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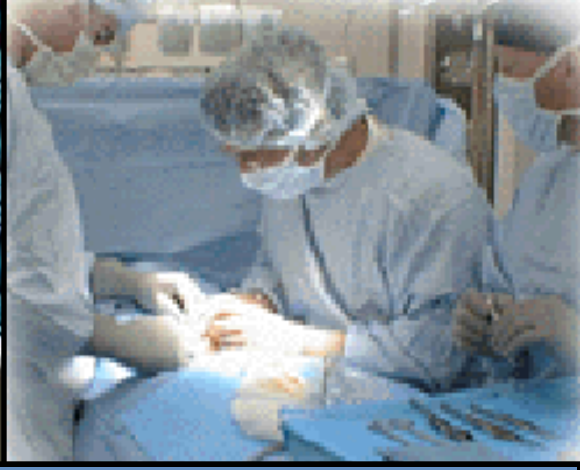

Cancer Pharmacogenomics: Setting a Research Agenda to Accelerate Translation

James H. Doroshow, M.D.
Director, Division of Cancer Treatment and Diagnosis

Bethesda, MD
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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Critical Requirements for the Development of Personalized Cancer Treatment: Phase I-III Transition

- Timely prioritization & dedicated resources for essential biomarker validation studies, utilizing standardized laboratory practices
- Accelerate prioritized translational research initiatives in the area of personalized therapy
- Support for the coordination of hypothesis-driven biomarker studies across the entire clinical/translational science continuum

Focus: Improve the specificity of treatment while reducing the high rate of failure (and cost) during the Phase I to III transition

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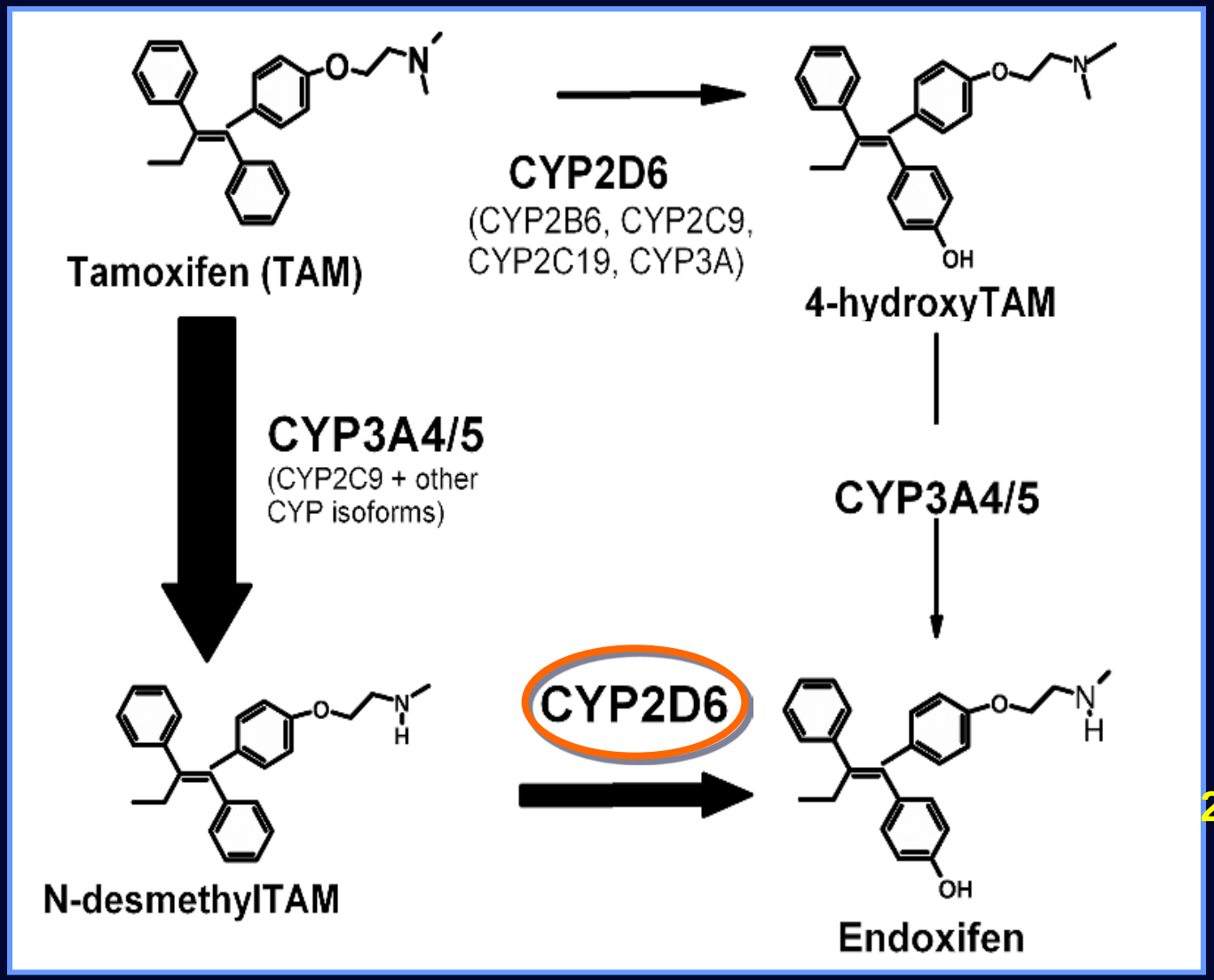
Critical Issues in the Development of Personalized Therapies

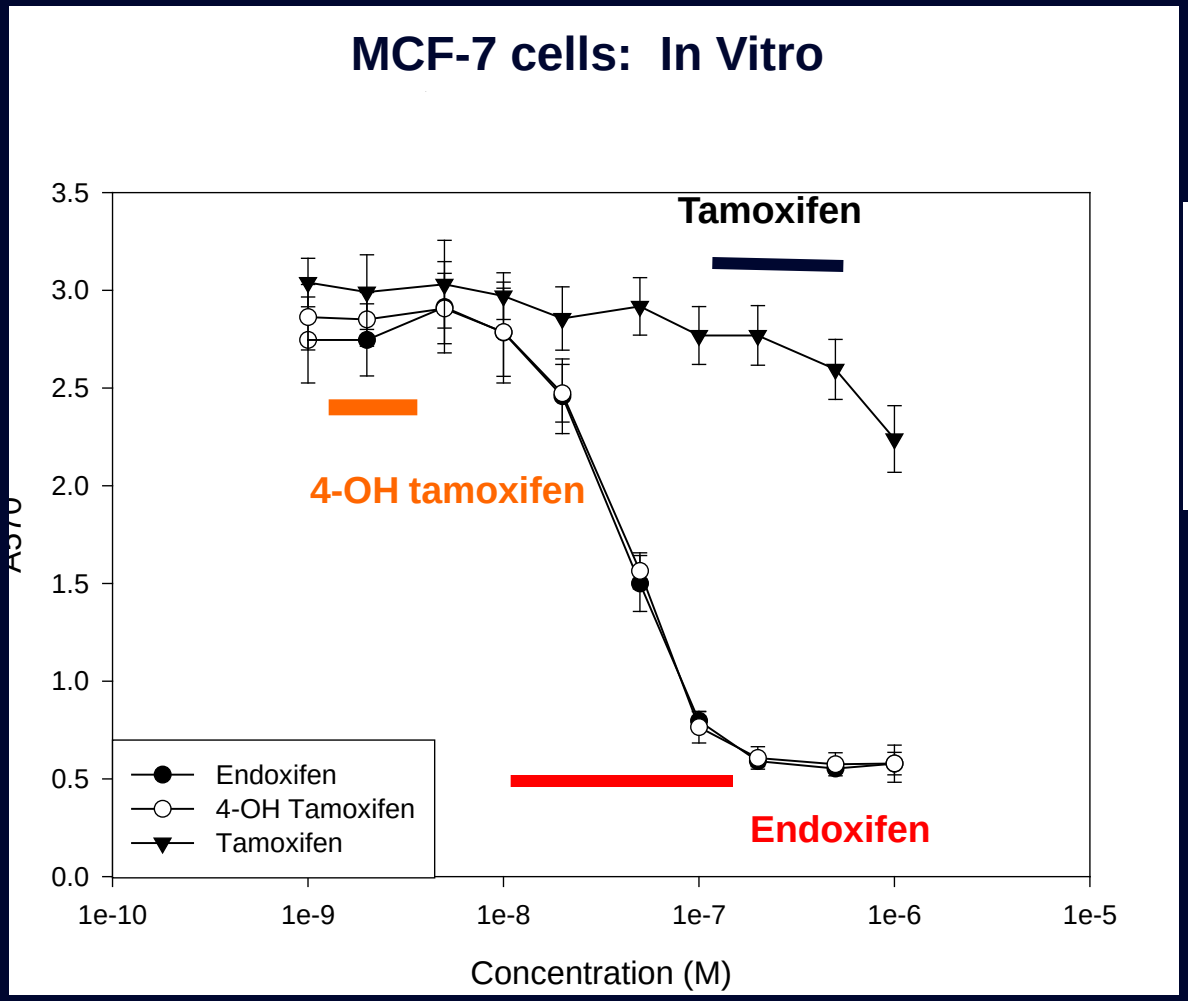
- How best to support academic investigators who wish to move from target or molecule discovery to clinical trials (preclinical testing, toxicology, GMP production, and regulatory support)
- Addressing the “pharmacogenomics divide” (courtesy of Drs. Ames and Goetz, Mayo Clinic)
- How to support the integration of pharmacogenomic studies into the NCI’s clinical trials system

Tamoxifen Metabolic Pathway (Humans)



Jin Y et al. *J Natl Cancer Inst*. 2005; 97:30. Reprinted by permission of Oxford University Press.

Endoxifen and 4-OH-Tamoxifen are Equipotent as Inhibitors of Estrogen Stimulated Cell Proliferation



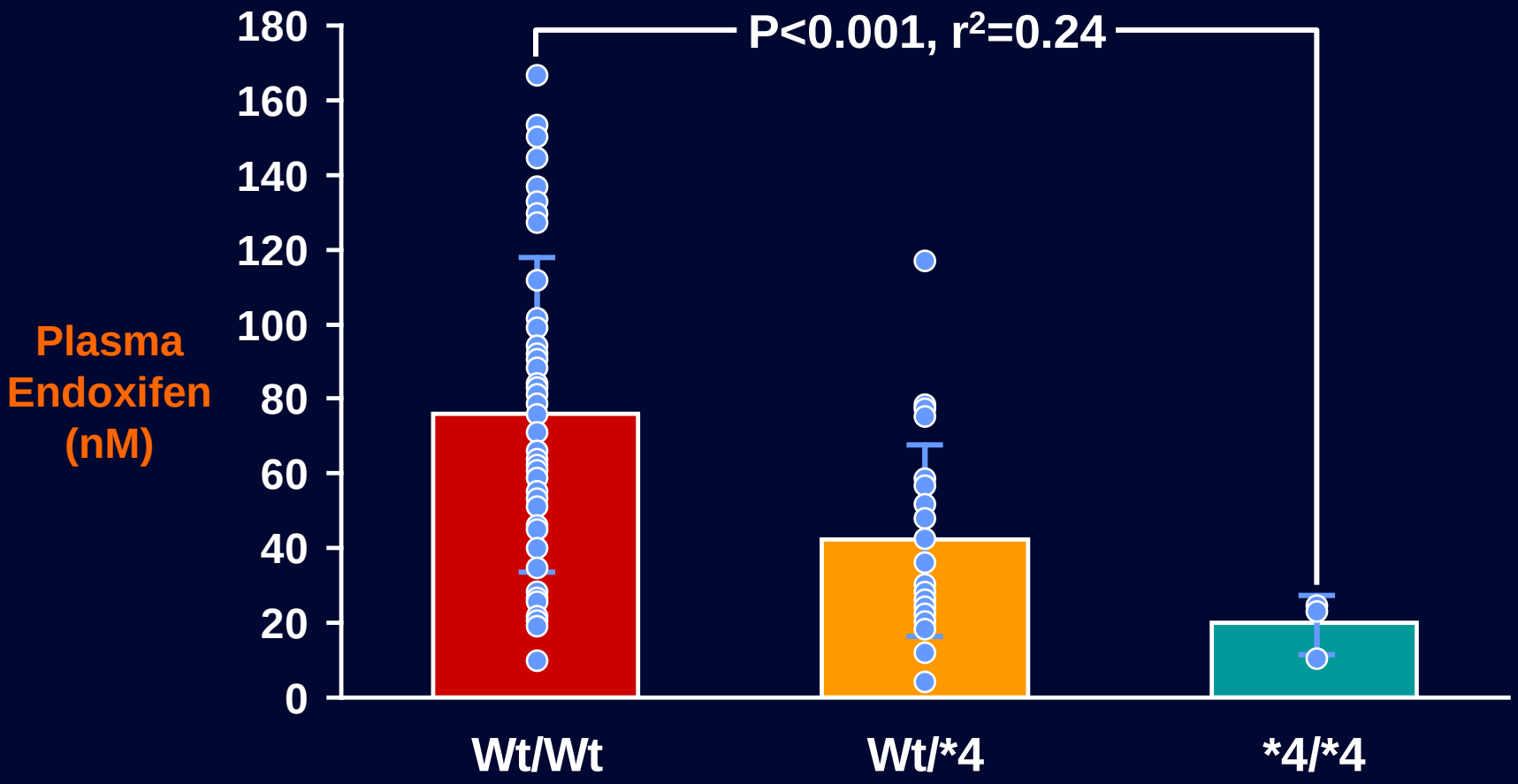
Concentrations in humans

- **Tam (300-500 nM)**
- **4HT (5-10 nM)**
- **Endoxifen (20-180 nM)**

Concentration

Johnson MD, et al. *Breast Cancer Res Treat.* 2004; 85:151-9.

CYP2D6 Genotype and Endoxifen



CYP2D6*4 (most common genetic variant associated with the CYP2D6 poor metabolizer state)

Jin Y et al. *J Natl Cancer Inst*. 2005; 97:30.
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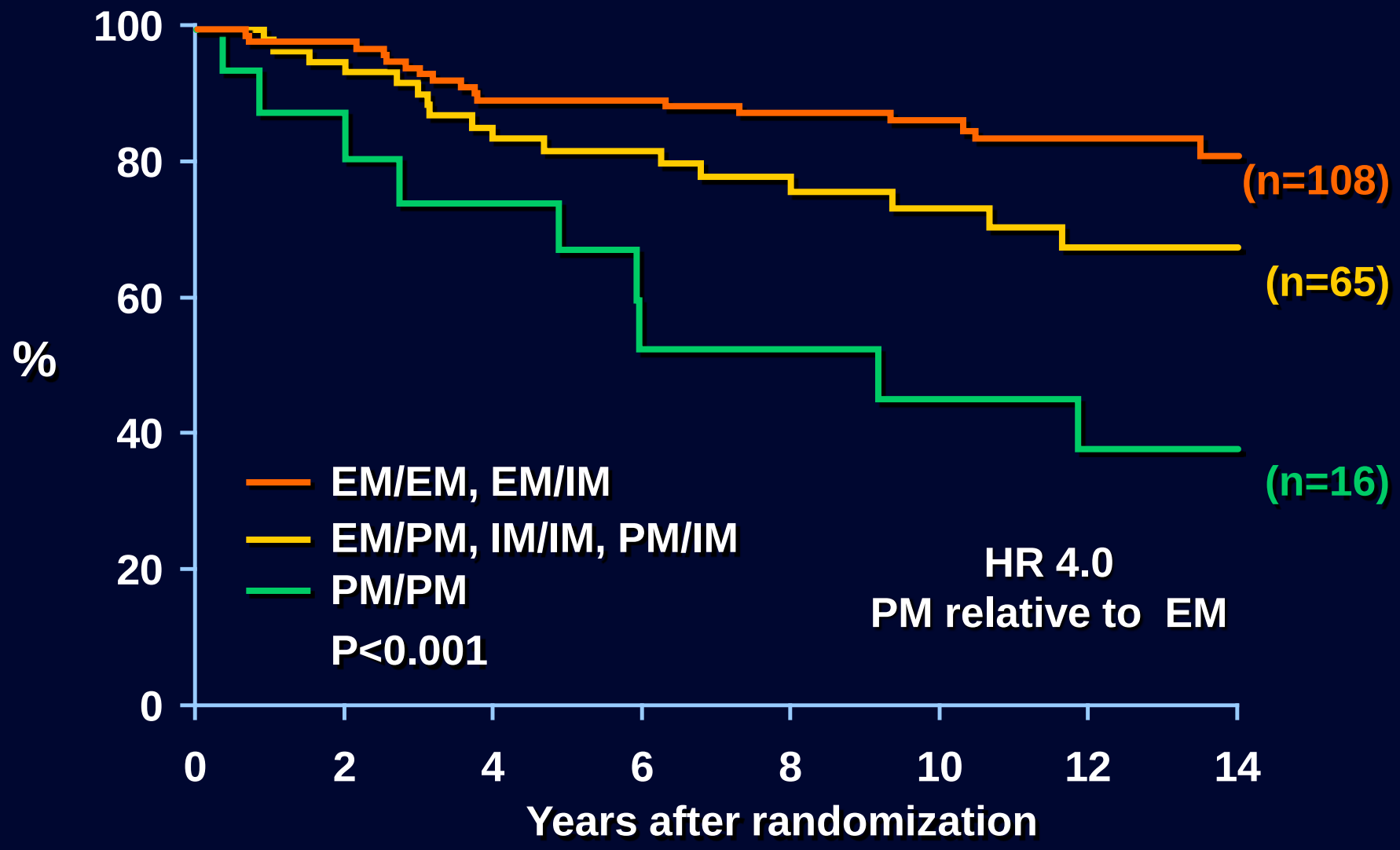
Time to Recurrence According to CYP2D6 Metabolizer Status* in Women Receiving Adjuvant Tamoxifen



Goetz et al., Updated NCCTG 89-30-52, SABCS 2008

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Crossing the Pharmacogenetic Divide

- CYP2D6 critical for endoxifen exposure and, thus, tamoxifen drug effect; endoxifen potently inhibits ERα as well as other traditional mechanisms
  - Metabolic activation of tamoxifen limits drug activity
  - Administration of endoxifen would bypass pharmacogenetic limitations of tamoxifen

- However, no IP possible for 30-year old metabolite, even though it is a new “drug”
  - Preclinical pharmacology, toxicology
  - Drug formulation and GMP production
  - IND submission
  - Phase I clinical trial

NCI has undertaken to produce clinical grade drug to begin the development process leading to a phase I study of endoxifen