

Public Policy Recommendations for Oversight of Molecular Laboratory Tests

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Laboratory tests have long been used to help diagnose and classify disease. Increasingly, these assays are used to predict disease in healthy individuals or to predict outcomes in response to a specific therapy (See Table 1). The subspecialty of molecular genetic pathology (MGP) has recently emerged to promote and recognize physician expertise in DNA- and RNA-based testing. In fact, the University of North Carolina at Chapel Hill has the nation's first accredited MGP fellowship training program to graduate a physician who subsequently became board-certified.

American Pathologists are voluntarily used by many testing laboratories to further check the quality of various DNA- or RNA-based assays. Indeed, laboratorians are widely recognized as leaders among health care practitioners in terms of measuring the quality of our clinical services.

Although demonstration of "clinical utility" for tests is not mandated by law, the vast majority of laboratory tests are known to be clinically useful even if they have not been reviewed by the Food and Drug Administration (FDA). The physician consultant in every testing laboratory has an ethical duty to look out for the

Table 1.
Clinical Utility of Molecular Assays

| Clinical Application | Diagnosis | Screening | Monitoring | Prediction |
|--|---|--|--|---|
| Heritable trait or disease | Detect germline mutation causing inherited disease | Determine carrier status | | Predict disease presymptomatically, predict drug toxicity or optimal dose |
| Oncology | Help diagnose tumor based on acquired genetic defects | Screen high-risk individuals for cancer | Measure tumor burden, detect early recurrence | Predict drug efficacy, resistance, or toxicity |
| HLA typing & identity testing | Help diagnose HLA-linked disease | Match potential organ donors to recipients | Measure engraftment of transplanted hematopoietic stem cells | Predict organ rejection or graft versus host disease |
| Infectious disease | Detect pathogen based on unique DNA or RNA sequence | Screen blood donor for transfusable pathogen | Measure viral load during therapy | Predict drug resistance |

The public should be reassured that molecular genetic tests are analytically valid. All clinical laboratories in the United States (with the exception of certain government laboratories) are subject to regulatory oversight by the Centers for Medicare and Medicaid Services (CMS) involving, among other things, demonstration of accuracy and precision, periodic revalidation of assay performance, laboratory inspections, and biennial recertification.¹ Proficiency surveys offered by the College of

best interests of the patients whose samples are being tested, and the laboratory physician assumes the risk of legal action if harm ensues. There are abuses: A recent report from the Government Accountability Office warned that certain genetic tests being marketed directly to the public (via the internet) seem to have no clinical value.² These tests may not directly harm the health of a consumer, but they are likely to harm their pocketbook.

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Most people are surprised to learn that many genetic tests are not FDA approved. Achieving FDA approval is costly to those who prepare and submit a completed application (estimated at hundreds of thousands of dollars),^{3,4} and that money may be better spent on higher priority efforts such as improving access to health care. Furthermore, the FDA lacks the manpower required to review validation data for all genetic tests. Overcoming this shortage would be burdensome to the FDA and would likely have the unintended consequence of delaying and impeding the availability of testing for patients. Finally, there is no demonstrated evidence that the quality of laboratory testing would substantially improve if FDA clearance were achieved. In this regard, it appears that existing governmental oversight of laboratory testing is adequate.

The Pathologist as a Resource for Clinicians

It is estimated that at least 60% of medical decision making is based on laboratory test results, implying that the pathologist is among the most important members of the health care team.⁵ Clinicians are encouraged to consult pathologist colleagues for advice on which laboratory test(s) to order, optimal specimen collection and handling, interpretation of test results, and implications for patient management. Pathologists, in turn, may formally document each consultation in the patient's medical record (using, for example, procedure codes 80500 or 80502) so that their expert advice and any links to additional resources are recorded in a way that may be accessed immediately by the requesting clinician and later by other members of the health care team.

Clinicians face tough challenges as they are bombarded with massive amounts of medical information, including both patient-specific data and never-ending piles of published literature.^{6,7} The amount of medical information is estimated to double every five years, and the pace of progress seems even faster in the realm of molecular pathology where new technologies are now available to inform translational research and clinical practice. These new tools for analyzing DNA or downstream RNA transcripts and proteins encoded by the human genome (or by human pathogen genomes) have resulted in many new opportunities to diagnose and classify disease and to predict outcome in response to various alternative therapies. Every medical journal now seems to deal with novel genotype-phenotype associations or proposed targeted therapy based on analysis of the biochemical pathways that are altered in disease.

Pathologists are well positioned to keep up with the medical literature on the tests that their laboratory offers, as well as guiding use of esoteric tests available from outside laboratories. An increasingly important role is understanding and conveying

useful genetic information to clinicians. This consultative role extends to surgical pathologists since molecular assays are increasingly applicable to a wide variety of sample types including formalin-fixed, paraffin-embedded tissues, thus helping to reunite the two major subdisciplines of pathology—atomic pathology (dealing mainly with biopsy tissues) and clinical pathology (dealing with blood and other body fluids). Furthermore, quantitative DNA amplification assays are being used to monitor disease levels (eg, tumor burden or viral load) so as to inform how a given therapy is working. The exquisite sensitivity of molecular assays can allow us to predict early on (before complete drug resistance develops) that the therapeutic regimen should be altered.^{8,9}

Predicting Drug Efficacy, Optimal Dose, or Toxicity

Pathologists have traditionally been involved in diagnosis of disease, whereas clinicians select therapy. But novel laboratory assays are increasingly informative with regard to optimizing therapy, making it all the more important that each laboratory physician is well versed in validating, interpreting, and assuring quality of test results. An excellent example of the drive for quality improvement is a recent guideline jointly issued by the American Society of Clinical Oncology and College of American Pathologists on the performance of ERBB1 (Her2) assays for predicting trastuzumab (Herceptin) efficacy in breast cancer patients.¹⁰ Some of the early work developing molecular assays for Her2 was done at the University of North Carolina at Chapel Hill.¹¹ Another pharmacogenetic test with local ties targets the VKORC1 gene and predicts (at least in part) optimal dose and toxicity of warfarin (eg, Coumadin) therapy. The VKORC1 gene was first characterized in 2004 at the University

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of North Carolina in Chapel Hill by Darryl Stafford and colleagues.¹² The clinical importance of this discovery was quickly recognized so that, within two years, molecular tests for alterations in VKORC1 were being correlated with clinical outcome in response to warfarin therapy.¹³

Progress through Clinical Research

New molecular tests further expand our ability to predict as well as detect disease. This creates new challenges for policy

makers who will be asked to support the costs of these tests as well as fund the new knowledge necessary to optimally apply them. More backing for translational research is needed to support clinical trials that will ultimately define algorithms for managing patients based on molecular test results. The utility of our powerful new molecular tools is only just beginning to be understood, but already their promise is quite evident. **NCMJ**

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