***Public Health Approach to Genomics***
**Muin Khoury, M.D., Ph.D.**

DR. McCABE: Good morning, everyone. I hope everyone had a restful night and is ready to go this morning. Because we will be finishing up at 3 o'clock this afternoon, we have a very tight schedule, and we'll be following that today.

We're going to start the meeting this morning with a presentation by Dr. Muin Khoury on the CDC's public health approach to genomics. Muin has a booklet that -- are you going to pass that around, Muin?

DR. KHOURY: Yes.

DR. McCABE: -- that is really quite intriguing about public health genomics. The committee expressed interest at a previous meeting, and CDC's efforts to address questions about the public health significance of genes and gene variations, as well as on the development and use of evidence-based approaches to establish this knowledge for entire populations, a topic we touched on briefly yesterday.

Muin will describe the CDC's efforts to integrate genomics into public health, and we're looking forward very much to your presentation.

DR. KHOURY: Good morning, everyone. Can you hear me?

There is a book that's going around. Actually, I only have two copies of the book, but each member of the committee will have their own book that's now being mailed as we speak, because we just had them fresh out of the printer last week.

Thank you, Ed, for the introduction and for the opportunity to address the committee this morning. What I'd like to do in the next few minutes is talk about the public health approach to genomics, and I have really three themes. I'd like to set the stage first with a brief discussion of the changing landscape of genetics, because that really affects the way public health does business. The way I captured this here is the concept of the continuum from genetic disease to genetic information. Then I'll move on to describe the public health role in general as an honest broker convening function that's science based, and then I'll describe briefly some of the roadmap activities that CDC and other partner organizations have begun to develop, including a few initiatives. I mentioned some of them yesterday. I'll probably run out of time, but we can discuss those more in detail later on.

Briefly, what do we mean by this continuum business? This is obviously the group not to talk to about this because we've been talking about this paradigm shift. But it seems to me that every time we talk about issues related to genetics, we always fall back on what we know, which is the concept of genetic disease. I'm not trying to minimize that because genetic diseases or single-gene disorders are individually rare, but collectively they account for about 5 to 10 percent of human disease and illness, and they are inherited through the germ line. You have usually a few mutations or many mutations, but in a few genes, and very high penetrance of high lifetime disease risk.

Then all of the environment as we know it, from diet to behavior to chemical to infectious agent, may or may not be there for many of these diseases. We don't know about all of the environment

very much. The concept of the delivery of services revolves around the genetic services model, counseling/testing, et cetera. What we are finding ourselves in this new era is that we are moving towards the concept of genetic information that affects all diseases, or the 90 to 95 percent of diseases that we normally don't think of them as genetic, where you have variation in many, many genes and normal variation or variation that puts you at higher or lower risk. Some of that variation is inherited, but you can also detect variation in somatic cells. We talked about this briefly yesterday.

For each one of these genes or their variants, there is a low disease risk, and that's where the role of the environment comes in in a big way. There is really complex gene/environment interaction. The way we're going to increasingly be faced with the situation of integrating this information in general practice, we'll go back and forth on this but it's an important paradigm shift. It's a continuum, really. It starts with the pure genetic disease to the pure environmental disease, but there is a break somewhere in the middle where the genetic services model will not apply.

Just as an example, for every disease, and I chose the most common human ailment, which is coronary heart disease, you have many single-gene disorders associated with these common diseases. In this case, familial hypercholesterolemia, which is 1 in 500 condition, it's an autosomal dominant condition of the LDL receptor, deficiency is a cause of premature coronary heart disease, but it only accounts for less than 1 percent of heart disease in the population. All of these rare diseases combined probably will account for less than 5 percent of heart disease in the population.

Now, that doesn't mean that these are unimportant diseases. They are very important to the individuals and the families that are affected by them, and as a point of fact there is a public health approach to all of these diseases. I talked briefly yesterday about the fact that familial hypercholesterolemia, which is a treatable condition, you can prevent premature heart disease, the medical system currently today misses about half, if not more, of these cases in the general population because high cholesterol level is so rampant that this entity is missed altogether.

But most of heart disease is due to this. This is a quote from Bob Hegele a few years ago, and for those of you who don't know this gentleman, this is Jim Fixx, and the other person is well known. But Bob said in 1992 that some vegetarians with acceptable cholesterol levels suffer myocardial infarction in their 30s. Other individuals seem to live forever despite personal stress, smoking, obesity, and poor adherence to a Heart Association-approved diet. Really what we're talking about here is a complex puzzle of gene/environment interaction.

By last count, there are probably about 270 risk factors, non-genetic risk factors for heart disease, and each one of these interacts with each one of the genes in our system, and it's very difficult right now to find a pathway for use of that information for the prevention of the 95 percent of heart disease in the general population which is not thought of as genetic.

So occasionally we see articles like this. People are working hard on the prediction of MI using polymorphisms and candidate genes, and this is one example of many that we are seeing, and this happens to be a case/control study in Japan where people looked at a large number of cases of myocardial infarction and looked at 71 candidate genes with 112 polymorphisms in these genes. To cut a long story short, they found a few associations with small odds ratios, and there was an accompanying editorial that said, "Findings should be used to initiate further research, and recommendations for primary prevention cannot be based on these findings."

This is the state of affairs we find ourselves in right now in the use of genetic information in the

prevention or management of most human diseases.

So let's come back to public health. Why do we need public health in the first place? What is public health? There has been over the years several pronouncements by the Institute of Medicine. In 1988 they had a meeting that led to a pronouncement called "The Future of Public Health," and then last year they revisited the future of the public's health in another report. The 1988 report did not mention genetics. The one from last year did mention genetics.

But briefly, public health is what we do as a society to assure the conditions for population health. So in public health we focus on three things. We focus on the population, the community as outpatient, not the one-on-one interaction with a patient in a clinic but the community or the population as our unit. We focus on prevention, and we would like for it to be primary prevention; i.e., the prevention of the disease before it happens. If primary prevention is not possible, then we move on to secondary prevention, like early detection, and then tertiary prevention.

Public health is very much science based. The tools of science and public health are complementary to those in the biomedical sciences, but nevertheless they are tools, and I'll mention some of them later on.

Now, in terms of public health functions, they were laid down in the 1988 report. The three major functions are assessment, policy development, and assurance. These are very important functions, and there are lots of misconceptions about the role of public health when it comes to genetics, because people sometimes think of it as mandated population screening programs or delivery of genetic services, but these two functions are only a small fraction of what public health can do for the delivery of health care and prevention. I'll mention examples of those.

But it's the report from last year that really set a different stage for us as we talk about the role of public health. It talks about the public health system, and it really talks about the partners that work together to assure the conditions for population health. Typically, we tend to think about public health as the government public health infrastructure, which is on the left-hand side. That's us, the federal government and the state and local public health. But those units alone cannot assure the conditions for population health. The public health system as defined by the IOM is all of the partners coming together, including academic, the health care delivery system, employers and businesses, the media and communities.

As a matter of fact, when you think about this, this committee is an example of the public health system in action because you represent the various stakeholders and the groups coming together hopefully to make some policy recommendations and pronouncements that assures genetic information can be used for population health, to improve the health of the public in general. Toby Citrin mentioned yesterday this report, which is another IOM report that was published a couple of years ago about the training of the public health professionals. When you think about it, and the IOM made this estimate, there are probably about half a million professionals in the U.S. that are considered in one way or another as public health professionals.

Public health professionals are those that have a population focus in mind. In other words, they are not engaged in the delivery of health care one-on-one with patients and families but community-based activities. Many of them are actually not trained in public health, but nevertheless they are public health professionals. As Toby Citrin mentioned yesterday, the IOM made a pronouncement a couple of years ago that the public health professionals of the 21st Century will have to deal with critical areas in training, including genomics, and you can read

some of the other important areas as well.

Now, what can public health do for genomics as the gene sequence and the gene discovery gets out from the bench to the bedside? What public health brings to the table is an approach to translate all of this new science into activities that improve everybody's health. The way I've captured it here is that I think about public health as contributing in three major areas, or three boxes if you will, three major gaps we're trying to fill.

The first one is probably the most important one at this point, figuring out what does it mean to have genetic variation. What's the role in genomic information in population health? I mean, we have 30,000 to 35,000 genes and thousands of variants, and many, many proteins and protein variants that are going to be discovered, and we are just skimming the surface right now of what that information means to the burden of disease and disability in different community and how this genetic variation interacts with the environment, and the environment, if I didn't say it so far, has been the major point of intervention for public health so far in our quest. So that's an important role to consider, and that's a population research agenda.

The second role is to figure out really, truly, the value added of genetic information in both treatment but primarily in prevention, because right now we have a one-size-fits-all public health approach to the major common chronic diseases that involves behavior modification, diet, exercise, smoking cessation, et cetera, and we have to figure out scientifically, based on the best available science, why should we change that approach in favor of a personalized prevention medicine approach.

Then the issue of implementation is really crucial because you can discover all the genes and figure out what they do, you can figure out that they are good to be used in a genetic test, but the implementation can be messy in a health care system that's really not prepared for genetics. I'd like to cite to you what Claude Lenfant said last year. Claude Lenfant was the outgoing director of NHLBI and had a nice piece called "Lost in Translation." That's not the title of the movie, by the way. He basically was citing a number of areas in the heart, lung and blood area where basic research has not been translated into practice, and he used one of many examples, the issue of aspirin, that less than a third of patients that need aspirin for the prevention of coronary artery disease are actually using aspirin. At the end of the article he had this rather cynical remark, saying "Let's be realistic. If we didn't do it with aspirin, how can we expect to do it with DNA?"

Now, I don't prescribe necessarily to a pessimistic view of the world but more of an optimist in this department.

Now, CDC and many partners have begun thinking about these issues and drawing a roadmap. It's a bit tortuous right now, having landmarks as we move forward from one box to another, a population health research box, building an evidence base for prevention, and then moving genomics into practice. These things are not necessarily sequential because many genes are on different parts of this continuum. Certainly for rare genetic diseases and newborn screening, we are already in practice. But for many of the common chronic diseases, we are somewhere at the beginning of this map, where genes are coming out of the test tube, if you will, and going down the translation highway.

Since I don't have that much time, I just want to give you a brief overview of the kinds of initiatives that CDC and others are developing, and then we can have some more discussion. In the department of genomics and population health research arena, we have three major initiatives going on: the Human Genome Epidemiology Network, the NHANES projects, and genomics and

acute public health investigations. The Human Genome Epidemiology Network is an international collaboration that has been sort of watching over the science of gene discovery and gene disease associations. We have many collaborators from around the world that use epidemiology as the basic science of public health, and those people are engaged in methods development, training, and knowledge base development, and we're also working with NIH and others on the pooling and synthesis of the many cohort studies that are going on around the world. You'll probably hear a bit more from Francis Collins about the U.S.-proposed study later on.

As of May 1st, we've had a number of products that are online. We don't have time to go through this, but a knowledge base and a searchable database is what I would like to show you here briefly, and you can all go online and figure it out. This is sort of a running database that changes from week to week that you can search by either gene -- we use the HuGE nomenclature; disease -- we use ICD codes; or interacting factors, like smoking and drugs, et cetera, that summarizes the status of the epidemiologic knowledge on gene/disease association, gene/environment interaction, gene/gene interaction. I am told that this is a good adjunct for many researchers who are trying to figure out how to get genes out of the test tube into population-based work.

To summarize, this is sort of the literature over the last three years. This has been going up, obviously. I mean, every day there are more papers in this regard. We capture about 50 to 100 articles every week. These are your top 10 genes: ApoE, ACE, MTHFR, and HLA. We don't have time to go through them, but these are the most epidemiologically studied genes in the literature.

The second initiative is the NHANES DNA bank. This is very important because we don't know the prevalence of the major variants of public health significance in the U.S. or around the world. NHANES is a national survey that CDC does on a regular basis. In the NHANES III cycle back from 1988, DNA was immortalized in about 3,000 nationally representative samples from the U.S., and we're currently, in collaboration with NCI, looking at the prevalence of the top 57 genes of public health significance. I'll leave it at that for now.

The initiative we started last year is figuring out how human genetics and genetic variation can explain outbreak investigations. We're currently in the midst of evaluating which outbreak investigations, which is the bread and butter of many public health activities, both in environmental health and infectious disease outbreaks, figuring out why some people get sick but not others when exposed to the same virus, bacteria, or environmental agent.

The second area along this continuum of building the evidence base, we have two major initiatives, the genetic testing evaluation and family history. For those of you who have been around from SACGT, you may recognize this wheel. SACGT recommended that genetic tests needed to be evaluated along the continuum from analytic validity to the ethical, legal and social implications. For the last three years, we have been engaged in fleshing this out a little bit more through the collaboration with the Foundation for Blood Research using five genetic tests as examples.

We have essentially developed a methodology for how you can begin to evaluate genetic tests as they move from research to practice. At the end of this year we're going to have a methodology meeting where we compare this methodology with other methodologic technology assessments that exist, both in this country and around the world, hopefully coming up with a consensus way of evaluating genetic tests. We're using this information in this next initiative, which will be a collaborative initiative both within the government and with the private sector. We call it EGAPP, or Evaluation of Genomic Applications in Practice and Prevention.

I don't have too much time to go through the specifics, but we are going to be experimenting with a non-federal multidisciplinary independent working group that will begin to, using the tools of methodology assessment, evaluate genetic tests, with a priority for the ones that will be used for prevention and population health, evaluate them one at a time using a stakeholder group for input, and then commissioning reviews through evidence-based centers of the kinds that AHRQ supports, and then coming up with summary statements and recommendations.

The good thing about this project is that it not only involves pronouncements, but there will be some funding for pilot data collection projects to fill some of the gaps that the group will identify. I'll be happy to talk more about this.

Family history is a big one because, as we talked yesterday, it's sort of the initial genomic test, if you will, that we all have, and we don't necessarily have to have a lab test for it, and we know that family history is underutilized in preventive medicine, and it is a risk factor for most common chronic diseases of public health significance. It's frequent. If you look at the major five or six common chronic diseases, half the population has at least a first-degree relative with either cancer, heart disease, or diabetes. It is a risk factor for almost all these diseases. Depending on the number of relatives and the age of onset, those relative risks change. But it's the most consistent risk factor for all common chronic diseases, and yet very few people actually need a genetic work-up as a result of family history.

So the initiative that was started two years ago is now fully under way. We are using the simple classification scheme that Maren Scheuner, Dr. Scheuner from Cedar-Sinai at the time, and now at UCLA, proposed a few years ago to classify people into a qualitative risk classification scheme for any disease depending on their family history: an average risk, a moderately increased risk, and a high risk. We are currently developing a family health tool for five or six common chronic diseases, three cancers, heart disease, diabetes, and using a complex algorithm to classify people into these three groups. We will be conducting a controlled clinical trial to evaluate the clinical utility of this tool in order to change people's behavior.

The good thing about this tool is it actually bridges the gap between genetics and public health, because in public health we live in this average scheme. We treat everyone in the population as an average person for any given disease, and we give everyone the same recommendation for disease prevention. Geneticists, on the other hand, are always looking for people and families with single-gene disorders, but these are only a few in the general population. Most of us, if not all of us, are not average. We fall in this moderate risk group for most diseases.

Today, we don't know the genetic basis for the moderate risk group. Ten years from now there may be enough genetic discoveries to find out that there could be a genomic profile test that will dissect this moderate group. But the good thing about family history is that it's more than genetics because it involves shared behavior, shared culture, shared diet, and a family-centered prevention approach.

Finally, since I'm running out of time, I just wanted to mention three initiatives in building the capacity and practice, building a public health capacity, developing approaches for population-based monitoring and outcomes research, and I'll mention all the efforts that CDC is doing in ensuring the lab quality of genetic testing and practice, the CLIA efforts that you all know about, et cetera.

But in terms of building the public health capacity, we have three activities, briefly. Back in

2001, as NCHPEG was developing its genomic competencies for health care professionals, CDC and many partners developed genomic competencies for the public health workforce, and there is quite a bit of overlap between the two. You've heard from Toby Citrin yesterday about the development of Centers for Genomics in Public Health. There were three that were funded over the last three years, and hopefully there will be many more, both in schools of public health and medicine across the country.

Last year, CDC began actually funding state chronic disease capacity grants to supplement what HRSA and others are doing on the maternal and child health side with respect to genetics and public health.

Last but not least in terms of outcomes and monitoring, you'll hear more about the direct-to-consumer campaign. But last year, as you know, Medical Genetics had this campaign in two test cities, Atlanta and Denver, and the public health response to this was to do a survey or a series of surveys with health departments in the two exposed cities to the campaign, Atlanta and Denver. We had two control cities, Raleigh and Seattle, in which we had surveys of women that were targeted by the campaign, about 400 in each city, and the health care providers, about 250 in each city. I don't have time to present the results of this since I am running out of time, but here they are, and we can discuss them later on.

So in closing, I'd like to kind of reiterate this long and winding road beyond the bench to the bedside concept. Really, as we all engage in what I call activities in improving the public's health, we have to realize that what we do on the population level really influences to a major extent what is done at the bedside level, and population-level information on either the epidemiology of genes or the evidence base for why we should use a genetic test and how we actually use it in practice and ensure the quality of delivery of the services is really impacting in a major way on the practice of medicine.

So I'd like to close here, and if you have any comments, I'll be glad to take them. Thanks.

DR. McCABE: Thank you very much, Muin.

Any questions or comments for Dr. Khoury?

(No response.)

DR. McCABE: I'd seen a published report from the Myriad experience, or maybe it was just some preliminary data that suggested that there had not been much increase. While people were aware of the ads, it had not really changed practices. From looking at your data, it looks like it did change practice. Is that the case, Muin?

DR. KHOURY: Well, I mean, we have some limitations from these data because we don't have actual utilization rates. We have what physicians told us in terms of the interest and their own practices, and it does look like there was a bit of an increase. We are also working with Myriad to analyze their own utilization data for the country and related to the denominators, which is the whole U.S. Census. So I don't have the final word on this, but in the next few months we should be able to actually map it out.

DR. McCABE: Did they continue their ad campaign?

DR. KHOURY: Not to my knowledge. They're pondering whether or not to go national right now.

DR. McCABE: Other questions or comments for Dr. Khoury?
Yes, Agnes.

MS. MASNY: In your systematic review of genetic tests that you showed the wheel, and I don't know if that's in your new book, your report, if you would think that any of the materials from there could be utilized as guidelines for us in the work that we'll be doing to try to both categorize and give guidance for the coverage and reimbursement?

DR. KHOURY: Absolutely. I mean, any of the stuff I mentioned this morning, which was a high-level discussion, there is plenty of material and back-up. So you guys tell me what you need and I'll be happy to give it to you.

DR. McCABE: Thank you very much, Muin, for that very interesting presentation