

Association for Molecular Pathology
Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology
9650 Rockville Pike, Bethesda, Maryland 20814
Tel: 301-634-7939 • Fax: 301-634-7990 • Email: amp@asip.org • www.amp.org

March 4, 2008

AMP's Response to NACB: Guidelines and Recommendations for Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice

Dear Authors:

AMP is an international not-for-profit professional association representing over 1,500 physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing based on nucleic acid technology. AMP members practice their specialty in widely diverse settings: academic medical centers, independent medical laboratories, community hospitals, federal and state health laboratories, and the in vitro diagnostic industry. In this capacity, AMP members are involved in every aspect of molecular diagnostic testing: administration and interpretation of molecular diagnostic tests, research and development, and education. As the only professional association dedicated solely to molecular pathology, AMP provides national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing in the health care industry.

The authors should be commended as there is much improvement in this document over previous versions. Below we have listed some comments.

Some general comments:

Throughout the document metabolizer status changes between “metaboliser” and “metabolizer”. Consistency is recommended. Standard American spelling of “metabolizer” would be preferred.

HGVS nomenclature is recommended to be used throughout the document in describing genes (especially gene names in italics) and description of variants.

The format of references varies. Consistency would be preferred.

For the definitions, using CLSI harmonized definitions would be preferred. Many of the definitions are circular.

Specific comments are listed below:

Section II, page 8, line 4 (Genotyping and drug dosing requirements) – Is a review from 2000 considered recent? Please consider revising.

Section II, page 8, line 8 (Genotyping and drug dosing requirements) – “time” should be changed to “times”.

Section II, page 14 – In the second paragraph, there is a discussion of a gene duplication that is not defined. This duplication needs to be better described by using HGVS nomenclature.

Section II, page 15, Recommendation 2 – The purpose of this recommendation is not clear and perhaps needs to be removed.

Section III. Methodology and Quality Assurance considerations in Pharmacogenetic Testing.

1. Section III, page 20, General Introduction – “United States” and “College of American Pathology” need to be capitalized.
2. Suggest referencing appropriate CLSI documents in applicable sections (in addition to the CAP checklist). These include:
 - a. MM9-A: Nucleic acid sequencing methods in diagnostic laboratory medicine
 - b. MM01-A2 - Molecular Diagnostic Methods for Genetic Diseases
3. Also applicable is the American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories - this should at least appear in the references.
4. Recommendation 2
 - a. The report should differentiate between the Coriell repository and the GeT-RM database. The database provides linkages to cell lines and their level of verification. Many of the cell lines listed, but not all, are available through Coriell
5. Recommendation 3
 - a. This, in part, is also discussed in CLSI document MM01-A2
6. Recommendation 4
 - a. Alternate proficiency testing is not described - we recommend referencing CLSI GP29-P Validation of laboratory tests when proficiency testing is not available.
6. Section III, page 23, Recommendation 6, Rationale 1 – What is an “abhorrent” analytical result? Consider revising.

Section IV. Clinical Laboratory Services Considerations

1. Recommendation 1
 - a. instead of "or as required by other states" change to "and as required by other states" - Two states are CLIA exempt by having their own system of oversight comparable to CLIA and other States have licensing requirements on top of (or at places in lieu of) what is required under CLIA
 - b. Replace "appropriate accrediting agency" with "appropriate authorizing agency". Not all labs in other countries use accreditation.
2. Recommendation 2
 - a. Laboratories should validate all appropriate samples from which to perform testing in accordance with appropriate CLIA, CAP, CLSI, ACMG standards. This recommendation seems inappropriate.
3. Recommendation 5
 - a. Please clarify. This recommendation is related to revised risk analysis (Bayesian calculations).
4. Recommendation 6
 - a. Recommendations from the EGAPP working group regarding cytochrome P450 polymorphisms may be useful example to include when current evidence is not available indicative of cost-effectiveness.

Section V. Reporting and Interpretation of Pharmacogenetic Test Results

1. Recommendation 2; Rationale 2
 - a. While it is ideal to try and obtain a patient's current and past drug regime to provide an interpretation for CYP testing in a report, this practice will be difficult to implement. Also of note, dietary and other environmental factors can influence CYP metabolism. We recommend removing or revising this rationale.
2. Recommendation 5
 - a. Discussion of HIPAA guidance is too US centric, we recommend revision of this section.

Section VI. Under Clinical Practice Considerations

1. Recommendation 2; under rationale 2) - remove the word reference
2. for 3) please clarify "having levels of specificity and sensitivity consistent with other diagnostics in clinical use"? Is this referring to clinical or analytical sensitivity and specificity?
3. Please comment upon the EGAPP working group recommendations on testing for cytochrome P450 polymorphism in adults with nonpsychotic depression treated with SSRIs (Genet Med 9:819-825). There should be mention of a finding of insufficient evidence supporting a recommendation for or against use for CYP450 testing in adults about to begin SSRI treatment.
4. Table on page 37 – needs to be reformatted.

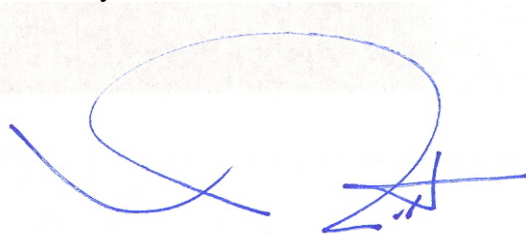
Section VII, Page 52, Recommendation 2, Rationale 1 – Please remove track changes.

Section IX. Regulatory Considerations – this section seems to be entirely FDA considerations and should be renamed to reflect that, otherwise CLIA, EU or other appropriate regulatory requirements should be discussed.

Since AMP has provided significant input to this document, we would respectfully request acknowledgement in the document. Individuals were acknowledged, Elaine Lyon and Vicky Pratt. We would like this changed to the Association for Molecular Pathology.

Thank you for the opportunity to comment on this very important document. Please do not hesitate to contact me at victoria.m.pratt@questdiagnostics.com if we can be of further assistance.

Sincerely,



V.M. Pratt, PhD
Clinical Practice Committee Chair