CYP2C19 Genotyping Recommendations: AMP PGx Working Group

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Why a "Must-Test" List?

- Genomic Medicine X: Research Directions in Pharmacogenomics Implementation
  - Call for assay standardization
- Recent GeT-RM paper (Pratt et al., 2016), no 2 PGx assays tested same variants.
- Standardization of testing
  - Similar to *CFTR* testing
- Allele function derived from *in vitro* models may not directly translate to a clinical phenotype
- Allele function can be substrate and/or drug concentration dependent.

https://www.genome.gov/27568408/genomic-medicine-x-research-directions-in-pharmacogenomics-implementation/

Why NOT a “Must-Test” List?

- High throughput DNA sequencing has become more common
  - PGx genes have many pseudogenes
- May quickly lose relevance
  - AMP PGx Working Group plans to periodically reassess

AMP PGx Working Group

- **Victoria M. Pratt** (Chair), Indiana University
- **Andria L. Del Tredici**, Millennium Health
- **Houda Hachad**, Translational Software
- **Yuan Ji**, Department of Pathology and ARUP Laboratories, University of Utah School of Medicine
- **Lisa V. Kalman**, Division of Laboratory Systems, Centers for Disease Control and Prevention
- **Stuart A. Scott**, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai and Sema4, a Mount Sinai venture
- **Karen E. Weck**, Department of Pathology and Laboratory Medicine and Department of Genetics, University of North Carolina

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- First deliverable: consensus expert opinion recommendations for clinical *CYP2C19* testing

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Defining a “Must-Test” List

- Needed to develop a framework for evaluation
  - Functional status
  - Multiethnic allele frequencies
  - Availability of reference materials
  - Commercially available genotyping platforms
- Started with *CYP2C19*
- Other PGx genes with clinical relevance planned

Defining a “Must-Test” List

- Development process
  - Review of available literature and testing resources
  - Identification of available reference materials
  - Review of clinical testing currently being offered
  - Review of available quality programs
  - Identification of heterogeneity / gaps in practice
  - Discussion
  - Expert consensus recommendation/opinion development

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Proposed system

- **Tier 1**
  - Minimum “must-test” set
  - Well-characterized alteration of activity that has been shown to have an effect on drug response and for which the functional variant is known
  - Appreciable minor allele frequency in a patient population
  - Available reference materials
- **Tier 2**
  - Extended panel
  - Meet at least 1 but, not all of the criteria for inclusion in Tier 1

CYP2C19

Allele	Allele Function Status	Tier
*2	No function	1
*3	No function	1
*17	Increased function	1
*4A	No function	2
*4B	No function	2
*5	No function	2
*6	No function	2
*7	No function	2
*8	No function	2
*9	Decreased function	2
*10	Decreased function	2
*35	No function	2

We want to hear from you!

- Does the proposed two tier system
  - Account for established /establishment of clinical utility?
  - Reflect appropriate clinical implementation of PGx testing given current knowledge?
  - Flexibility for testing in a variety of practice settings?
  - Place appropriate emphasis on reference material availability?
- Other *CYP2C19* alleles that should be included?
- Do you agree with the current tier assignments for the listed *CYP2C19* alleles? If not, why not?

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A Special Thanks

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- **Robyn Temple-Smolkin**

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