

**Update on Evaluation of Genomic Applications in Practice and
Prevention (EGAPP) Activities**
Linda Bradley, Ph.D.

DR. TUCKSON: Well, Linda, we're happy that you're going to tell us something about -- can I say EGAPP?

DR. BRADLEY: You can.

DR. TUCKSON: As opposed to EGAPP.

(Laughter.)

DR. TUCKSON: You've got to have a rule that says that you say either the first letter and then the whole thing or the whole thing, but you can't have combinations.

The Evaluation of Genomic Applications in Practice and Prevention efforts. Now, your goal is to develop a coordinated process for evaluating genetic tests and other genetic applications that are in transition from research to clinical and public health practice.

Our first report on this was from Muin Khoury back in '05 when the program was about a year old, back in January of '05.

We're very pleased that you, with Muin, are deeply involved in supporting the work of EGAPP and have agreed to provide an update on this important program. Thank you very much.

DR. BRADLEY: Well, thank you, and I want to thank the committee for inviting us to come and provide an update on what's been going on because a great deal has gone on since the last time we spoke with you.

I feel like I should take off my ex officio hat and put on my EGAPP hat, but I'm not as prepared as Deb Leonard.

Just to give you a little bit of basics on EGAPP, for those of you who aren't as familiar. It's the CDC-funded pilot project that began in October of 2004. It is non-regulatory in its approach, and it's focused around an independent, non-federal, multidisciplinary -- I've heard that word before today -- working group.

The goal is to integrate existing processes for evaluation and appraisal. In other words, we didn't want to start over. We wanted to take all the knowledge that had been collected through the Task Force for Genetic Testing and SACGT and SACGHS and all the other processes like the U.S. Preventive Services Task Force and the Community Guide and see if we could come up with a methodology.

Another important objective was to minimize conflicts of interest and essentially to develop and implement an evidence-based, transparent, and ultimately publicly accountable process.

This is the more updated version of the goal. That was our original planning goal that you just read, and it hasn't changed much. But to establish and evaluate a systematic evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to practice.

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It's important to throw the caution sign out, I think, particularly at this point in where we are here in that EGAPP's methods are still under review. We're still in the process of development. We're starting to move into the product phase, but most of our products are not yet final. So what I'm doing here is presenting from CDC's perspective a description of a work in progress with a great deal of work, including an important stakeholder evaluation, to come.

The working group, as many of you know, was established in May of 2005. The 13 original members are still there. I did put a list of the working group members and the steering group members on the back of the handout and was kind of horrified last night to notice that in the process of doing that, I lost two of the working group members, and we don't like to lose them. So just to point out that James Van Allen and Carolyn Sue Richards are also very active members of this group.

The group has met six times. They meet for a day and a half in a forum very much like the one you're sitting in. As I'm sure all of you can relate to, they have had countless subcommittee teleconferences. They have three standing subcommittees: topics, methods, and products. In addition to that, each of the members sits on topic-specific groups that are working on specific evidence reviews, and some of them now are actually also working on writing teams. So they're very busy, as I'm sure you can relate. The next meeting will be at the end of January in 2007.

In terms of support, we've relied very much in the first two years on an interagency agreement with AHRQ so that their evidence-based practice centers could conduct five of the reviews that are part of this pilot project.

In terms of staff and consultants, in the CDC National Office of Public Health Genomics, where I'm located, we have a support staff there that works quite closely with the working group. We also have a number of technical consultants and contractors who work with us.

And our centers for genomics and public health that are funded through CDC have also been very helpful in thinking about some of the stakeholder issues and talking with us about dissemination and translation of products. In fact, the University of Michigan center has set up a stakeholder advisory group on EGAPP that started meeting a couple months ago.

The steering committee which is an interagency, mainly federal steering committee, although we've added some new members now, was a group that was incredibly critical in the early development of EGAPP, was involved in many of the early planning discussions, and certainly was totally important and involved in the selection of the working group members. We are now moving into sort of a next phase. We went into sort of a phase where we were beginning a lot of reviews, but we didn't have any products and we were just sort of working forward. I think now that we're moving into the product phase, we're sort of rejuvenating that group. We've added some new members, replaced some wonderful members who have rolled off the committee. Alan Gutmacher was just a tremendous help in the beginning, and Suzanne Feetham, who's since retired from HRSA.

But we're going to start meeting again quite intensively with this group to look at the review of where we are now, the processes and the products. We want a lot of input from them on the evaluation phase which starts this spring, and really now that we're starting to produce some products and starting to get a feel for this process, begin to consider again how this becomes a sustainable process, which any of you who know Muin Khoury know that this is a very important part of this process.

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In terms of the scope of topics for the pilot phase, we decided not to try and take on the whole world of genetic testing, but rather to try and focus a little bit and to begin with applications recognized as important or more common -- there are some examples there: tests used in a clinical scenario, screening tests -- but tests with a potential for a broader population application and, therefore, a broader public health impact. Also, when they choose tests, they're also looking to maintain a portfolio of tests that can challenge the methodologies that they're trying to develop. So they have sort of two main reasons for prioritizing topics.

The approach they're taking is really to start with the lessons from the ACCE process. I use that acronym to mean a couple of things. Certainly from the Task Force on Genetic Testing and the SACGT, who really laid out the analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications as components of review -- and we are carrying on from the ACCE project which also did a formal assessment of analytic validity and relevant ethical, legal, and social implications, which at least the analytic validity part has not really been a component of most evidence reviews up until this point.

We're also still using questions to organize collection of information with a focus on attempting to synthesize the information and find out where the gaps are.

We're also integrating from existing evaluation processes a number of, I would say, gold standard methods. We started with reviews from evidence-based practice centers because of their credibility and their experience. We're using formal analytic frameworks with key questions and explicit search strategies. We're assessing the quality of individual studies and the strength of evidence, providing recommendations with a clear linkage to the evidence. I think that's really important for others to follow behind and see how they drew the conclusions that they did. And obviously, to identify the research agenda.

I think EGAPP has tried to do some newer things and that is, because there's such pressure of these products and tests moving into clinical practice so quickly, to attempt shorter time frame reviews that are targeted and practical, to focus on hard medical outcomes, morbidity and mortality, but also to consider specific family or societal outcomes when appropriate. They've begun to look at the usefulness of modeling and have commissioned some modeling in a couple of the evidence reviews, and it's become clearer and clearer as we move forward, that really it's going to be necessary to address cost effectiveness in a formal way as well.

The products of the group are, obviously, evidence reports that come from AHRQ or from other contractors in some situations. There is a peer review of these drafts as part of the process. When they're released by AHRQ, they're posted on the Web, and then under usual situations, a summary of the evidence is then published.

The recommendations, based on the evidence developed, are being written by the working group. There will be peer review of these drafts as well. We are planning publication and posting. What we're hoping for, in situations whenever it's possible, is concurrent publication of the evidence summary along with the recommendations. We have been talking with our friends at Genetics and Medicine who are very interested in working with us on this.

The publication of methods and evaluation, obviously, needs to follow very quickly, and that will include the results of the stakeholder surveys.

Just to give you an idea of the topics that are in the pipeline right now and where the different topics are, there was an EPC evidence report released by AHRQ a few weeks ago now. This

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particular topic was actually funded by CDC's Division of Cancer Prevention and Control who asked for a partnership with EGAPP to look at the results. It was more of a horizon scan on genetic testing for detection and management of ovarian cancer. The working group is currently working on a draft recommendation that's focused on proteomic tests, and that draft is in internal review.

There's also an EPC evidence report that's complete and pending release on testing for cytochrome p450 polymorphisms in adults with depression treated with SSRI drugs. And there's also a draft recommendation that's in internal review with the working group right now.

Draft reports. Testing for hereditary nonpolyposis colorectal cancer in newly diagnosed colorectal cancer patients and family members. This is a final EPC report in development. The draft review has been reviewed and has gone out for peer review, and they're now working on the final report.

And UGT1A1 mutation analysis in colorectal cancer patients treated with irinotecan. This is a non-EPC review that is quickly moving toward peer review as well.

Topics recently selected. The impact of gene expression profiling tests on breast cancer outcomes was awarded to an EPC in late October, and that's underway.

Screening for CYP450 polymorphisms to predict response to pain management with codeine. This request for proposals is in development. That will also be an EPC review.

And the use of genomic profiling to assess risks for cardiovascular disease and identify individualized prevention strategies is a review that's in planning currently.

I think it's important to point out that EGAPP is not alone in this, for sure. It's one of a spectrum, I think, of non-regulatory initiatives for translation and evaluation of genetic tests, and I think it's important to remember that all of these groups are learning from these processes and that all of this information really needs to be collected and considered. Certainly the U.S. Preventive Services Task Force has done two reviews on genetic topics, BRCA testing and hereditary hemochromatosis.

There are a number of technology assessment groups working in the country. This is not a comprehensive list. This is just to give examples. The American College of Medical Genetics Foundation recently funded a rapid ACCE review on warfarin and CYP2C9 and VCOR.

The Blue Cross/Blue Shield Association Technical Evaluation Center has done a couple of very nice reviews.

Intermountain Healthcare is working on internal reviews using the rapid ACCE format.

You heard from the CETT program, which is more of a translation program, but certainly looks at some of the issues of translating and the quality of testing for these rare diseases.

HRSA had a very interesting meeting a few weeks ago on evidence-based evaluation and decision processes for the Advisory Committee on Hereditary Disorders and Genetic Diseases in Newborns and Children.

And I think there are a number of funded projects, and I mentioned one that I know about because it's CDC-funded, and that's the Genetic Alliance project on access to credible genetics resources network.

For EGAPP, I think the next steps are very much about maintaining momentum. It takes a lot of work to get a process like this started and to continue to use what we're learning from each review and roll that into what we do for the next review. The working group is, obviously, spending a lot of time thinking about these issues.

Publication of methods and what's been learned, obviously, is going to be very important for the group to publish what their experience has been.

Publication and dissemination of products. Obviously, we need to make sure that these evidence reports and recommendations are widely disseminated to professional organizations and health plans and a number of other groups.

Initiating a project evaluation. We really need to know what is the value and the impact of these kinds of products and how they're being used and are they reaching the folks that we're trying to reach. So we're going into an evaluation phase that will take a year and that will involve a lot of stakeholder surveying.

Then there's a step that we feel is very important that I think is going to be very challenging, and that's the translation of the knowledge gained from the evidence reports and the recommendations into informational messages that are for different target audiences and finding ways to appropriately get that information out.

This is sort of a happy announcement. The EGAPP Working Group is very comfortable with their relationship with CDC, but has also made it very clear that they want to emphasize their autonomy in terms of the decisions that they're making for the recommendations. So one of the requests that they made of CDC was an independent website. This turned out to be something more of a high hurdle than we anticipated, but we actually got formal notification of a waiver approval yesterday, and so we should be able to get this interactive website up by the end of the year. And we're very excited about that because I think it's going to allow us to enhance interaction with stakeholders, which has been more limited than we had hoped. We'll allow the working group to post topics lists, their methods and process, evidence reports or links to those reports as they come out, obviously, to post the recommendations, and to post informational materials as they're developed. It will also allow the group to solicit feedback and to get input from stakeholders on suggested topics for review. So egappreviews.org coming soon.

I think that the real challenge that both the working group and the steering committee and CDC as well will be thinking about going into the next year is really how to build a sustainable process. Where do you go with a process like this? Obviously, we're going to learn a lot about methods and what works and what doesn't and the quality of information that exists and all of those things.

But I think there are other questions that need to be addressed, and I think one of them certainly is the future composition of the working group. We have a very committed group that's committed for the pilot study, and they've all stayed with us. This group was put together very much with a science focus. The first year was spent almost entirely thinking about methodology and approaches and looking at a very dispassionate process that avoided pretty much any stated position either from the advocacy or the criticism point of view.

But now, as we move into a policy phase, I think there's a need to think about what's the role of consumers and industry and other folks in a group like this.

Do we expand the scope of topics? Certainly the methods that are being developed could be used to look at any kind of emerging technology. Right now, we've been very focused on sort of the population-based applications, but should that change?

Should we go on and evaluate with a broader range of stakeholders? We're really focusing on health care providers and pairs, policymakers, and consumers on this first round, but should we move out from that?

And how do you support such a sustainable process? What's the role of the different Health and Human Services agencies and what's the role of public-private partnerships?

And then I think something that we think is very important is the need for a postmarket data collection process of some kind because we've really got to understand how these tests actually work out in the real world. So we figure we have enough to do for a while to keep us very busy scratching our heads.

I can't tell you how many people it takes to do something like this. So I really want to give a lot of appreciation to the EGAPP Working Group. What a hard working group they are. Our wonderful partners, the people on the steering committee, our interagency partners have really been great supporters, and Gurvanet, who we just bug to death, and our Centers for Genomics and Public Health who really have also become very invested in this process. My wonderful staff. We have a tremendous group of technical consultants you can see there, including Deb Leonard, who have done a tremendous amount of work for us, and our technical contractors who we could not live without.

DR. TUCKSON: So remember all the stuff we went through painfully about clinical validity?

DR. BRADLEY: Yes.

DR. TUCKSON: Show us how what you're doing relates to that activity. And also, are people like CAP the end users, do you envision, of the kind of stuff that you're going to be producing? Because to me, what you just presented is extremely optimistic-making in my heart.

DR. BRADLEY: Mine too, but I hope we're right.

I would like to point out that we have a working group member in the audience. So, Joan, feel free to jump in here.

I think there are a couple of points that come to my mind, relative to your question, from what I've listened to for the last two days. I think one of them is that all of these groups, CAP and ACMG and all the professional organizations, and CLIA and FDA -- I think everyone benefits from the information that's developed by a process like this. I think how they use it is going to be the interesting thing that we need to learn about. And how useful is the information? Are we getting the right information? Is it presented in ways that are useful? We're really trying to take that practical approach. I know the working group spent a great deal of time talking about that.

This is me talking now, Linda Bradley, clinical geneticist. But analytic validity I think is something that really seems to keep cropping up as this problem, and I think it is part of what

every laboratory does, to do the basic validation of a test. But if you think about the numbers that most of those labs are able to generate and how wide the confidence intervals are and what they know about these tests, there is a need also for aggregate data, for someone to take a dispassionate look at studies from different groups and say, okay, overall, how well do these tests perform in practice?

And I think then you get to clinical validity, which is really the crux of the matter. Are we getting to what we think we're getting to when we run these tests, and then how useful is that information? How is it going to impact management and the outcomes for the patients and potentially, in some cases, their families, as with HNPCC.

So I hope that they will be able to show where the gaps are with these different examples that we've chosen to test the methods, what does the data look like, what's the quality of the data, how much data was out there. Where are the gaps? How big are they? Can they be easily resolved? Are they really problematic? Those are the types of issues that we're trying to get to.

DR. TUCKSON: Your other challenge is going to be scale. So let's just say this is wildly successful. I mean, at the end of the day, how many of these things can you do and what are the economics? Is that the legitimate role of government, or are you proving a process that then gets reproduced?

I think it's extremely important for you all to be wildly successful. My God, if you are successful, think about all the hassle you take out of stuff, moving from bench to bedside on these kinds of things and speeding that up and giving an analysis that everybody can use, and you don't have to reproduce the wheel. This is terrific except you could probably do like one a year.

DR. BRADLEY: Well, we've done four in one year. No, it is very challenging.

Joan, I'd love it if you'd comment on this. I think one of the things that surprised me is that there aren't as many topics or tests or new applications out there that are ready for review as you might think. I think that what we've got to do is to figure out how do we prioritize that. And then do they all need the same level of review? Do you need a comprehensive review on everything, or can you do targeted reviews on certain types of things that are going to be less expensive and a little faster? These are questions that we're looking at but we don't know the answers to.

DR. TUCKSON: Well, maybe AHRQ will get a whole lot more money in their budget.

DR. BRADLEY: That would work.

(Laughter.)

DR. TUCKSON: Emily?

DR. WINN-DEEN: So, Linda, looking at the list of topics that you're reviewing, I imagine that the review process for some of these might say ready for prime time and some of them might say either not ever going to be ready, that your review basically concluded it was not suitable, or that your review concluded that there's not enough data yet to support it.

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For that last category, what do you envision as a rereview kind of thing? You say it's not ready for prime time. You identify certain gaps, but at some point, you presumably would like to look at it again when some of those gaps have been filled.

DR. BRADLEY: I think that's one of the most challenging things that we've talked about is how do we do that update process because this group I think -- again, jump on me if I get off base here -- is trying to be very practical in not just saying, insufficient evidence, and throwing up their hands, but saying, here's what we know right now and here's how that might be appropriately applied. Here are the gaps and here's potentially what could be done to resolve those gaps.

She's the chair of the Topics Committee.

MS. SCOTT: Yes. I mean, a lot of this has been a learning experience and trying to decide what are the priorities of tests to address. We had a certain set of priorities for this demonstration project to try different methodologies and different types of tests. But going forward, what are we going to recommend for an ongoing process as to how to prioritize tests and what to do about looking at things again as more information comes up? We're also trying to look at tests within very specific clinical scenarios. So we're really addressing a particular test in a particular indication as opposed to a wide spread. We do think that perhaps the biggest thing we can contribute is to help identify just where the gaps are and help set the research agenda around those issues.

DR. WINN-DEEN: I guess my concern is, in the spirit of what Reed was asking, if you come up with not ready for prime time, but it just needs more data -- we really can't make a firm decision. It needs more data -- at what point when there is, hopefully, more data, do you then turn around and rereview that and say to FDA or CAP inspectors, whoever, now this analyte used in this way is ready for prime time? It has a clinical validity that's established. So anyone who wants to make a test for that only has to be concerned about sort of the analytical side of it rather than the clinical utility side.

MS. SCOTT: I think part of the process will have to include some mechanism either for continued review or some process by which a group can say, well, now there have been some additional studies. Can you relook at it? I don't think there's going to be one process. And the interval is going to vary from test to test, depending on the information that's needed and how --

DR. WINN-DEEN: So I'm just really encouraging you, when you put your website up, to try and think about how to give people guidance on that kind of a process as well. You know, we're going to list five gaps, and when at least three of them have been filled through studies, we would look at it again to see if we're now -- or some kind of something for the things that are in the intermediate phase.

DR. TUCKSON: Let me just do a quick process check. We're going to take one more question from Andrea. Then I want to make a natural segue in two minutes to easily allow some of our members to exit and have Sharon start to come up and talk about the discrimination stuff. So those that are worried about having to slip out, don't worry. The chairman is on the ball. I got it. We're cool.

One more question. Andrea.

DR. FERREIRA-GONZALEZ: I have a couple.

DR. TUCKSON: So much for being in control.

(Laughter.)

DR. FERREIRA-GONZALEZ: I was just wondering how these topics are selected. I mean, you have a committee. How did it come up with the different areas that you think the test must be ready for prime time?

DR. BRADLEY: Again, the first set of topics that were selected were selected rather deliberately to test different methodologies in different clinical scenarios. So it's not necessarily the method that would be going forward. CDC tried to do initially a broad scan from stakeholders as to what groups and individuals thought would be appropriate tests that are ready for prime time that would be useful to look at. We tried to mix and match, given a number of different criteria, including clinical scenarios, how well developed the test was, how complicated the clinical scenario was going to be, whether or not we thought there was going to be a lot of information versus what do you do when you have just a little bit of information. Are they different kind of reviews? So we really tried to be thoughtful for these first topics to test different methodologies, different types of tests.

Going forward, I think that's a different issue as to how new tests will need to be brought into the pipeline because, as Reed says, it is somewhat of a narrow pipeline.

DR. FERREIRA-GONZALEZ: Well, I would strongly encourage you to seek public advice from stakeholders and professional organizations because they, as they're at the forefront, might be more aware of these.

DR. BRADLEY: We have solicited from a number of groups, but I think it's been difficult for people to get to us without this interactive website. So we're hoping this will --

DR. FERREIRA-GONZALEZ: Well, that's what I was getting at, how to more widely communicate you're seeking topics, and then the question that Emily had, that maybe you can seek input with a specific metric maybe when there's more data available for some of these things.

DR. TUCKSON: All right. Thank you all very much. I've got three minutes before the hour.

By the way, that was terrific. Thank you for coming up and thank you so much, Linda. I appreciate it. That was a terrific way to do it.