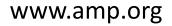
CYP2C19 Genotyping Recommendations: AMP PGx Working Group

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Expertise that advances patient care through education, innovation, and advocacy.





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



AMP PGx Working Group

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



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





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?





A Special Thanks

- AMP Clinical Practice Committee
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- Robyn Temple-Smolkin

