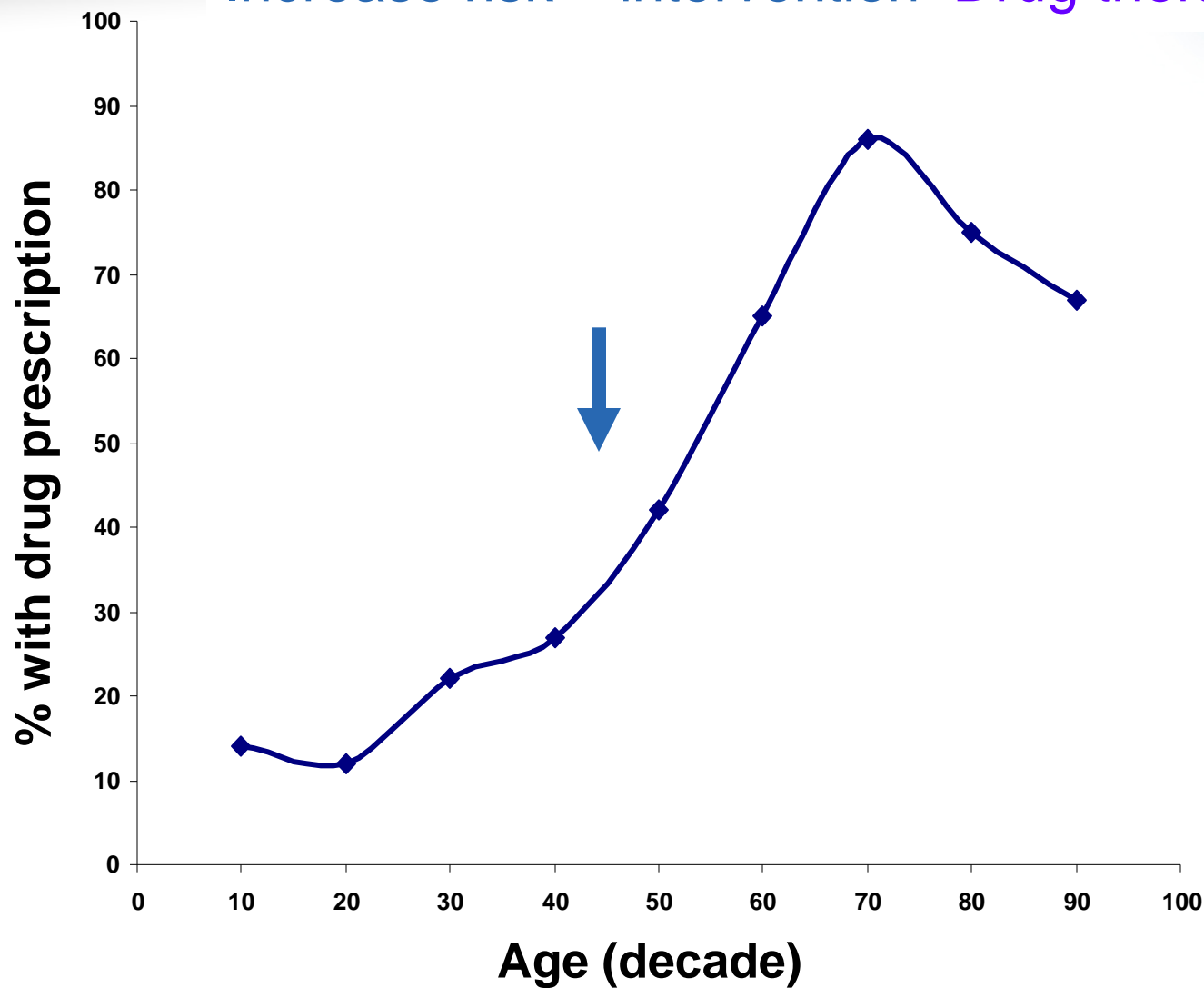Increase risk = intervention Down Syndrome screening

Drugs are toxic

- Adverse drug events are 5th leading cause of death in USA

- Adverse drug events are heavily litigated

- Many adverse drug events are predictable

Increase risk = intervention Drug therapy

Why wait for a problem?

- We know who is 'at risk' for needing prescription medicines
- We know examples where a particular genetic configuration = risk of toxicity or altered benefit
- We know our current model of 'wishful waiting' isn't adequate

There is enough data to start thinking about a preemptive strike

Genes	Drugs	Issue
CYP2C9/VKORC1	warfarin	bleeding
HLA-B*5701	abacavir	hypersensitivity
HLA-B*1502	carbamazepine	SJS/TENS
HLA-B*5801	allopurinol	SJS/TENS
CYP2C19	clopidogrel	stent thrombosis
CYP2D6	oxycodone,	delayed discharge
	antidepressants,	readmission
	antipsychotics	readmission

Not a rare issue!
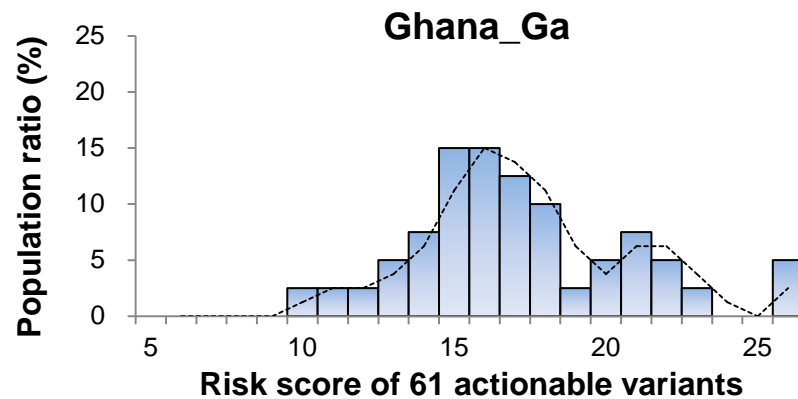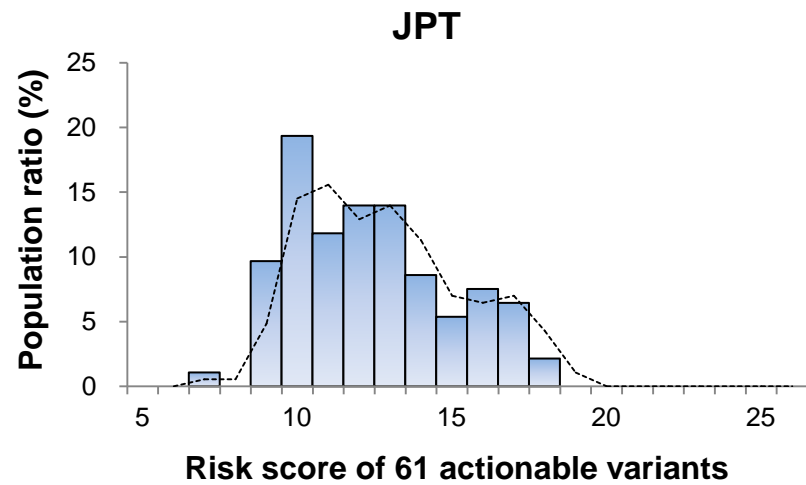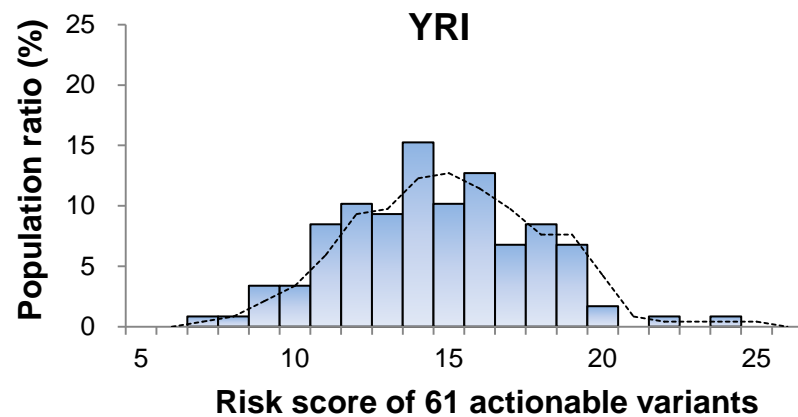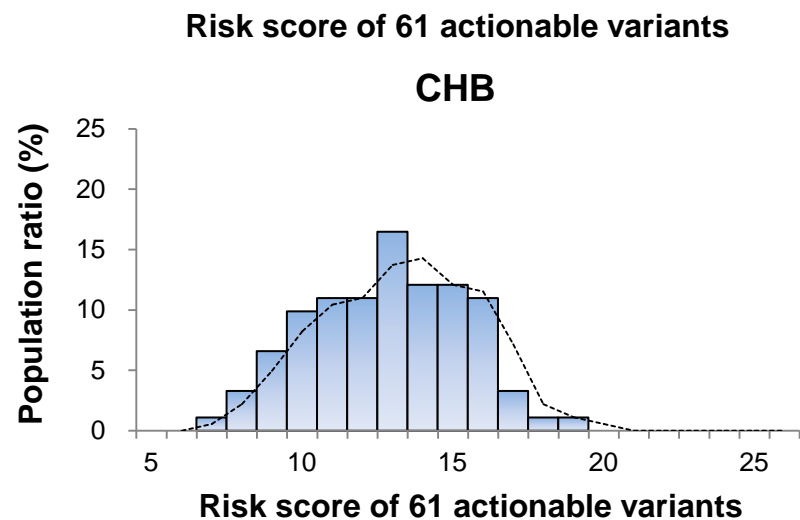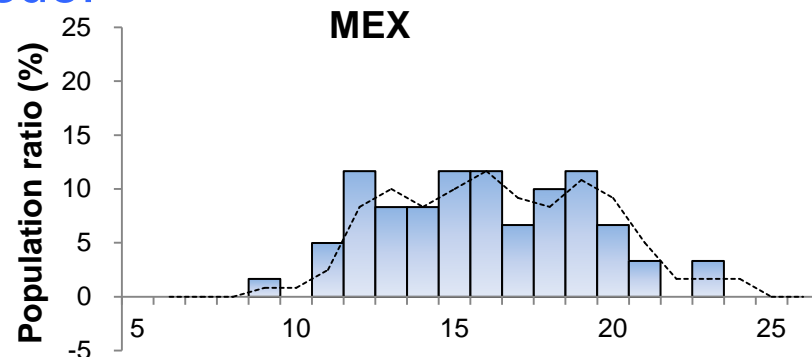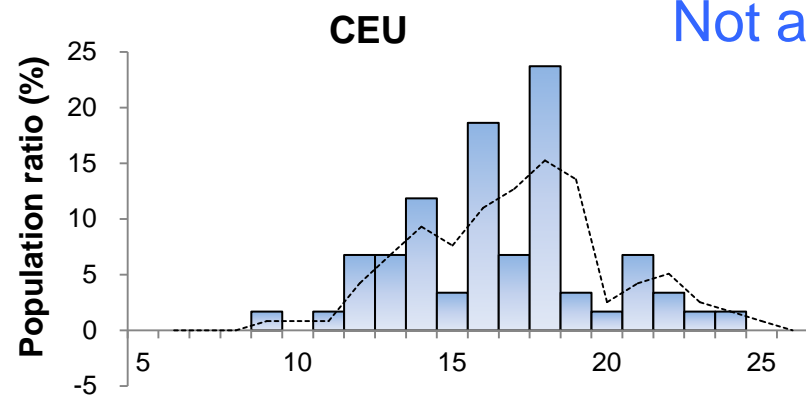
Applications of pharmacogenetics

- Explanation for untoward event (DPYD, CYP2D6)
- Required for insurance coverage (KRAS, EGFR, ABL)
- Identify low utility (KRAS)
- Dose selection (CYP2C9, CYP2C19)
- Therapy selection (CYP2C19)
- Preemptive prediction (HLA-B*5701)

- Bundled care
- Patient safety
- 'bounce back' avoidance
- Pharmacy & Therapeutics committee
- National formulary
- Others.......

} Boring!

Opportunity to conduct preemptive activities
Roden is king

-Target high risk populations

-using 'health system' endpoints

-use panels of variants to ask cross cutting questions