CYP2D6 Allelic Percentage Activity Estimation for Tamoxifen

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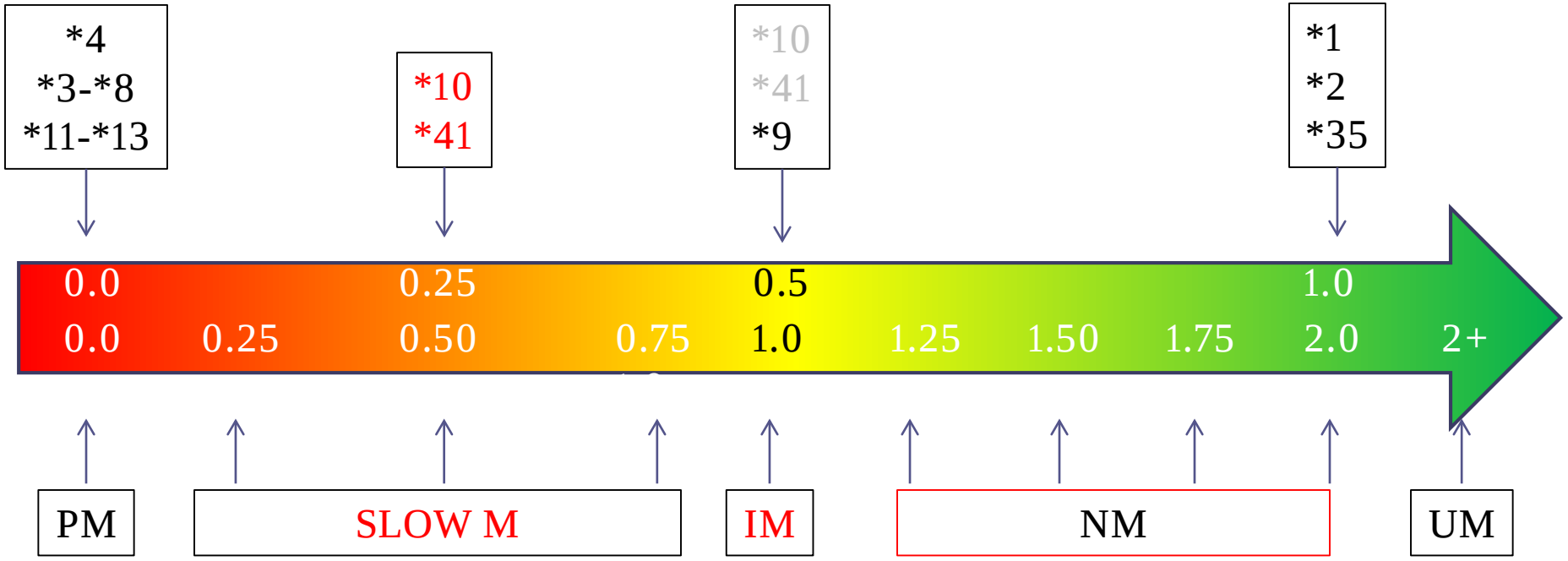
CPIC Conference Call
9/7/17

AS System

Allelic Activity Assignment

Assignment in units of 0.5 (now 0.25?)



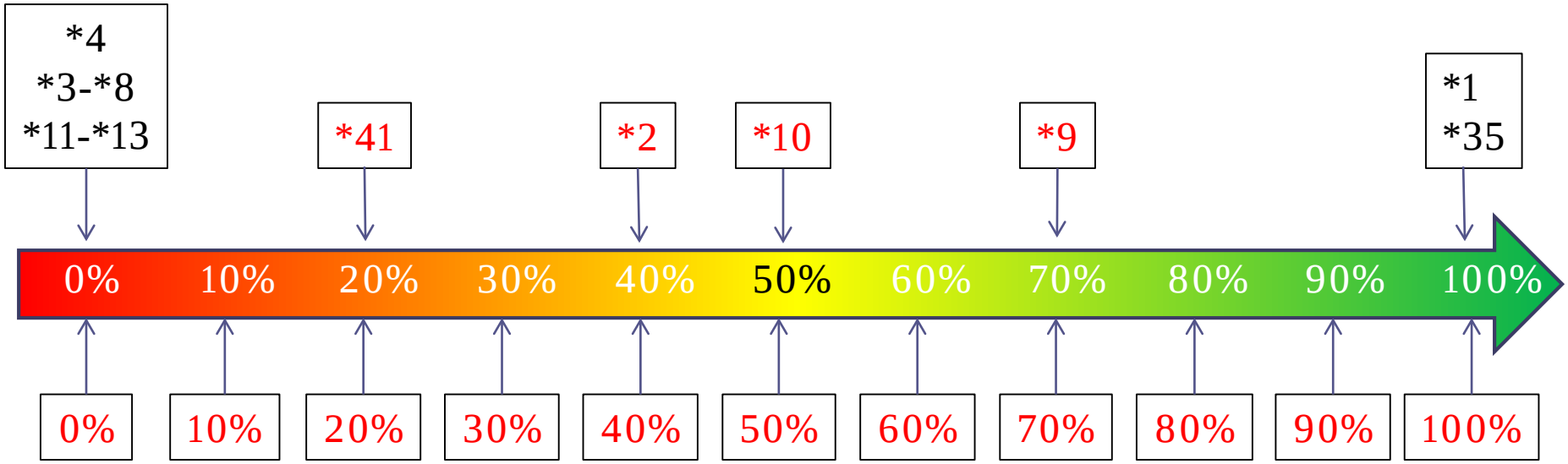
Phenotype Assignment

Sum of 2 alleles on a 0-2 scale

PA System

Allelic Activity Assignment

Assignment in units of 10%



Phenotype Assignment

Average of 2 alleles (rounded up to nearest 10%) on a 0-100% scale

Benefits of PA System

- Allelic activity empirically derived and informative
  - Greater accuracy in phenotypic activity estimation
  - Inherently intuitive scale (0-100%)
- More easily accommodate substrate dependence
- Greater flexibility for treatment recommendations

Feedback from CPIC CYP2D6 G2P

- Enthusiasm for PA concept
- Concerns included:
  - Lack of published data to estimate PA
  - Activity variability within genotypes
  - AS -> PA transition for implementers
- Plan for moving forward:
  - Short term: reconcile AS with other systems
  - Long term: generate data to consider PA system

Proposal:
CYP2D6 PA Estimation for Tamoxifen

- Tamoxifen selected due to:
  - Personal interest
  - Datasets with CYP2D6 genetics and endoxifen PK
    - 30+ cohorts with 5,000+ patients
  - Upcoming CYP2D6-tamoxifen CPIC guidelines

- Methods
  - Collect datasets
  - Comprehensive CYP2D6 genotyping
  - PA estimation within datasets
    - Meta-analysis across datasets -> variability

Final Comments

- PA is a preliminary proposal for development
  - Suggestions for improvement are strongly encouraged

- If you have datasets with endoxifen and DNA/CYP2D6 genetics (or clinical data) and want to collaborate PLEASE contact me
  - DLHertz@med.umich.edu

Thank You

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Percentage Activity Estimation

- Directly from data via linear regression
- Indirectly from published data
  - PA=100*((X-PM)/(EM-PM))
- From estimated activity data:
  - *10=100*((0.051-0.034) / (0.079-0.034))
  - *10=38% -> 40%
- From diplotype data with shared allele:
  - *10=100*((5.54-2.15) / (7.42-2.15))
  - *10 ->60%
- Published data is VERY sparse

Allele type	Allele	*n*	Median	Standard deviation	Scaled activity*
UM	Composite	9	0.056	0.053	0.71
EM	*1 (wild-type)	250	0.079	0.058	1.00
	*2	109	0.050	0.036	0.63
	*35	31	0.081	0.046	1.03
IM	*9	20	0.067	0.029	0.85
	*10	11	0.051	0.044	0.65
	*17	21	0.031	0.022	0.39
	*29	10	0.046	0.031	0.58
	*41/*41XN	87	0.042	0.035	0.53
PM	Composite	162	0.034	0.039	0.43

Hertz et al. British Journal of Clinical Pharmacology 2015

CYP2D6 genotypes	n	9-OH risperidone (ng/mL)
EM: *1/*10	39	7.42
*10: *10/*10	27	5.54
PM: *4/*10	3	2.15

Natchaya et al. Journal of Child and Adolescent Psychopharmacology. 2017

PA CPIC Recommendations

- Use CPIC (left) or more precise thresholds (right)

Codeine Recommendations PA CPIC Equivalent	
>100% (UM)	Avoid
10%-100% (IM-NM)	Standard dose
0% (PM)	Avoid

Codeine Recommendations PA Precision*	
>200%	Avoid
130%-200%	Decrease dose 50%
40%-120%	Standard dose
10%-30%	Increase dose 50%
0%	Avoid

*For illustration, NOT suggested recommendations

- CPIC (or an institution) can have as many bins as desired
- NOT recommending to change doses in increments of 10%!

Potential Secondary Objectives

- Discover/validate clinical and genetic predictors of endoxifen
- Apply algorithm to cohorts with efficacy outcomes
- Create tamoxifen dosing algorithm to achieve target endoxifen