



Professional Practice Guidelines for Genetic Testing Hyatt Regency Bethesda, February 1, 2006

Introduction

Today, more than 1,200 genetic tests exist, 900 of them clinically available. That number will continue to grow as genetic variations associated with an increasing number of conditions are identified. How can the medical community ensure that safe, valid genetic tests are accessible to individuals who need them? And how will health care providers know when to order, and how to use, a given test?

The Genetics and Public Policy Center (GPPC) has initiated a Genetic Testing Quality Initiative to address these and related issues. Working with stakeholders from a variety of backgrounds, GPPC is examining policies to ensure that tests are clinically valid, that genetic testing laboratories have the expertise and the experience to perform the tests accurately and reliably, and that health care providers have the necessary knowledge and tools to know when to order tests, to whom testing should be offered, and how results should be interpreted.

As part of this effort, GPPC convened a meeting in February to explore the lack of genetic testing guidelines for health care providers. During the meeting, representatives of more than two-dozen health care professional organizations gathered to assess today's genetic testing landscape and strategies for health care providers to effectively use genetic tests. At the meeting, organizations shared their perspectives and their approaches to developing practice guidelines, particularly those for genetic testing.

Genetic Testing Practice Guidelines: Defining the Challenges

Dr. Linda Bradley of the CDC began the meeting with an overview of practice guidelines. Practice guidelines help health care providers translate new research findings into practice. They can provide practical information about a genetic test's benefits and limits and help health care providers make informed decisions about appropriate use of the tests in practice.

Developing guidelines of any sort, however, is not a trivial undertaking. The guidelines that now exist are a mixed bag, reflecting diverse sources and development processes, consensus levels, cultural and political advocacy issues and developer interests. Professional organizations may draw different conclusions about the same subject depending on the review that was done or the assumptions that went into the review. Some guidelines lack a plan for implementation. Guidelines must also be assessed and updated on a regular basis.

When developing practice guidelines, an evidence-based approach is considered the "gold standard". Evidence-based reviews enhance transparency and credibility by minimizing bias and clearly linking recommendations to research. They can also be

very useful in identifying gaps in knowledge. Observational studies, as well as randomized clinical trials, can be incorporated into evidence-based practice guidelines.

One widely recognized approach to guideline development is that used by the U.S. Preventive Services Task Force, an independent panel of experts in primary care and prevention that systematically reviews the evidence and develops recommendations for clinical preventive services. The Task Force's methods work best for common, serious diseases where there are clearly defined outcomes and interventions, a substantial body of evidence, a range of study designs, substantial existing information on cost and cost-effectiveness, and slow changes in evidence.

Genetic tests typically do not meet these criteria, however, and pose considerable challenges to an evidence-based approach. Genetic tests often involve rare diseases, limiting the ability to gauge a test's predictive value or to document how effective an intervention might be. Many genetic tests are supported purely by descriptive evidence, with no clinical trials. Industry and patient interest groups often advocate for a test to be made available. And the ethical, legal, and social issues that characterize genetic testing generally have not been amenable to an evidence-based approach.

Despite these issues, genetic tests are rapidly emerging, and are expected to increase in number and complexity and move into primary care. Health care providers and consumers have a real need for timely and objective information about appropriate test use.

To address this need, the Centers for Disease Control and Prevention has funded a three-year pilot project called Evaluation of Genomic Applications in Practice and Prevention (EGAPP). The goal of EGAPP is to establish and evaluate a systematic evidence-based process for assessing genetic tests as they emerge from research into practice. EGAPP is pursuing a non-regulatory process, based on an independent, nonfederal, multidisciplinary working group. Designed to minimize conflicts of interest while integrating existing processes for evaluation and appraisal, EGAPP is evidence-based, transparent, and publicly accountable.

Partnering with the Agency for Health Care Research and Quality, EGAPP is evaluating tests used in specific clinical scenarios or as screening tests. EGAPP's methods include formally evaluating a test's analytic validity, clinical validity, and clinical utility. For three of four reviews currently in progress, EGAPP is using the Agency for Health Care Research and Quality Evidence Based Practice Centers, with a standard approach to analytic frameworks, key questions, search strategies, and assessments of study quality. This effort looks at potential outcomes ranging from morbidity and mortality to issues such as therapeutic choice and familial and societal impact.

EGAPP's current projects include 1) CYP450 testing for individuals with depression being treated with selective serotonin reuptake inhibitors; 2) colorectal cancer and HNNPC testing; 3) genetic testing for the detection and management of ovarian cancer

(in collaboration with CDC's Division of Cancer Prevention and Control); and 4) UGT1A1 testing in colorectal cancer patients treated with Irinotecan.

When a review is completed, the working group will publish a summary of the review and their recommendations. It is expected that other groups will take these evidence reviews and draft their own guidelines.

EGAPP's long-term goal is to develop a uniform process that can be used to evaluate genetic tests. EGAPP hopes to create an expectation by patients and providers that tests have undergone a certain level of review prior to being offered routinely in clinical practice. That, in turn, could stimulate test developers to collect and publish data in a standardized way, making it readily available to end-users. CDC also hopes this process will identify gaps in knowledge, facilitate research agendas, and enhance post-market surveillance of utilization, performance characteristics, and outcomes of testing.

EGAPP is, therefore, taking a pragmatic approach to the variable amount of evidence for genetic tests by summarizing what is known and not known about a given genetic test, what can be concluded with a reasonable amount of confidence about that test; and what information is missing. Health care provider organizations can then use this information to draft guidelines that health care providers can use to make care decisions.

Although EGAPP is initially evaluating tests already in the marketplace, the group plans to study more rapidly emerging topics. Ultimately, to be most effective, practice guidelines must address genetic tests before they enter the marketplace.

Health Care Provider Organizations' Experiences with Genetic Testing Guidelines

After hearing about the role of guidelines in clinical practice and the particular challenges posed by genetic tests, several health care provider organizations shared their perspectives on developing practice guidelines and their experiences with genetic testing guidelines.

American College of Medical Genetics

Reporting for the American College of Medical Genetics (ACMG), Mike Watson informed the group that ACMG issued its first laboratory guidelines in 1993. Rather than issue disease-by-disease guidelines, the College initially developed generic technology-based guidelines issues by the laboratory quality assurance committee. Thus, its laboratory standards and guidelines are broadly applicable to any genetic test and include recommendations for control, standardization, and related factors. ACMG has moved on to consider disease-specific guidelines and has a number in the pipeline that address clinical application as well as the testing.

In general, ACMG issues guidelines for its own specialty membership of medical geneticists. When the College looks at tests that affect other areas of practice, however, it uses a more multidisciplinary approach. For example, ACMG has pilot-tested

guidelines with family physicians in Minnesota and with pediatricians through the American Academy of Pediatrics on responding to positive newborn screening results. Ultimately, these guidelines will become point-of-care educational materials that accompany newborn screening test results. The idea is to resolve deficiencies both in genetic testing guidelines and in health provider education.

American College of Obstetricians and Gynecologists

With a membership of roughly 50,000, the American College of Obstetricians and Gynecologists (ACOG) represents 95% of board-certified OB/GYNs in the United States. When developing practice guidelines, ACOG conducts a formal vetting and approval process that includes the executive board. ACOG has a committee dedicated to addressing genetic issues.

Several factors may inspire ACOG to develop a new guideline. New and substantial scientific data is a primary driver. New professional and federal recommendations, such as an NIH consensus report, are another factor. Inquiries from ACOG fellows and members about a particular test being marketed are a third catalyst for guidelines. Other professional organizations, too, may inquire about guidance.

ACOG's practice bulletins are all evidence-based and reflect the level of the evidence available. Where data is scant, but fellows need guidance, practice bulletins or committee opinions are developed. Additionally, ACOG issues technology assessments and also distributes patient materials. Through a cooperative agreement with the National Center for Birth Defects and Developmental Disabilities at CDC, ACOG is able to reach other groups and state and local health agencies.

ACOG has just established a task force to examine broader issues related to genetics policy, education, and practice. They will consider a number of testing issues, including what criteria should be used in recommending a particular genetic screening test; interventions available; a test's sensitivity, specificity, and false positive rate; cost; resources needed for professionals and patients, and availability of genetic counselors. In addition, ACOG's task force will examine ethical issues, direct-to-consumer genetic testing, the College's working relationship with other groups, physician education, the sufficiency of ACOG practice guidelines and patient materials in genetics, and tracking and interpretation of laboratory results, and prenatal care guidance. This task force will submit their findings and recommendations to ACOG's executive board, which will likely propose new activities.

The College recently surveyed fellows to better determine how their members use ACOG guidelines. The survey found that ACOG's guidelines are a primary resource for OB/GYNs and that guidelines do dictate and change practices. A survey about the CF screening guidelines found that 40-50% of members were using the guidelines.

The CF screening guidelines are a good example of the ideal process for developing testing guidelines. In this case, the recommendations made by the NIH consensus conference were put on hold for two years while ACOG and ACMG developed the

guidelines and educational materials to support the program. Unfortunately, this kind of time lag before a test is widely marketed typically does not occur. The collaboration between ACOG and ACMG, however, is an instructive example of how two organizations can jointly develop guidelines for practice.

American Academy of Family Physicians

Nancy Stevens spoke on behalf of the American Academy of Family Physicians (AAFP). The strength of the evidence to support clinical practice decisions is the most important factor in deciding which guidelines to embrace. The Board of Family Medicine is updating board certification standards and emphasizing the use of high-quality evidence and randomized trials to support clinical decisions. Similarly, AAFP's journal is increasingly incorporating evidence into every published article. Family Physicians are interested in evidence for outcomes that matter to patients.

AAFP just completed a "Year of the Genome" during which it developed educational materials to convey complex genetic testing issues to its members. In providing services to families, fairness, equitability and access are issues that are of importance to family physicians. Family physicians are concerned about offering services that only some patients in the community can access, or services that patients do not want or need.

AAFP evaluates practice guidelines by considering who wrote a given guideline and considering what practices it might replace. If family physicians start doing this, what do they stop doing? And which is more important? Family physicians particularly need guidelines that clearly specify available interventions. Primary care providers are uniquely positioned to see the downside of genetic testing: diagnoses that leave families in agony, with little recourse for intervention. In fact, one challenge is helping health care providers determine when *not* to pursue a genetic test.

Challenges to Developing Genetic Testing Guidelines

After hearing from several organizations about their perspectives on and experience with genetic testing guidelines, meeting participants discussed a number of issues regarding genetic testing guidelines.

An issue faced by all organizations is how much evidence is needed before drafting a guideline. This is especially problematic for genetic tests. Of the 900 genetic tests available today, many are for rare diseases. And although emerging tests are directed toward more common conditions, such as diabetes, testing will most likely sort people into subtypes, each of which may be uncommon. So in that sense, the number of people affected by "rare" genetic diseases will grow. Evidence about rare disease testing may be limited, requiring the use of expert opinion, observational study, or case reporting.

Additionally, interpreting genetic testing results will be more complex as research advances. For example, a patient's overall risk for a particular condition may be determined by many different genetic markers acting together. Or, as is the case with the cystic fibrosis gene, there may be many thousands of variants possible in a given

gene. We may know very little about some of these variants, making it difficult for health care providers to advise patients about the likely pathological outcome associated with a particular gene sequence variation.

There is usually no bright line neatly separating clinical investigation from clinical testing. In rare diseases clinical investigation is ongoing as each patient brings new information to the clinical picture. Complicating matters further, when a genetic test becomes promising, its use rapidly spreads out of the hands of those who initiated the research and clinical investigation to determine the genotype-phenotype correlation or the performance characteristics of the test becomes more fragmented.

Cardiovascular disease is a good example of these difficulties. The American College of Cardiology and the American Heart Association have drafted practice guidelines for more than 20 years. They grade evidence on an A, B, and C scale. Randomized trials are considered the gold standard and are rated “A”, followed by nonrandomized studies and registry data as “B,” and, finally, expert opinion as “C.” At least two randomized trials are needed to warrant a class 1 recommendation, meaning that health care providers should do it. Genetic testing for cardiovascular disease poses considerable challenges, including the lack of established genotype-phenotype relationships. Hundreds of genes have been linked to heart health and many are large with scattered mutations. Subtle variations confer an unknown level of risk.

Participants pointed out that this uncertainty helps explain why relatively few physicians in the U.S. order genetic tests today, aside from those who are medical geneticists or working in areas of medicine where genetics plays a defined role. Although clear-cut genetic tests, such as for sickle cell disease, are routinely ordered, health care providers wrestle with more nuanced tests and express some confusion about what level of certainty can be obtained from a genetic test. Cost is another factor in deciding whether to order a test.

Establishing a solid evidence base takes a long time, however, and some genetic conditions will never be subject to randomized clinical trials. As a result, some organizations have taken alternative approaches. For example, the National Cancer Institute’s Cancer Genetics Editorial Board reviews what evidence is available and writes a summary of the literature for the primary care provider.

Similarly, the American Medical Association does not write guidelines, but the Physicians’ Consortium for Quality Improvement at the AMA examines guidelines from specialty societies and medical associations. Although randomized controlled trials are the gold standard, they are not always available. So AMA looks for transparency of evidence in deciding whether to support the guideline and recommend it to its members.

Because of the lack of the gold standard for clinical data, the American Society of Hematology has only published three sets of guidelines, all now out of date. Rather than develop more guidelines, the organization plans to develop an annotated guideline directory.

In an attempt to generate evidence-based reviews, some organizations have looked to outside consultants. The American Gastroenterological Association shared their experience with contracting reviews out to evidence-based companies at prices ranging from \$10,000 to more than \$50,000 per guideline. They had mixed success. Their members who were responsible for authoring the guidelines felt compelled to repeat much of the review and read all the literature, so no time was saved.

Time and cost are major challenges to many of the organizations represented at the meeting. Developing guidelines is a costly enterprise. And even if part of the work is contracted out or the organization has staff to help move the process along, much of the work must be done by busy volunteer members. It is not uncommon for guidelines to take 18 to 24 months to develop.

Developing and Implementing Genetic Testing Guidelines: Tools for Health Care Provider Organizations

Participants were asked to comment on what kind of genetic testing guidelines would be useful to their members and what would help their organizations develop and implement them.

According to the participants, a critical requirement for clinicians is that guidelines be accessible at the point of care. Guidelines that are written as a “just in case” scenario end up getting shelved. Clinicians need to know where to find a guideline when they need it. One approach might be a database for documents. Linkage to a site such as GeneTests is another option.

Patients should also have access to information. Guidelines in a waiting room can be helpful, particularly for more common conditions.

Guidelines should be kept simple. For example, ACMG has dropped the use of “fact” sheets for what it calls “act” sheets with clear recommendations for health care providers to follow. Guidelines should also address how testing will make a difference in patient management.

Guidelines should also include information on when a referral to a genetics expert is recommended. Physicians need guidance to know when test considerations may be too much to handle in a brief 15-minute visit and when specialists are needed to help figure out whether a given test is appropriate.

For organizations, the amount and quality of the evidence for genetic tests is the major obstacle to developing a statement, opinion, or guideline. Population-based studies are lacking for many newly emerging tests and these studies are costly and time-consuming to run. However, clinicians need to know when and how to use genetic tests. Participants felt that practice guidelines should assess the quality of the evidence

available so health care providers know what is known about a test, its limits, and what gaps there are in knowledge. Projects like EGAPP can help fill provide that information.

Time, money, and expertise also top the list of issues facing organizations in developing guidelines. Guidelines are expensive to develop, take a long time, and there may be limited expertise within the membership. And guidelines must be updated on a regular basis or they quickly become obsolete – again taxing limited resources in an organization. Resources to fund guidelines development would help ease this burden.

Collaboration between organizations in developing guidelines can help maximize limited resources. AMA has developed a process for bringing together a consortium of the relevant medical societies when a gap between clinical practice and the scientific data is identified. The end result is a standard endorsed by all the organizations. Although it requires substantial negotiation, the model works.

Participants also felt that because genetics is a rapidly evolving area and guidelines are difficult to draft, it would be useful to create uniform procedures that can be easily replicated and adapted in future circumstances. This “gold standard” for genetic testing guidelines could simplify future guidelines development.

Summary/Conclusion

Genetic testing is a rapidly emerging discipline that will affect more areas of medicine. Given that many genetic tests are making it into the market without a great deal of evidence-based studies, guidelines can help health care providers understand the uses, and limitations, of genetic tests. The goal is to guide the physician today about whether it's appropriate or not to do a test, and under what circumstances. In addition, guidelines should highlight gaps in the knowledge that need to be addressed. The consequences of failing to provide formal guidance on rapidly emerging genetic tests could be significant. Millions of patients suffer from complex diseases for which genetic tests could become available. Resources are needed for health care provider organizations to increase the number and quality of guidelines.

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