

**Update on Collaboration, Education and Test Translation (CETT) Program**  
*Stephen C. Groft, Pharm.D.*

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DR. TUCKSON: Welcome back, everybody. Right on time as always.

Steve are you here? We are very pleased to be able to welcome Steve Groft, Director of the NIH Office of Rare Diseases, to provide us an update on the Collaboration, Education, and Test Translation Program, or the CETT, which promotes the translation of tests for rare genetic diseases and also works actively to encourage clinical labs and research collaborations.

Steve briefed us about CETT in early 2005, and we're eager to hear how the program is progressing. Steve, I think you've got about 15 minutes of presentation and 5 or so minutes of questions. Thank you very much.

DR. GROFT: Thank you, Reed. This has been a real unusual program in which we've had the opportunity to start something right from the beginning and learn as we go. I have to say we've met with a lot of very, very good comments from many people. This was a program that was an idea that we really needed to do something to facilitate the translation of genetic testing from the research laboratories to the clinic situation. So we developed this program.

Some of the people involved in it are, unfortunately, on the last slide. I did hand out copies of the slides. I won't use all of them. I've tried to reposition. I think maybe 10 or 11 of these I will actually use. There was just a lot of background information that we've used to explain the program to others, and I didn't want to just limit it to the ones that I would talk about here. So I'll try to go forward on this.

You see there the partners that we've been involved with. I've made several presentations to the advisory committee in the past. We really haven't changed partners. Just I think we've solidified partnerships particularly with the CDC folks and HRSA and the CMS people talking about genetic testing. And then in have come these societies, and they're very supportive of what we'd like to do and how we want to move forward in this program of translating research of genetic testing into the clinic.

You see there some of the program objectives where we're really talking about new genetic test development and then the translation of that from research to practice.

We'd like to increase and improve the education about the rare genetic disorders, and we're also thinking about trying to find ways of collecting and storing the clinical and genetic information so that there can be some genotype/phenotype correlations. Of course, there are other programs going on in research and through the NIH that people have been discussing at length. So we think we have a nice jump on this aspect.

We have had several meetings focusing on genetic testing. The first one really was to identify the issues and the needs, and that was focusing primarily on molecular genetic testing. So after we started the CETT program, the biochemical genetic testing is an area that we felt needed to have some emphasis. So we were able to pull together a conference, I guess about six weeks ago, on biochemical genetic testing.

The other two URLs there are for the reports from those meetings, and we are circulating the current report from this meeting. I would say within a couple weeks there should be a website and we'll pass it on to Sarah or Amita for them to distribute out to you. We have a draft that's

been reviewed by the steering committee, but we wanted to pass it out to all the participants to give them an opportunity to comment on it before we move forward.

I just want to go over briefly some of the recommendations that came out of the meeting and then some of the programs that have been implemented as a result of this.

The first one was that the CETT program should be expanded and include biochemical genetic testing. The other emphasis that we found was that we really need to start to look at those tests that are only available in non-U.S.A. laboratories really to get a feel for what's going on, why tests are not available here in the United States. If we're going to run into problems -- and there are different groups working on the international collaboration and how to facilitate transfer of samples and quality assurance of the labs outside of the United States. So we are going to be looking at this as well as we move forward.

As we did with the molecular testing, we had a laboratory consortium that volunteered to help get things started. It's been very successful and we've been able to provide some support almost as a pilot project to really begin to initiate these activities of developing the genetic tests. We'd like to see a similar consortium be developed in biochemical genetic testing, and we seem to have a group of individuals who are willing to bring themselves together and form this consortium.

Where we go in the future we're really not sure. So many things depend on the availability of funds, but certainly this is a program that has gained a great deal of acceptance in the outside world with the laboratories and the patient advocacy groups who have a need for having the genetic tests developed and made available. But we also have been gaining acceptance within the NIH structure itself, to gather resources to facilitate the translation of the test and the development of the test. In fact, we just had a co-funded project with the National Institute of Diabetes, Digestive, and Kidney Diseases to help fund the development of some genetic tests that I'll just mention here in a few minutes.

So things have been growing. They've been moving very nicely. Again, as I mentioned to Linda Bradley before the presentation, I just can't believe the amount of support and collaboration that has come about in this whole area. So it's been really rewarding to start a program and have support and have it grow. Now, of course, our big problem is having enough money to sustain the growth and have it grow even further.

There's a great deal of concern about the training of laboratory and clinical personnel in biochemical genetic testing. I think as many of us -- not too many people here who are as gray as I am or maybe thinning hair or losing hair. But in the biochemical genetic testing area, particularly, the issue has been raised that we really do need to find a way to increase the number of individuals who are willing to participate in this activity and become the practitioners and the lab directors in the future. Again, there was a feeling that there's going to be some consolidation of some of the laboratory activities with the refinements in genetic testing and other things in the future. But at the present time, there is a need that we have to start to look at for increased training and sustaining the training sites. I know there are people at NIH who have this concern as well, that we really do need to look at this.

There was mention that guidelines should be developed to ensure the quality of testing, result interpretation, and diagnosis for inherited metabolic disorders and other genetic diseases. This is something we're looking to the American College of Medical Genetics and the Society of Inherited Metabolic Disorders and others to help develop some of the guidelines that will be

useful to the clinicians and the laboratory people as well to help them really get a better understanding and appreciation of the test and what is needed.

Quality assurance measures need to be enhanced for the various laboratory tests, and we spent some time talking about that. These are several of the programs that the other individuals will work on outside of the government people. We feel it's society's responsibility and the professionals' to bring these ideas together.

We noticing more and more international collaboration in research efforts. This is going to just move right into this whole idea of quality assurance and transfer of samples across borders. So this cooperation and collaboration is going to become even more important as we move into the future, and particularly for the rare diseases, we're finding this more and more, that the collaborative research efforts are extending beyond the borders and truly becoming international with the scarcity of patients in any individual countries. We're finding more and more collaborations being formed, and they're working on all aspects of research. So this is another area that needs to be worked on.

Again, as is usually always the case, information resources need to be enhanced to provide easy access to that user-friendly information on biochemical genetic testing. The availability of testing services and testing strategies need to be expanded and exposed to the public and other practitioners more extensively than what we've done in the past.

So the outcomes of the meeting and something that everyone has agreed to do. In our office, we're taking steps now to expand the CETT program to include biochemical genetic testing by adding several advisors and several individuals on the review teams to help review the biochemical genetic tests when they come in for consideration for support for development.

GeneTests, that Bonnie Pagon has primarily responsibility for, will be providing specific information on biochemical genetic testing either by expanding the current capacity or by setting up a companion site through subcontracting. So we're going to have an equal emphasis on biochemical and molecular diagnostic testing.

You can see there the ACMG and SIMD are committed to developing testing guidelines needed by users and providers in collaboration with other professional organizations. So again, this is something that this issue just needs the cooperation of everyone in order to make it work appropriately and really to get the best information out to the public and to practitioners and researchers, laboratory directors and staff. So many, many things are starting to develop.

CDC. The folks there will prepare a report of the meeting and will soon be posting that report on the websites and will be making that available.

The steering committee will review the recommendations to refine the roles and responsibilities and then to begin efforts to see what else is needed in the near future. We usually give ourselves about two or three months after the meeting, and then we start to think about, okay, where do we have to go after this meeting and what needs to be done.

Usually we've been running, about every year or so, a meeting to follow up and review what has happened during the past year. Again, it's a good way to look at responsibilities and see who has taken up the initiative and moved things forward. So we will continue to do so.

Here are some of the tests that have been developed through the network. It's

quite a few different ones. You can see there the spread to various laboratories that are developing the tests, a couple of commercial organizations that are helping out, and then a couple different methodologies that are being used to develop the tests.

I would like to add one other thing. What we have done also, since we are involving the patient advocacy groups extensively, we've got a group of about six or eight individuals, leaders of patient advocacy groups, now that have come together and have gone through a little bit of a training program. They are now serving as a resource to other patient advocacy groups to explain the program and what does all of this mean. What is the CETT program and what are the values of having the genetic tests developed and made available. So they've come in with a great deal of enthusiasm, and we have them broken out into the various review groups.

Some of the experiences that we've had up to this point. Again, the need for templates of educational materials so that people can understand what genetic tests really mean, what can they expect both before and after, before the test is administered and then looking at the results, what should they be aware of. So people will be working on these templates. I guess we have to figure out better ways for the test results to be understandable by everyone. That's a major, major issue. I think it's hard breaking down the information sometimes out of the scientific and medical language that we're so used to using to make it really understandable and useful to patients and their families.

I think I will just end it there. I've got several slides on procedures and activities, but those you can look at. They're highlighted within the website for you to look at at your leisure.

So I will try to answer questions, if you have any.

DR. TUCKSON: First of all, thanks a lot, Steve, again for coming.

Yes, please. The floor is open.

DR. EVANS: I was wondering if your group had thought about the issue of patents, how they affect what you're trying to do. Has that been an issue on your radar screen?

DR. GROFT: That's when we dance quickly. We do more than the two-step.

DR. EVANS: You have 30 seconds.

DR. GROFT: Oh, my goodness. Yes, we've stayed away from the patent issue a little bit by trying to pick up some of the tests that have no patent life on them, just for now. I think we wanted to gain some experience here first in seeing how can this all be done, and then we'd start to address the issue of tests with patents and rights.

DR. EVANS: So is that fair to say, though, that your decision about what tests to develop and all has been informed, to some extent, by whether patents exist?

DR. GROFT: I would say yes. I mean, it's an area we're not really prepared to deal with yet. It's something we'll be getting into, I think, as we gain more experience. Again, you run into problems. We didn't want to run into a lot of logjams here when it comes to developing tests and be held up in the legal circles, as far as developing the tests. We thought let's just go ahead and get started and gain some experience and use an Internet approach and gain the experience and

keep growing and keep changing as we go along. Then we will begin to start to address that problem. It is a big issue.

DR. EVANS: Yes. It's really straightforward.

DR. GROFT: And that's been with us for about the past two and a half years. Even at the Clinical Center when we were paying just to have a few tests developed, it was an issue that Bill Gault stayed away from because he said it's going to bog us down, but it is something we have to address.

So if you can give us help later on or any suggestions, we'll be happy to have a forum on this, if you like. I mean, we'd be happy to sponsor a workshop or part of a conference on this issue. So always open.

DR. TUCKSON: By the way, Jim is all over this patent thing.

Andrea?

DR. FERREIRA-GONZALEZ: I really want to commend you in your attention to the biochemical testing now. It's an area of genetic testing that is not receiving enough attention, and we're starting to see that it is not being offered as widely as it used to. So I commend you on taking these issues.

There are two comments I want to make. One of the issues that we have regularly in genetic testing is the availability of controls. What are the efforts? Are you working with CDC with the Genetic Testing Quality Control Materials Program, or do you have any efforts within NIH to deal with these issues?

DR. GROFT: That's one of the nice things, the partners that we have. Everyone brings some different expertise, and certainly we're in close contact with the people from CDC in the quality control area. We had the partners listed, and it really didn't reflect the attendance of the different groups. There were people there from CDC who were really keeping us up to speed on quality control, and we recognize this as a potential problem.

DR. FERREIRA-GONZALEZ: The other issue that we wrestled with is there's a continuous lack of standardization in the reporting of genetic testing, not just rare disease. It seems you're going through that process, understanding how to report. I will strongly encourage you to work with the professional organizations, in addition to the ones you have, other ones, that are going through some process of trying to standardize, really understand how are we going to post these results so clinicians can fully understand.

DR. GROFT: Again, you're right. That's where all the partnerships have to come in and have input into what's going on because we need the professional societies and organizations. We need the patient groups to really help us get the message correct when we're putting it out to the public. And then the health professionals that have to deal with working with the patients and the families. That's why I think this coordinated and collaborative effort is really so important. It's a nice model to try to develop the information that's so badly needed by so many people.

DR. FERREIRA-GONZALEZ: Yes. The idea is to learn from what we have already gone through. The idea is not to reinvent the wheel. We've gone through this process already. So just gain information from that.

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DR. GROFT: It's quite a process to make sure you get the right message and the right timing of information out.

DR. TUCKSON: Any last questions? Oh, good. Emily?

DR. WINN-DEEN: I just was wondering if you could comment a little bit more on how the educational materials that you're developing would get out to the people that need them when they need them.

DR. GROFT: Again, our plans are to put the educational information on the website, but then to interact with the professional societies, the specialties that would see the patients, and the genetic counselors who would be counseling the patients. So it's a multi-system, multi-agent approach to try to get that information out to people. So we're going to be using different resources to contact the professional societies, the genetic counselors, the patient advocacy groups, and then whatever physician groups, nurses group, whoever is most likely to see the patients. That's who we're looking for.

We do have one example, the Cornelia de Lange. That's the first one that has really hit the market with educational materials and information. Again, it's going to be the first model that we have, how is this working, and then we have to go back and assess are we really reaching the audiences that should be reached with this message about the genetic test and all the information that accompanies it.

DR. WINN-DEEN: Have you thought about linking to GeneTests or something?

DR. GROFT: Oh, yes. There will be gene reviews for each of these, as we go along. So they're working on those as we move forward. As we develop the genetic tests, I think a gene review also is going to be made available. That's one of the good things of having Bonnie Pagon working with us as one of the directors. She's making sure that we're tuned into everything that's going on there.

DR. TUCKSON: Kevin, you actually have one more before you.

DR. RANDHAWA: I can yield to Kevin.

DR. TUCKSON: No, no. You were right there.

DR. RANDHAWA: Will you give us a sense of the criteria chosen for prioritizing the tests for translation?

DR. GROFT: They go through a review. Here's a review board, the team of reviewers who participate in looking at the information that is provided. Is the test ready for translation yet? Just what is the current status? We look at little bit at the cost and can we afford that right now where we are. So thus far, we haven't had to turn anyone down because of the cost of developing the test.

But we do look into a lot of the background. Has the laboratory that's involved completed the test in the research laboratory? Has it been useful? So we're looking at the utility and a lot of other factors that come into play before the decision is made.

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What I would suggest, if anyone has a test that they're really thinking about, get in touch with somebody like Andy Faucett, who's really the distributor of information, and have him lead people through what is needed and how we're going to move forward. So we've been very, very open and accessible to people trying to educate them about how to get a test translated.

So it is a decision process that the review team goes through, and then they make a recommendation to the steering committee. Then we try to find funds if we don't have them. This is where we've been turning it over to some of the institutes at NIH, especially if they are in a research protocol at the time, to try to gain some funds from them to develop the test.

DR. TUCKSON: Great. Now, Kevin.

DR. FITZGERALD: Well, I forgot my question. No.

Again, thanks very much for the update. Just a quick question. Is there a procedure that you're employing? Are you collaborating with somebody on how you're setting up to collect and store clinical and genetic information?

DR. GROFT: You know, I can't say that. I know they are looking at collecting that information on a database and storing it, trying to maintain the anonymity that's required. But I couldn't say for sure. I don't know myself, but I certainly can get the answer for you and get back with you. There are people who certainly are more knowledgeable about what's going on. Unfortunately, I haven't been able to spend the time that you'd like to on this issue, but I'll get back with you on that.

DR. TUCKSON: Yes, Scott.

DR. McLEAN: I just wanted to mention that the biochemical aspect of GeneTests has been needed for a long time. But do you think that that availability of information will increase the demand for biochemical genetic services, to the extent that that will become problematic more so than it is already?

DR. GROFT: We've been confronted with a few of the labs shutting down and some other issues because of legal problems arising. It's certainly something we don't want to look at in the future, but I think the reality is we need to have an emphasis on this to make sure that the biochemical genetic tests remain available. I don't want to say until such time as molecular testing becomes available.

But there are certain issues here with biochemical genetic testing that we have to address. There are weaknesses that people have expressed that we need to look at and make sure that it's shored up enough that people have confidence in the results that are coming out. We're looking at a decreasing population of practitioners and laboratory directors in the area, and these are all issues. The biochemical genetic testing is not going away because of molecular testing. So we have to make sure that the services are still available, the best we can. So we are looking for ways to increase the training aspect of this that hopefully will take care of part of the situation.

I hope I answered your question because I'm dancing a little bit there too because it's loaded with problems that we're trying to resolve. Of course, if we had unlimited funds, you could do some of these things and have lots of training programs. The parties are interested. Now it's a matter of putting things down on paper and getting them out and start to work on them.

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DR. TUCKSON: Any last ones?

(No response.)

DR. TUCKSON: Terrific. Thank you so much. Thanks for coming back.

DR. GROFT: I'll get back with you.

DR. TUCKSON: On that patent thing.

DR. GROFT: Yes, and the patent issue too.

DR. TUCKSON: Thank you so much.