



Association for Molecular Pathology
Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology

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Rochelle M. Long, Ph.D.
Chief, Pharmacological and Physiological Sciences Branch
Division of Pharmacology, Physiology, and Biological Chemistry
NIGMS, NIH
45 Center Drive, Room 2AS.49G
Bethesda, MD 20892-6200

Challenges and Barriers to Pharmacogenetics/Pharmacogenomics Research

Dear Dr. Long:

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, including 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.

Pharmacogenetics/pharmacogenomics (PGx) research and molecular diagnostics embody personalized medicine by maximizing the likelihood of therapeutic efficacy while minimizing the risk of drug toxicity for individual patients. While the potential benefits to patients are immeasurable, there are significant barriers and challenges to access, to effective implementation, and to clinical utilization at this time, as outlined below.

Barriers:

- In order to drive adoption of PGx in clinical testing, new evidentiary standards should be developed from robust, prospective, randomized clinical trials. The NIH is uniquely positioned to fund such long-term, large scale studies.
- Gene patents on major components of drug metabolizing pathways prevent the application of novel technologies and restrict access to diagnostic testing.

- Genetic variants are often described using cumbersome nomenclature that is not proper genetic nomenclature. This is confusing and leads to difficulty in communication and interpretation.
- The absence of well-characterized correlations of gene variants and functional protein activity, particularly for different drug substrates of the same gene, greatly increases the complexity of clinical test development and interpretation.
- Few prospective clinical studies have been designed to demonstrate that using genetic testing to determine stratification to treatment alternatives or dose modifications truly yields a better clinical outcome for the patient.

Challenges:

- There is currently a lack of well-characterized genetic material to use as controls or standards. For example, few of the lines that are genotyped and available from Coriell are genotyped for ALL the markers even in the current CAP PGx Proficiency Test.
- There are highly variable interpretations of genotype-phenotype correlations, for predicting protein function such as enzyme activity, receptor recognition, or membrane transport as well as overall drug response, both among labs and among testing platforms.
- PGx research and molecular diagnostics require professional interpretation in order to achieve clinical utility. There is currently no consensus regarding the clinical implications of PGx assays, *i.e.*, no patient management guidelines. The results of genetic testing alone are not sufficient to determine optimum drug dosage but should be used with clinical evaluation and other tools to determine the best treatment for patients. These tests do not simply allow for a recitation of genetic variations, duplications, and deletions alone to achieve effective integration into clinical practice algorithms.
- There are currently few multi-specialist approaches to patient management (physician, pharmacist, genetic testing lab, etc).
- There is an absence of good PGx educational materials for clinicians.
- The diversity of lab specialties performing the testing and interpreting the findings leads to many different levels of understanding.
- The continued collection of medical utility data is paramount to expand research studies and informational gaps for the unique, transformative knowledge provided by PGx technologies. Encouraging industry leaders to continue to develop such technologies remains a challenge, given the high costs involved in research and development and the uncertainty surrounding any return on these investments. It is not, however, insurmountable.

AMP is committed to working toward achievable goals that will advance pharmacogenetics/pharmacogenomics research and knowledge into the clinical practice setting. Thank you for the opportunity to respond to this very important RFI. Please do not hesitate to contact Vicky Pratt, PhD, Clinical Practice Committee Chair, at victoria.m.pratt@questdiagnostics.com if we can be of further assistance.

Sincerely,

A handwritten signature in black ink, appearing to read "Gregory J. Tsongalis". The signature is fluid and cursive, with a prominent initial "G" and a long, sweeping tail.

Gregory J. Tsongalis, PhD
President