

Development of a Pharmacogenetic Predictor “CYP2D6 for Tamoxifen”

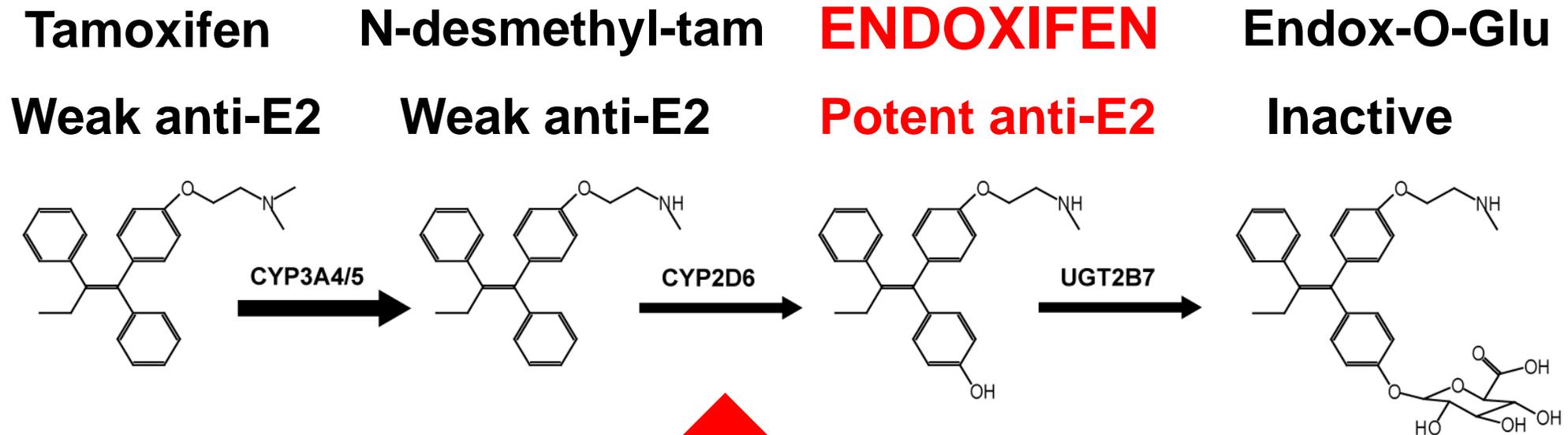
Defining Clinical Utility of Molecular
Diagnostics for Cancer Treatment
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Cytochrome P450 2D6 (CYP2D6)

- Liver enzyme that metabolizes 25% of drugs
- Metabolizes many antipsychotics, β -blockers, antidepressants, codeine, **Tamoxifen**
- Gene variants result in 3 main phenotypes:
 - Poor Metabolizers (PM) = ~7-10%**
 - Intermediate (IM) = ~20%**
 - Extensive (EM) = ~70%**

CYP2D6 is Responsible for Endoxifen Production



Known Genetic Variants

CYP2D6 / Tamoxifen Facts

- Endoxifen is 50-100X more potent anti-E2
- Endoxifen is the predominant anti-estrogenic metabolite of tamoxifen (6X over 4-OH-tamoxifen)
- Endoxifen serum concentrations correlate with CYP2D6 Genotype (PM, IM, and EM)
- Concomitant CYP2D6 Inhibitors (eg/ SSRIs) suppress endoxifen concentrations

Is Tamoxifen a “Prodrug”?

CYP2D6/ Tamoxifen Hypothesis:

Women who are CYP2D6 poor metabolizers (PMs) receive less benefit from tamoxifen therapy due to low endoxifen serum concentrations than.

CYP2D6 / Tamoxifen Association Studies

Study	Journal (Yr)	Tam treated N =	Control Group	Prosepective-retrospective	Association w/ CYP2D6
Goetz	JCO (2005)	190	No	Yes	Yes
Schroth	JCO (2007)	206	Yes	No	Yes
Schroth	JAMA (2009)	1325	No	No	Yes
Abraham	BCR (2010)	3155	No	No	No
Rae	JNCI (2012)	615	Yes	Yes	No
Regan	JNCI (2012)	1243	Yes	Yes	No

***Evidence is *NOT* Sufficient to Recommend CYP2D6 Genotyping for Tamoxifen**

CYP2D6 / Tamoxifen Lesson Learned

- Initial small studies providing low levels of evidence could not be validated in the larger “prospective-retrospective”⁽¹⁾ studies.
- None were true prospective investigations of CYP2D6 representing the gold standard of biomarker studies.
- Significant problem with publication bias. Positive studies published without validation sets or control groups.
- Together these have created a great deal of controversy!

⁽¹⁾ Simona, Paik, et al. “Use of archived specimens in evaluation of prognostic and predictive biomarkers” JNCI, 2009

CYP2D6 / Tamoxifen: Remaining Questions

- Is a prospective adjuvant study justified given the prospective-retrospectives were negative?
- Does CYP2D6 genotype correlate with tamoxifen “response” in advanced disease?
- Are there contributing factors that prevent us from detecting a CYP2D6 association: 1) adherence to therapy, 2) de novo tumor resistance due to somatic changes, 3) interaction with other genetic factors
- Or is this just another example of good hypothesis not being true?