Evaluation of Genomic Applications in Practice and Prevention: Implementation and Evaluation of a Model Approach
Linda Bradley, Ph.D.

I next want to turn to Dr. Linda Bradley, who is going to give us a presentation. It was done really at the request of the committee from the last meeting. We discussed the need for some sort of mechanism for assessing when the evidence base is sufficient for establishing clinical utility and making coverage decisions, as well as a mechanism for addressing gaps when there is no real evidence to support coverage necessarily for genetic technologies. It was brought to our attention that the EGAPP project, Evaluation of Genomic Applications in Practice and Prevention, which is really the next step in the ACCE process Muin had identified for us the last time, really would be a potential model for us to consider.

So at our last meeting we requested a presentation on the EGAPP project so that we can assess whether it's something that we want to incorporate, either some of its work or all of its work in our coverage and reimbursement report.

So with that, I'd turn to Dr. Linda Bradley for her to brief us on this project.

DR. BRADLEY: Mr. Chairman and members of the committee, we really want to thank you for allowing us this opportunity to provide a brief review of a recently launched model project by the CDC.

It's important to point out that this project does not represent a new concept as much as an evolution of ideas and methods dating back to the 1997 report of the Task Force on Genetic Testing. As most of you know, this report emphasized the need for evidence-based review of new tests during transition from research to practice, and for a coordinated process to collect data in pre- and post-market periods. It also described assessment criteria, analytic validity, clinical validity, and clinical utility in the context of genetic tests.

SACGT, through its subsequent deliberations, affirmed the task force assessment criteria and added emphasis on ethical and social issues as a component of evaluation. SACGT also encouraged collaboration for data collection and education and made other specific recommendations, among them that CDC play a coordinating role in data gathering and analysis.

In 2000, CDC took a step in addressing the need for pre-market review of data by funding a cooperative agreement with the Foundation for Blood Research to evaluate the ACCE model system, which has been referred to here. ACCE, as most of you know, simply reflects the components of evaluation laid out by the task force and SACGT. The ACCE process is based on the premise that you first define the specific disorder or phenotype to be tested for, then the test, and the setting in which the test is to be performed -- for example, diagnosis or predictive testing -- then an analytic framework -- in this case, sets of targeted questions can be used to systematically review evidence on each component -- analytic validity, clinical validity, clinical utility, and related ethical, legal, and social implications.

This process was designed to assess availability, quality and usefulness of data on DNA-based tests for disorders with a genetic component. ACCE differed from some other standard methods, and some characteristics of the ACCE process included a broad focus. ACCE aims to provide a first look at all the available data, not just the published literature, and also reviewed all evaluation components, including analytic validity.

ACCE used an ad hoc approach to grading quality of evidence versus a more structured approach in order to extract maximum information. ACCE reports included review, analysis and integration of data, and identification of gaps in knowledge and the data needed to resolve them. An objective of ACCE was not to suggest policy or make recommendations but to provide complete, accurate, up to date summaries in formats useful to a range of audiences.

Five ACCE reviews have been posted for comment, and you can see the titles here. We've learned a great deal from this process. I think two points that I would raise is that we learned, as I expected, that this information is eagerly received. We've had rapid uptake and application of the evidence developed. For instance, data developed for the CF report was utilized in preparing the 2004 revision of ACMG's mutation panel recently published in Genetics and Medicine.

We've also learned that in moving beyond the published data, we can uncover new and useful information. For example, in the absence of any other data, new estimates of analytic validity in the CF, HFE, and Factor V reports were derived from external proficiency testing data. Though not an ideal approach, it provided a reassuring snapshot of U.S. performance as not perfect but really pretty good. It also highlighted situations in which understanding of analytic performance could impact how a test is implemented in some settings.

So as we considered the next step from a public health perspective, the question really was what might a non-regulatory process for evaluation of genetic tests look like? Well, certainly evaluation needs to occur at two key points. The first is transition from research and development to clinical practice, ideally before a test enters widespread use. It should include systematic review of evidence on clinical validity, and with the rapid development of new complex technologies with very little performance data, systematic review of analytic validity needs to be part of this process, too. In some cases, certainly a first step.

Assessment of risks and benefits, while focused on outcomes, needs to include more, including consideration of resources for the testing process, counseling and education, the need for pilot trials, and cost-effectiveness analysis. We need to identify more effective approaches for assessing ethical, legal, and social implications of testing, and there needs to be a plan for dissemination of the information developed to all relevant target audiences.

The second key point for evaluation is in the post-market period to assess performance in practice and public health impact, beginning with very basic information that we currently lack on utilization and access. We need to be able to document problems and successes with implementation and fit with health care delivery systems, and we need to be able to update the knowledge base after the test has been in practice.

Evaluation of Genomic Applications in Practice and Prevention, or EGAPP for short, is a three-year model project. The goal is to establish and evaluate a systematic mechanism for pre- and post-market assessment of genetic tests and other genomic applications in the U.S., hopefully one that can be sustained in some form beyond this model project. EGAPP is a public health initiative with a population focus, and like ACCE the objective is a first or early look at new tests and technologies to determine what is known and to identify important gaps in knowledge.

The project plans to utilize information and recommendations developed through this and other advisory processes, as well as the knowledge gained from the ACCE project. Partnerships and collaborations are vital to the success of this project. Examples include existing evidence-based processes -- for example, the Agency for Healthcare Research and Quality, the U.S. Preventive Services Task Force, evidence-based practice centers, and the CDC's Task Force on Community

Preventive Services. We began talking with these groups early in the planning process, and ongoing discussions have been helpful as we sought to define the scope of the project. These and other agencies and organizations, many represented here today, will have a continuing role in advising the project.

We're also interested in collaborations with the international health technology assessment community, and we are developing very productive contacts with groups in Canada, the United Kingdom and the Netherlands who are involved in similar projects.

We're also interested in relationships with other projects and initiatives. There are certainly too many to cover here, but just to mention a few, with regard to quality assurance and improving laboratory practice, CDC's Division of Laboratory Services is currently developing a process to obtain and distribute quality control materials for genetic testing to labs, researchers, and the diagnostic industry. CDC Division of Laboratory Services, in collaboration with Emory University and the National Institutes of Health Office of Rare Disease, held a May meeting on promoting quality laboratory testing for rare diseases. Outcomes included the formation of this laboratory network and planning for a second conference to move into implementation of the recommendations developed. There are also a number of other initiatives related to policy, programs and services, and research.

The process aims to provide a clear linkage between the evidence developed and the recommendations made, minimizing conflicts of interest in the review process, but keeping in mind some very good advice from Al Berg of the University of Washington and the U.S. Preventive Services Task Force, that evidence-based requires that the linkage be transparent, explicit, and publicly accountable, not that it be objective. The project will develop a plan for effective dissemination of information to target audiences.

The question of are genetic tests different or exceptional comes up here again, and whether or not genetic tests are exceptional or different in other ways, methods for assessment of genetic tests have basic similarities to those used for other tests. However, there does seem to be an increased awareness and concern about genetic testing and a public perception that it is different, and I think the compelling testimony you heard this morning about potential harms makes that very clear.

EGAPP is focused on genetic tests and other genomic applications, responding to the demand from health care professionals, policymakers, and the public for a source of reliable and reasonably objective information about appropriate use of genetic tests. However, the knowledge gained about successful evaluation approaches, methodologies and infrastructure should certainly be applicable to assessment of other tests or emerging health care technologies.

Technical and logistic support for the project will be provided by RTI International, a non-profit contract research organization, and this contract was awarded in late August. RTI brings to the project a wide range of scientific expertise, but one resource we feel is very relevant to this process is the RTI University of North Carolina Evidence-Based Practice Center.

So the central element of the project is the working group, independent, non-federal, multidisciplinary, made up of 10 to 12 experts from fields such as health care, genomics, epidemiology, health technology assessment evidence-based review, public health, health economics, and potentially others. Two in-person meetings are planned in year 1, three meetings in each of years 2 and 3.

Proposed roles of the working group -- and this is the concept -- is that the working group would first develop an organizational plan defining protocols for evidence-based review and development of recommendations. The working group will certainly consider input from stakeholders, develop criteria for selecting topics, and then select and prioritize topics for review. When a topic is selected, the working group will request that RTI commission or conduct an evidence-based review. The working group will ensure appropriate review of reports and develop recommendations based on the evidence. They will consider needs and strategies for post-implementation monitoring and data collection studies and will take part in evaluation of the project.

Stakeholders, very important. The project will identify and engage a wide range of stakeholders. The primary focus for this project is health care providers and consumers. A secondary focus is policymakers and health care payers and purchasers. RTI will conduct needs assessments and set up a process for ongoing dialogue with stakeholders. Basic information that will be sought from stakeholders in the early parts of the process include recommendations on specific topics for immediate consideration by the working group, an also on the content and format of the information needed by the stakeholders and useful from their perspectives. Stakeholders will also be a source of content experts, and their roles will include technical assistance, review of reports, and involvement in development of informational messages for key target audiences.

This just provides sort of a very simplistic overview of how the process might work, beginning with the working group and a large group of stakeholders. The stakeholders provide input on topics and priorities. The working group makes decisions on their criteria, selects a topic, and requests an evidence-based review. I put the little RTI on there just to remind you that as we go through this, RTI underlies this process in terms of making these things happen. The request will go to an evidence practice center where systematic review will be done that identifies the gaps and the data needed to fill them. Then that information comes back to the working group for appropriate review and comment, and then they will prepare recommendations, reports, and disseminate these materials to the target audiences of consumers, providers, policymakers, and purchasers and payers of health care, with an opportunity again for stakeholder input on the development of these targeted informational messages.

Under certain circumstances, the working group may decide to refer a topic out to other groups for further appraisal, for instance the U.S. Preventive Services Task Force, and they will be involved in developing collaborative projects for pilot data collection with stakeholders.

The first year of EGAPP really begins, obviously, with process development, recruitment of the EGAPP working group, two organizational meetings to follow, and the development of the working protocols by the working group. There will be a methodology conference which I'll come back to in a moment, preliminary needs assessment activities, two small pilot data collection studies, and an evaluation that's based mainly in this first year on process.

In years 2 and 3 we'll see continuing support of the working group, commissioning and oversight of evidence-based reviews, four full reviews in these two years, and three what we're calling fast track reviews. There will be dissemination of reports, working group recommendations, and informational messages. There will also be ongoing dialogue with stakeholders who will be involved in the development of these informational messages for target audiences, as I mentioned, and who will provide feedback on the value of the process and the products.

There will be two pilot data collection studies in each of those years, and there is a comprehensive plan to evaluate the success of the process, the quality and usefulness of the

products, and the impact or value of the project overall. At the end I think we really want to be able to consider mechanisms for sustaining whatever we can validate from this process for evaluating genetic tests.

So why talk about methodology when there are standard and sometimes gold standard methodologies that are being used? Well, it's been pointed out, and I think many people have seen this, that the standard process and methodologies -- for instance, the U.S. Preventive Services Task Force -- may not be as effective when we're dealing with conditions that are uncommon to rare, where interventions and clinical outcomes are not well defined, where the evidence base is limited, and that obviously is going to be the case very often here, and where there are problems with study design or quality of data. We have already noted that ethical, legal, and social issues are less amenable to the evidence-based approach. We need to think about that. We need to consider the influence of advocacy, which I'll talk about in a moment.

So the plan that we're working very hard on right now is to have a methodology meeting in July of 2005 to bring together a relatively small group of U.S. and some international experts in evidence-based review, health technology assessment, epidemiology, genomics, and health economics, particularly those having experience in evaluation of genetic tests, for a working meeting that focuses on elements of evaluation, selecting and defining topics, developing an analytic framework for evidence-based review, literature searches, grading quality of evidence, and translating evidence to recommendations.

We will also address questions about the use of unpublished data sets and the gray literature. We'll consider how to deal with proprietary data. We'll seek information and agreement, in some cases we hope, on minimum standards for determining when a test is ready to move into clinical practice, how much information is enough, what is a reasonable threshold for quality of evidence for genetic tests, is the threshold different for different evaluation components such as analytic validity and clinical validity, and how do we optimize the quality of data to be collected in the future. The results will be used to inform the EGAPP working group deliberations and will be published, we hope.

We feel that the timing is right to use what's been learned and to move forward from ACCE. Certainly the situation is not going to become simpler. More tests are certainly coming, testing will move into primary care, and health care providers and the public need a source of reasonably objective advice about appropriate use of tests. In the short term, whatever is learned will be useful and is likely to provide information to address questions posed by this committee related to oversight of genetic technologies, coverage and reimbursement, access, potentially public awareness and understanding.

In the long term, we hope to create an expectation that a certain level of review will occur prior to acceptance into routine practice. We hope to facilitate standardization of data collection formats. We hope to identify specific gaps that may stimulate research, and we hope that what we learn will support the need for postmarket review of testing practices, clinical guidelines, and recommendations based on new information.

Thank you for your attention, and I'd be happy to answer any questions you might have.

DR. TUCKSON: Any questions?

MS. MASNY: My question is, is your process for review the same process as the methodology meetings that you're going to have, or are they two separate types?

DR. BRADLEY: Yes, that's a good question. We know that the standard methodologies that are being used in many evidence-based review practices are going to be problematic with genetic tests because we have a lack of quality evidence in many cases. So what we're hoping to do is to have this methodology conference in order to look at different ways that we might approach some of these issues. What comes out of that methodology conference or meeting in January will certainly inform the working group's deliberations on how they want to proceed, but it will be separate.

DR. TUCKSON: Have the requests gone out, the letters inviting people to the meeting in January? Do we have a sense of who you're inviting?

DR. BRADLEY: We're certainly working on a list, and I think we're about to make final decisions in the next week or so. It's been a tortuous process trying to decide on who are the right people to invite to the meeting, as you can imagine.

DR. LEONARD: This may sound like I'm self-serving, but it's a little disturbing to me to see in the stakeholders list laboratories. Since you're talking about genetic testing, I liken this to investigators who want to study breast cancer or lung cancer and they have no knowledge of what those tumors are, and so they treat them all the same. You really need an intimate knowledge that breast cancer comes in lobular and adenocarcinoma forms and stuff, what you're actually talking about.

So to see the laboratories that are doing this testing as a stakeholder rather than an active participant in this process informing the group as to the details of the testing and what it means to do it one way versus another way and applications is a little disturbing to me.

DR. BRADLEY: Well, in fact, they will be filling just that role. As I told you, we see a number of roles for stakeholders. It's a very broad group in there, and I appreciate what you're saying. But, in fact, they will have a very important role in this process as experts and will be involved in providing technical assistance to the working group, doing review of reports that come out in their preliminary stages so that the working group can be sure that the evidence is accurate and complete and there aren't issues that they don't understand. I think, very importantly, we're hoping to get guidance from this group about what priority topics are and why, and also I think a very, very important role, especially for laboratorians and people in the genomics and genetics communities, is at the other end of the process. Once you have an evidence-based review, the evidence has been collected and it's been presented, helping to develop appropriate informational messages to go out to these different target audiences.

So I think, in fact, that it's a very big role of stakeholders, and I think obviously laboratorians are going to be a big part of that.

DR. TUCKSON: Thank you very much.

Cindy, I think we can move on.