UNITED STATES FOOD AND DRUG ADMINISTRATION

PUBLIC WORKSHOP

IDENTIFICATION AND CHARACTERIZATION OF INFECTIOUS DISEASE RISKS OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS

College Park, Maryland

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JESSICA YOZWIAK

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SHIMIAN ZOU

SUSAN ZULLO

* * * * *

P R O C E E D I N G S

(8:30 a.m.)

MR. BRUBAKER: Welcome back, and we'll begin Day 2, which is just a halfday, of course. So, what we thought we would do is try to get together yesterday after the workshop and a group of us put together some points that were made. You know, we tried to generalize a lot of this, so there's not too much detail and, really, this is just to help you remember what happened yesterday. There was a lot of discussion, so if you think we left something out, don't worry about that. Actually, there are transcripts that will be produced, and be publicly available in the weeks ahead; so keep a look out for those.

So, these are grouped by session, and the first one was estimating magnitude of emerging infectious diseases or EIDs. And the following points are what we gathered from it.

Modelling methods are available that can simulate and predict the potential impact of an EID in specific populations. A variety of EIDs

and re-emerging diseases can affect the U.S. population and some can be influenced by vaccination trends and resistance to antibiotics. Statistical analysis of incidence and prevalence estimations can be influenced by not only the population and the vector disease studied, but also by geography, length of time of analysis, surveillance methods used, such as what's sampled and the sample size, assumptions that are made, and scaling to estimate risk.

There are almost certainly differences between the blood donor and HCT/P donor populations. Blood donor data used to determine a residual risk for infectious disease may be leveraged for estimating incidence and prevalence in the HCT/P donor population, but differences may be influenced by a couple of things -- communicable disease testing that's performed; gathering donor medical behavioral history interview information, such as deceased donors verses living donors; lack of follow-up testing of most HCT/P donors; and the lack of longitudinal

studies as a reference.

So, this is the last summation of Session 1. An integrated approach to surveillance of zoonoses in the U.S. may be beneficial in identifying EIDs. Global movement of people, animals, and microbes defies constraint of communicable diseases by a national or a natural border; and based on new knowledge for a specific disease, there is interest to evaluate methods that could be used to consider whether requirements for donor testing or screening can be adjusted.

Sorry, there was one added this morning. Modeling disease incidence and prevalence among the collective HCT/P donor population may be challenging especially when comparing distinct donor types, such as those for HPCs, reproductive HCT/Ps or conventional tissues from deceased donors.

For Session 2, the topic was potential for donor derived infectious transmissions by HCT/Ps. The risk and benefits are diverse for

different types of tissues. Although rare, transmissions of disease to HCT/P recipients have occurred. They vary with the type of pathogen and type of HCT/P, and certain methods appear to mitigate some risk. However, preservation methods may not.

Surveillance and reporting in regard to transmission of communicable diseases by HCT/Ps and tracking HCT/Ps to a final disposition both take place. However, these functions can be improved. HCT/P donor screening and testing has evolved and improved. Donor eligibility determination timelines differ based on the HCT/P type and its utility, and testing and screening performed by tissue establishments may surpass minimum regulatory requirements. HCT/Ps are widely distributed nationally and internationally, and imports of HCT/Ps occur but only for specific types, such as HPCs. Donor derived infections from use of HCT/Ps have included viruses, fungi, bacteria, mycobacteria, and prion associated disease.

So, to finalize Section 3 yesterday, challenges of traditional screening and testing approaches for donors of HCT/Ps, correlation of positive and negative serology and NAT results with the medical history interview is effected by a number of influences, including the interviewee relationship to the deceased donor. The donor medical history interview is useful for avoiding unnecessary recovery of tissue but is not sufficient to assure recovery of sero/NAT-negative donors. Donor blood samples collected post-mortem demonstrate a higher rate of positive communicable disease test results and that appears to be related to hemolysis but the underlying cause has not been studied. Studies are needed to investigate why inaccurate communicable disease test results occur, both positive or negative. When testing needs for HCT/P donors differs from testing performed for blood donors, collaboration is needed between tissue banks and test kit manufacturers to advance scientific knowledge.

Persistence of disease can vary among

types of HCT/Ps, which is a very general summation there; and that's what we have. But, again, we weren't expected to try to cover every single point that was made; it's just a summary. So, I hope that was helpful as we lead into discussion today.

So, Rich.

DR. FORSHEE: Good morning, everyone, and welcome back for Day 2 of our workshop. We're all really excited about this morning's session. We're going to be talking about how to pull together all of the different aspects of benefits and risks that we talked about yesterday in a more systematic way in order to help aid the kind of difficult decisions that we need to make. So, I'm going to start off talking a little bit about ways to think about benefits and risks and ways to think about making those decisions. Then we're going to have a series of speakers talking about some of the things that are unique to a few of the different tissue types that we need to deal with; and then, finally, George Gray from George

Washington University is going to talk about some of his experience about using modeling approaches to make difficult decisions when there's a lot of uncertainty.

Again, my name is Rich Forshee. I'm with CBER in the Office of Biostatistics and Epidemiology. I wanted to start by reminding everybody that what we're talking about really isn't new. The FDA has been required to make difficult decisions requiring data from lots of different sources for a long time. I've taken this from -- Flickr's got a wonderful historical folder of FDA images, and I took this slide from that folder. What we're looking at is something from 1964 when, then Commissioner George Larrick, was trying to illustrate what the FDA did in order to make decisions and how it reached far beyond its own staff to obtain data and advice.

The issue still remains how do you put all this together when you're making a decision? So, I'm going to be talking about four main topics. I'm going to discuss some of the basics

in the field of benefit-risk assessment, particularly, as it regards medical products. I'll talk about the data needs, and here I'm going to be moving more into the tissue area. I'm going to discuss the role of modeling and simulation in integrating all of these different sources of data; and then I've got a few concluding thoughts.

I also want to say, given that I only have 20 minutes this morning, all of this is intended as a high-level overview. We teach multi-day courses going into the details of each of these topics; but, hopefully, this will give you a flavor of why this can be useful and what's needed to make it work.

So, I'm not going to be going over each element of this slide. This is taken from an older FDA guidance; but I just wanted to point out that there are a lot of important pieces when it comes to making decisions about how to manage the risks of medical products; and these involve both pre- market phases as well as post-market phases; and I also want to highlight two important pieces

that are generally applicable.

One is this notion of risk management. The benefits and risks of a product aren't something that's inherent to that product. The ways that we decide to use that product are going to affect what the benefit-risk balance looks like; and that's one of the things that we need to consider in making our decisions.

The other point from this that I want to highlight is the critical importance of risk communication. Indeed, at the FDA, a lot of times our risk management is risk communication, making sure that people are aware of the scientific base of knowledge, what the benefits and risks are, and how they can use a product effectively.

The overall thing that I want you to take from this diagram is that the benefit-risk assessment process is a complex and iterative process, and it involves many participants. This isn't something that's just done at the FDA. It's a process that involves all of the stakeholders in the field.

The cartoon on the left is just there for a little bit of amusement early in the morning talking about the importance of thinking about baseline risk when you're talking about relative risk. The statisticians in the audience should really get a chuckle.

So, I want to talk a little bit about some of the things that go into the risk management process. There are a few key things that need to be considered when thinking about risk management for medical products. The first is that, particularly, in the pre-market phase, we need to be assessing a product's benefit-risk balance. A lot of this is going to come from the whole body of pre-market data; but, especially, the phase 3 clinical trials will contribute a lot to our assessment of the benefit-risk balance of a given product.

Going to the point I made about risk management that the benefits and risks aren't inherent to the characteristics of the product, but it involves how it's used as well. Risk

management is also going to involve developing and implementing tools that are going to help to minimize a product's risks while preserving the benefits of that product. Then we'll get more experienced with the product as it begins to be used; and so, we'll need to be evaluating the effectiveness of the tools that we put together to get the right benefit-risk balance and we need to reassess when we see in practice how these have worked, what the actual benefit- risk balance in practice seems to be. And I mentioned that this is an iterative process. We need to be continually assessing what the benefits and risks in practice appear to be and making adjustments to continue improving the benefit-risk balance.

More recently the International Conference on Harmonization has released some new guidelines for thinking about benefit-risk. In particular, these guidelines are targeted toward the sponsors and how the sponsors should think about explaining their view of the benefit-risk balance of a product that they want regulatory

bodies to consider. The final guidelines were published last year, and they're available on the ICH website. The key idea from this guidance can be summed up pretty easily. What the ICH guidelines are asking from the product sponsors is that the sponsors should provide a succinct, integrated, and clearly explained benefit- risk assessment of the medicinal product for its intended use.

Diving down into this just a little bit further, some of the highlights from the document -- and, again, obviously, in 20 minutes I can't cover all of the details of it. I will say it's a relatively short document so it's something that's not too intimidating if you wanted to go to the website and read it. But some of the highlights in terms of thinking about the benefits, the guidelines ask that sponsors consider the nature and the clinical importance of the benefit. And in the topics that we're discussing here, that means that when we're considering the benefit-risk balance it's important that all of the

stakeholders understand the therapeutic context in which the product is going to be used.

In terms of risks, some of the things that the guidelines ask people to consider are the severity of the adverse event, frequency of the adverse event, whether or not it's reversible. It's a big difference whether something can be treated and people can recover versus whether it's going to lead to a lifelong condition that needs to be managed. And the final factor that was considered was the tolerability of the adverse event. In this case, it would be the tissue recipient.

Still from the ICH guidelines -- I was a member of that working group -- we spent a lot of time discussing how to identify the key benefits and risks; and this applies more generally when we're thinking about benefit-risk assessment. You're going to need to focus any benefit-risk assessment -- you usually aren't going to be able to address all of the benefits and risks that one might consider -- so, you need to figure out which

ones are going to be most important for the decision making process.

So, some of the things that the guidelines ask sponsors to consider for identifying the key benefits and risks -- for benefits, one is the clinical importance of the benefit. So, some of the things that you can consider here is whether the benefit in this case of the tissue product that we're considering whether it's curative; life-prolonging; whether it only provides symptomatic relief; are there other factors of the clinical importance that are relative to making the benefit-risk judgment.

Another question to consider is how likely is it that the recipients will receive the benefits compared to the controls. So, with some products almost everyone who receives the treatment is going to get the expected benefit. For others, there's a lot more variation in this. And it's also important to describe the strengths, limitations, and uncertainties of the evidence that's related to each of the key benefits.

Under risks, some of the things that the guidelines ask people to consider are the seriousness or the severity of the risk; the frequency; the reversibility; and the tolerability. And, again, under risks, people are asked to describe the strengths; limitations; and uncertainties of the evidence. So, I think all of these can apply to the kinds of benefit-risk decisions that we need to consider in the tissue world.

One of the next steps in a benefit-risk assessment process is to start identifying what some of your options are. After you've identified things related to the product, you have to consider what actions you might take; and I just wanted to highlight a few here. Some of the possible options that we could take with managing the risk of tissue products in the face of an emerging infectious disease -- first of all, we can decide that the status quo is fine, and the decision can be that we're not going to take any action. Another approach can be to use risk

communication to try and manage the additional risks that come up in the face of an emerging infectious disease.

Yesterday, we also talked about the possibility of using questionnaires to identify donors with risk factors. This is something that has been done frequently, especially when there aren't tests that are available. For example, with the risks from Variant Creutzfeldt-Jakob Disease, we have applied travel questions to identify people who've spent a considerable amount of time in areas that may have put them at risk for vCJD. However, this was also discussed yesterday, there are real limitations in terms of dealing with questionnaires, including -- as Scott reminded us this morning -- oftentimes when recovering tissues, you're not dealing with the individual themselves, but you're dealing with someone who is providing the information on their behalf.

So, another option that could be considered in the face of an emerging infectious

disease is to use some sort of screening test; and we had a lot of the discussion yesterday on the screening test. Some of the issues that can come up with regard to screening tests are -- in some cases, we can consider whether there should be regional or seasonal testing. This is, particularly, true for some vector-borne diseases where they may not be nationwide, and these are considerations that you should review.

We also have examples from the blood screening area in which a trigger has been used in order to require more thorough testing of donations; and the example from the blood screening world is that during periods of low circulation for West Nile Virus, they allow pooling of samples which reduces the sensitivity of the test, but still provides a means of identifying when West Nile Virus might be circulating. Once they get positive tests on the pooled samples, they are required to switch to individual testing in order to increase the sensitivity of the tests. So, these are all

options that could be considered to try and manage the risks of an emerging infectious disease.

Next, I want to talk about data needs. A lot of these data needs were discussed during yesterday's presentations. One of the things that a benefit-risk assessment needs to do is to combine all of this information for an overall assessment. So, some of the things that we need for doing benefit-risk assessment in the HCT/P world, we need information on the incidence or prevalence among donors. For an emerging infectious disease, we're probably not going to have historical data, but in other situations, historical data could be very useful. We need information on the effectiveness of the donor screening questionnaires, and NAT or antibody screening test. We talked some about this yesterday, but this is something that we would need to have available in a systematic way for doing benefit-risk assessment.

We also need to consider whether the risks increase or decrease between collection and

transplantation to a recipient. And, again, there were a number of items that were discussed about this yesterday. Some of the speakers discussed how processing failures can increase the risk of a product. We also discussed how there might be some interventions, such as the sperm-washing technique that was discussed in reproductive medicine, and how that might decrease the risk. All of these are factors that should be considered about what happens between the time we collect an HCT/P and when it's finally used.

Finally, we also need to consider information on the consequences of the transmitted infection and the benefits of the treatment. This is where we start trying to balance the overall benefits and risks of the product; and, again, historical data is useful if that's available.

A lot of the work that I do is in modeling and simulation. And modeling and simulation is a way to combine all of the many different kinds of evidence that we need to consider; and, in my experience, it's particularly

useful when the uncertainty is high and the data are limited. I want to just mention, at a high level, some of the things to consider when we are trying to make a good model; and some of the characteristics of a good model -- as many others have said in the past -- you want a model that's going to be as simple as possible, but as complex as necessary, to capture all of the factors that really affect the outcomes that you care about. You also want it to be an accurate reflection of reality. It's not going to be a perfect simulation of reality because models necessarily need to simplify in order for us to be able to understand them and use them; but you want it to be as accurate as possible.

It's also important that a model be robust to changes in assumptions. If there's one critical assumption in the model that would change the action that you would take, that's probably not a very useful model for basing your decision on.

I also wanted to talk about the

importance of models for communication. A good model is going to facilitate discussion about the nature of the risk and the risk management options, and it's going to be designed with future risk communication needs in mind. Finally, and perhaps most importantly, a good model is going to be useful to decision makers. Model making, particularly in the regulatory context, is not an academic exercise. It has a specific purpose of trying to help people make and communicate useful decisions.

I'm going to give just a quick overview of what a part of a benefit-risk assessment model might look like in the tissue world, and try and highlight how many of the things discussed yesterday would need to feed into a benefit-risk assessment model. And here I'm assuming that we're developing a model for a hypothetical emerging infectious disease that has just come on the scene. And one of the things that you'll want to consider is you'll want to get to this question of how many false negatives would we expect under

the different options that were considered. And for this, you're going to need lots of different kinds of data to estimate this. An intermediate thing that you want to estimate is the number of donations from infected donors that you're likely to see; and this is going to be a function of the incidence or prevalence of the disease among the donor population. It's going to be a function of how many tissues are collected from a potential infected donor; and it's also going to be affected by how well the medical history test is at excluding donors at high risk from being included in the process.

The next thing that would affect the number of false negatives is the sensitivity of the donor screening test that was being used, if one was available. The number of false negatives would then feed in to determining how many transfusion transmissions you actually see of the new emerging infectious disease. And some of the things that would affect the number of transfusion transmissions are the number of exposures, so how

many recipients from a given false negative donation would be exposed to different tissue products. You would also need to consider the probability of transmission. And all of this would have to be tailored to each type of tissue that we were dealing with because the probability of transmission could be affected by many things that happened between the collection and the eventual use.

So this is just a sketch of what a model would look like, but, hopefully, it gives an idea of the kinds of data that we could put together that would help stakeholders build these kinds of benefit-risk assessment models.

You're also going to want to address uncertainty and variability in models. All of the inputs are going to have some uncertainty or variability. Dr. Gray is going to be talking more about the difference between those two later, so I'm just going to gloss over that at the moment. It's important that models accurately convey the uncertainty and variability, and we usually do

this by using computer simulations where uncertain or variable inputs are represented by probability distributions, and we do multiple simulations in order to show how much uncertainty there is in our predicted outcomes.

Benefit-risk assessments are also going to need to do a good bit of work on sensitivity analysis and validation. Dr. Mark Roberts talked about this some in his discussion yesterday -- one of the real benefits of a model is it can help you identify which inputs are having the biggest effect on the outcomes that you care about, and that can guide future research by focusing your research on the inputs that are going to have the most impact on the model results. It's also important that when possible the model should be validated against external data sets that were not used to construct the model. This isn't always possible, but when you can do it, it increases your confidence in that model.

Some concluding thoughts -- I think there's a lot of value to these kinds of more

formal benefit-risk assessments, whether they're done in a quantitative or a qualitative way. One of the most important is that they provide a framework for discussion. When you start putting everything down in a document where you see what all of the inputs are, everyone is talking from the same set of data, and it really helps to understand where everyone is agreeing and disagreeing in the benefit-risk assessment. It's a great way to integrate large amounts of data from many different sources, and it can identify uncertainty in data gaps.

Benefit-risk assessments also help us to compare different policy alternatives. Again, the final benefit-risk assessment is going to depend on how the product is used and how the product is regulated, and benefit-risk assessments help us explore this. It also improves the transparency and risk communication. By having this more formal process where you've put together the benefits and risks, it's a way that we can show what led us to make this particular decision; what

factors we considered; and people can also observe what wasn't included in that model. The one caveat that I want to mention with regard to this is that, particularly, when you have a very complex risk assessment model, they can appear to be black boxes to other stakeholders and this is particularly true if you don't spend a lot of effort on communicating the models.

There're also important limitations -- if you don't have good data going into the model, you're not going to get good results. This is a garbage in-garbage out principle. The risk assessment models are only going to be as good as the scientific theory and data on which they are built. It's also a fact that if we have a lot of uncertainty about the data inputs, there's nothing magic about a benefit-risk assessment model. It can still be difficult to make the decision if you don't have the kind of data that you need and, so, the best decision may not be clear. It's also important to keep abreast of the scientific literature. A benefit-risk assessment is not

something that's done at one time and immutable after that. Changing circumstances or new scientific discoveries can force significant updates to a risk assessment.

And finally, benefit-risk assessment does not replace risk management. Benefit-risk assessment is a tool to help you understand how all the pieces of data fit together; but judgment is still required to choose the most appropriate option. This includes clinical judgment; judgment about regulatory policy and how that affects your options, as well as legal considerations.

So, with that, thank you very much; and we'll be turning to the next session with the speakers; one moment, please.

For the next session, we're going to have six speakers talking about specific HCT/Ps; and our first speaker is going to be Dr. William Tomford from Massachusetts General Hospital. Thank you, very much.

DR. TOMFORD: Thank you, Richard. Good morning. I want to first thank the FDA and Scott

Brubaker, in particular, for all their work, and it's been a terrific conference. I've really enjoyed it. I think we've learned a lot. So, I'm going to start off on the risks -- something about the recipients and the exposures. It's not quite as sophisticated as some of the models we saw yesterday; but, I think, hopefully you'll get a few facts that will help you.

So, I start off with something that I think is a good introduction to my talk. This is a national donor monument, which is found in Naarden, Netherlands. It's a suburb of Amsterdam, about 20 kilometers to the east, and the title is The Climb; and it's actually a recipient. It's called a national donor monument -- if you Google it, it's under the national donor monument -- it's actually a recipient. He's climbing out of this abyss here, supposedly. This is a gold tablet upon which he is beginning to stand. You can see his knee is hyperflexed there. He's probably going to tear that meniscus, but that's okay. At any rate, he gets a new lease on life by climbing

this platform, and he's able to do that through the organ or tissue donation. What I found interesting about it and the reason it relates to my talk is that it's actually a recipient, although it's called a national donor monument, but it's actually a recipient. So, in my opinion, we have to pay attention to both, the donors and the recipients are really closely tied together.

I want to first start off with a little a bit about tissue donors. There are 30,000 tissue donors annually, according to Donate Life. This includes all tissues. About 2 million tissues are taken from those donors and the ones we want to focus on for the next few minutes are the 1.5 million musculoskeletal allografts transplanted annually. I think it's particularly important to realize, doing the math, that's an average of about 50 donor tissues per donor. So, if you think about the possibilities, 50 recipients could be infected if that donor is sick. So, it really shows the responsibility that we have making sure those donors are not sick.

I wanted to look first at the allografts. There are two types of allografts. Allografts can be classified in many different areas, many different ways; but I have classified it into two types. First, is the process of sterilized -- two caveats about that -- one is processing has really two benefits. One, it removes the blood. The viruses are in the blood and the white cells. So that's a great benefit. They sterilize various ways -- gamma radiation, e-beam, various proprietary methods, chemicals; but, suffice it to say, this includes about 99 percent of the tissue allografts that are transplanted in the U.S. annually. And certainly includes all the bones, the bone void fillers, structural grafts, demineralized bones -- there are about 100,000 deposits of this or more used annually. All the ligaments, menisci and tendons -- there are about 30 or 40 fresh menisci transplanted a year in the U.S.; but that's, obviously, a very low number. This accounts for the great majority of processed grafts

transplanted each year.

So, the non-processed are mostly fresh, meaning the blood are still in them. If you just include the osteochondral grafts, it's less than

percent. If you include the mesenchymal stem cells, it's about less, or close to 3 percent; but I just used 1 percent because these are the main orthopedic grafts, at least. Osteochondral grafts are used in knee cartilage reconstruction -- people we don't want to put a joint replacement in -- only about 1500 grafts used in the U.S. annually. This area is increasingly very popular now, and these grafts are kept in culture for several days; obviously, treated in antibiotics but not sterilized. Someone else among our speakers may speak on mesenchymal stem cells, but there you can see there are about 50,000 of these grafts used a year now, mostly by spine surgeons. So, the other fresh grafts not processed accounts for a small number but, nonetheless, significant at 50,000, I think.

So, let's turn to the recipients a minute. You can see the definition I have there, someone who requires a tissue allograft, orthopedic tissue allograft, at least. So, about percent of the grafts that orthopedics uses are in sports or trauma injuries, bone defects -- scoliosis, for example. All of these are put in, generally, into healthy adults, young and old. Some in kids, but mostly -- I'll get into that in a second. About 10 percent of the grafts we use in degenerative conditions. They would be revision joint replacement, some non-unions; it's about 10 percent. These people are, generally, elderly; otherwise, we wouldn't be doing a joint replacement on them, and they are also healthy. About 1 percent is used in diseased or malformed or absent. These would be cancer patients, for example, pathologic fractures, or spina bifida, some congenital malformations. So, in the processed allografts, as I mentioned, diseased transmission is negligible. We've heard about that from Dr. Eastlund and other speakers

yesterday; and the recipients include all ages. So, I don't think it's a huge problem to worry about the processed allografts. Of course, we do all the testing; but, nonetheless, they are treated so they're sterile and the blood is removed.

Non-processed allografts, I think, is where we're vulnerable. These are the ones that are not sterilized, blood is still in them. Disease transmission in these is dependent upon the reliability of the screening test, both for the donor -- screening test, serological test, as well as culture of the tissue. The other recipients, as I mentioned, include elderly, MSC or spine fusions, but mostly athletes, young people, weekend warriors receive the OC grafts.

What's the availability? I was asked to talk about shortages. So, shortages are related to graft types. These, for example, bone chips in the struts are abundant. There is a concern among the sports medicine surgeons about anterior tib verses posterior tib tendons. That's really not a

concern for this audience because they're all sterile. The ones that we are concerned about are osteochondral grafts which are non-processed and fresh. There is a shortage of those. That will probably continue for the next several years.

What about the alternatives? Well, synthetic bone doesn't work as well. There's a tricalcium phosphate that mimics cancellous bone in the body. Nonetheless, it's about three or four times more expensive. It's not as available as bone chips, allograft bone chips. So, that's a concern as an alternative. There's no alternative for tendons, human tendons, obviously; and there's no alternative yet for bone and cartilage. Obviously, joint replacement is an alternative with cartilage, but not in a 20 or 25-year old patient.

One of the benefits of using allografts is surgical benefits are less operative time; it's less invasive; it's a faster recovery; and the patient benefits, obviously, from faster recovery, less pain, and only one incision. The shortages

-- most musculoskeletal grafts are used to improve function in, obviously, upper extremity, lower extremity, and in the spine. So, the shortage results in loss of mobility if reconstruction cannot be performed; and that's a concern for all of our patients.

Thank you.

DR. FORSHEE: Thank you very much. Our next speaker this morning is Dr. Richard Jonas from Children's National Medical Center.

DR. JONAS: Great, thank you very much. It's a great pleasure to be here. I'm going to be talking about applications. So, I'm the Chief of Cardiac Surgery at Children's National Medical Center here in Washington, D.C.

DR. FORSHEE: I'm sorry; could we have the presentation for Dr. Jonas, please?

DR. JONAS: That's the one. Again, I'm going to be talking to you about clinical applications of allograft tissue in congenital cardiac surgery. So, nearly 1 percent of babies born have a congenital heart problem so that

translates to about 40,000 babies per year in the United States. About half of these will require surgery at some point; and that's usually during the first year of life. So, there are around about 1 million children alive with congenital heart disease, and more than 1.4 million adults alive in the U.S. with repaired congenital heart disease.

Today, we attempt to correct most of these problems very early in life; so, if you look here at the age distribution for Children's National, around about a third of our patients undergo surgery in the first month of life; another third in the first month to a year of life, so infants; and you can see that nearly 10 percent of patients today are adults, and that's a growing number.

We're learning a lot about the genetic basis of congenital heart disease. Around about

percent of babies today are found to have copy number variants verses 5 percent in the non-congenital heart population; and there are a

lot of syndromes that co-exist with congenital heart disease, many of them associated with various levels of immunodeficiency like DiGeorge syndrome, which has been known for a long time with deletion of 22q11. What we attempt to do with kids with congenital heart disease is to take them in one of two tracts -- either they go in a biventricular direction, and basically have a normal in-series circulation with a right ventricular and a left ventricular; and that could include closing off communications. These are the commonest things we do like close ASDs and VSDs. There are various obstructive legions, like coarctations, valve stenosis; and then there are a lot of more complex problems like transposition of the great arteries where we have to switch around the aorta and the main pulmonary artery.

Around about 10 to 15 percent of babies are born with insufficient chambers or valves to achieve a biventricular circulation, and they will go along the single ventricle track which requires three operations -- one in the newborn period, to

allow for the high pulmonary resistance at birth; one at about four to six months as the lungs are becoming more mature and have a lower resistance; and the final stage, the Fontan procedure, at two years of age. So, our goal is to establish optimal cardiovascular physiology as early in life as possible because that will optimize the child's development of all organ systems, including the brain.

But, really, many, many of the operations really have to be custom designed to accommodate each individual's unique anatomy and physiology; and we do want to incorporate growth potential since we're operating mainly on newborns. So, our choice, number one in reconstructive material is autograft tissues -- that's where we use the patient's own pericardium, very frequently; but other alternatives include various synthetic alternatives, xenograft alternatives, and allograft tissue. It was Robert Gross at Boston Children's, 1945, who was the first to pioneer the use of allograft tissue in a

cardiovascular procedure when he resected a coarctation of the aorta. Now, once again, following the principles of avoiding lack of growth, the usual way to do this operation is by re-section and end-to-end anastomosis; but there are situations where the coarctation is too long, the tissues that are not elastic enough, and some sort of alternative is required; and Gross did not have the option of this synthetic graft. Today, we would have the option of a GoreTex or a Dacron tube graft, but he did not have that as an option; and, therefore, explored the idea of harvesting from a cadaver's heart the aorta and then dissecting out an aortic allograft and using that as an interposition graft.

He also looked at a number of methods of sterilization and, obviously, we're not talking real sterilization. What we're talking about is reducing the burden of bacterial contamination; and he was also one of the first to look at various storage methods such as 4 degree storage, freezing, carbon dioxide-type freezing. So, that

was in the 1940s. In the 1960s, following the introduction of the heart and lung machine in the 1950s, valve replacement first came along and the aortic allograft was initially used in this application, though it's rarely used to date. The commonest options used today, certainly in adults, are so-called mechanical prostheses, like this pyrolytic carbon St. Jude Medical cardiac valve, or a

(inaudible) heat-treated xenograft valve, like this porcine valve; and there are various other xenograft alternatives.

But, as I say, allografts are rarely used in this application directly as a valve replacement. And mechanical and prosthetic valves do have a number of disadvantages. In kids, they have poor hemodynamic performance in smaller sizes; they have no growth potential. Mechanical valves require anticoagulation and bioprosthetic valves have rapid calcification.

So, the sort of procedure that does

involve allografts today is an operation called the Ross/Konno operation. So, this is for a narrow and small aortic valve; and what we do is try to preserve growth potential because we are using the patient's own pulmonary valve and transferring that into the aortic position. We need to implant the coronary arteries and then we need to replace the patient's own pulmonary valve; and the way we do that is to use a pulmonary allograft to connect the right ventricle to the pulmonary bifurcation.

So, moving right along, in the mid-1960s, the concept of using an allograft as a conduit was introduced; and, so, for operations for babies who have this condition, this is transposition with VSD and pulmonary stenosis. We do a Rastelli operation where we baffle a left ventricle to the aorta, and then we need to connect the right ventricle to the pulmonary artery. So we've taken a transposed non-physiologic blue-baby circulation into a physiologically normal circulation with a right

ventricle to pulmonary artery conduit.

This is what happens if you use an alternative bioprosthetic conduit to an allograft. You get a lot accumulation of pseudointima within the Dacron and these conduits contain a xenograft valve that is very susceptible to calcification in young kids. So, pseudointima accumulation and all the disadvantages of xenograft valves; and there are many studies that have looked at the durability of allografts verses alternative bioprosthetics -- and this is verses the Contegra graft. It's a bovine jugular xenograft conduit treated with glutaraldehyde that does not perform as well as the allograft alternatives.

So, by the 1980s, cryopreservation of allografts had become available; and this really expanded availability and also at this time there was really an explosion of ultra-complex reconstructive procedures for congenital heart problems following the introduction of prostaglandin E-1 that allowed us to keep babies with very complex problems alive, and the

introduction of echocardiography for non-invasive diagnosis.

So, a condition like hypoplastic left-heart syndrome where there is aortic atresia, the ascending aorta is often no more than two millimeters in diameter. So, today, these babies have a reconstructive procedure called the Norwood operation, which involves reconstructing the aortic arch with some form of allograft tissues proven to be by far the most durable in this setting.

So, here we are reconstructing the aortic arch as part of this Norwood operation. And this is the first stage. As I said, the neonatal stage, with two subsequent stages at six months, and at 2 years. Rather remarkably, these kids -- this was a miraculous operation in the 1980s. Today, these kids can go on, go to school, play sports, do regular things.

Now, there's no question there's a chronic national shortage of allografts, particularly in pediatric sizes; and, as we have

already heard about, one does have to balance up the regulation of disease risk against the chronic inadequate supply of allografts.

So, in conclusion, cardiac allograft tissue is widely applied in congenial cardiac surgery. Performance characteristics and durability are better than prosthetic and xenograft alternatives.

Thank you very much.

DR. FORSHEE: Thank you very much. Our next speaker is Dr. Richard Kagan from R.J. Kagan Consulting.

DR. KAGAN: Thank you very much. I have no conflicts of interests. So, as a burn surgeon for nearly 35 years, one of the things that we had to grapple very early on was what's the skin there for in the first place because with major burn injuries, where our barrier to the environment is completely disrupted, we have to remember that the epidermis carries the barrier function; it has regenerative capacity; and it contains our skin appendages, such as sweat glands and hair

follicles.

The dermis, which is often not thought about by many not in the burn world, provides the mechanical strength to our skin; provides host defense, is important for repairs. So, in a full thickness burn injury where both the epidermis and the dermis are destroyed, there is no possibility of repair, merely contraction. And lastly, that layer contains the nutrients supplied to blood vessels and the nerves.

So what are the benefits of HCT/Ps in burn wound management? Primarily, it is used to reduce evaporative of water and protein losses, which in the case of patients with very extensive burn injuries, can be extremely important, will prevent tissue desiccation. For example, if we're to excise a third degree burn and leave exposed fat, if we leave it in the open, that fat will desiccate and become infected; so it requires a cover. The HCT/Ps also suppress bacterial proliferation by providing a temporary skin substitute, if you will. It reduces wound pain,

particularly when used in cases of deep partial thickness injuries where not all the nerve endings have been destroyed. It will also stimulate neovascularization in the wound bed, and promote epithelialization when used in the case of the partial- thickness wounds where there is that ability to regenerate from the dermal elements.

So, the traditional indications for use of HCT/Ps in burn patients have largely been in the area of excised burn wounds, where it becomes necessary to ensure, or at least try to have survival and function as an acceptable outcome. At one time, it was used to cover widely expanded autografts in the case of patients with burns in excess of 60, 80 percent body surface area. There's not a lot of donor skin left for the surgeon to use; and so we would go to a technique called meshing to expand that surface. Unfortunately, it's like a fishnet stocking where there's a lot more hole than there is skin and you need something to cover the subcutaneous tissues while those epithelial cells migrate across the

gaps; and, so, lots of times overlay technique was utilized -- rarely anymore. They're occasionally used in the case of exfoliative skin disorders such as toxic epidermolysis and Stevens Johnson Syndrome, but nowadays, mostly due to expense and availability of some more efficient dressings, most of them containing silver, that those are probably taking the place more than allografts are. It's also very useful in testing the wound bed for autografting. This tends to be the areas where you have an extremely deep injury. You're almost down to bone or deep tissues, and you don't want to take an autograft with the possibility that it'll fail. So, in many cases, using an allograft to determine if it will adhere or even vascularize will help you determine whether or not that's a wound suitable for autografting.

We've also used it when I was at the Shriners Hospital as a dermal template for autologous engineered skin that we were growing in our laboratory; and lastly, it's used quite a bit in the case of necrotizing wound infections to

cover the wound and allow the patient to stabilize before returning them for a procedure where you actually have to harm the patient by taking the donor site.

For the temporary wound coverage in the burn patient -- as far as the HCT/Ps -- in my hospital, we preferred to use fresh human allograft skin that was maintained in culture media at refrigeration temperatures for a maximum of 10 days. We also had used cryopreserved skin. That was what I was most used to until I came to Cincinnati; but, as I'll show you in an upcoming picture, there's a big difference in terms of the outcomes that you can expect. And, lastly human amniotic membranes -- for which I have almost zero experience -- and largely in the early days, this was due to its unavailability.

So, if you look at the differences between a fresh allograft, which is in the top panel, and a frozen allograft in the bottom panel, these are both from Caucasian donors and you can see it at Day 5 the fresh allograft skin has

actually vascularized and looks just as good as an autograft would. The bottom one shows you that there's already some epidermal blistering; and, actually, both of these patients were severely ill; both were under the age of two; both had severe inhalation injuries; both were on tracheostomies at maximum ventilator settings; multiple chest tubes had been placed, they were septic; and the best thing we could do was eliminate the wound from the physiology with this temporary wound cover.

So, we found that with fresh skin it had enhanced engraftment, better vascularization, better control of microbial growth; but it did require exceptional release. And so as the medical director of the tissue bank, and also the Chief of Burn Care at Shriners Hospital, I couldn't release the tissues and then ask these using-surgeons to sign off on it. So, we had to make deals with our partners that if I signed off on the tissue one of them would sign off; and we required this for the other burn centers that used

the skin from our skin bank. But I would specifically speak with each, the other burn surgeon, and let them know the risks and benefits of that so they could adequately explain it to their patient's families.

So, we look at the burn patient and the risk factors for susceptibility to disease and disease severity. There are actually some that are related to the burn injury itself. There's first of all, as I said, loss of a skin barrier, changes in local skin flora. We have to remember the skin isn't sterile. There are also changes in pulmonary and GI tract flora and wound ischemia because the skin -- largest organ of the body -- gets the least amount of blood supply after injury due to the basic constriction that occurs; and there are also patient-related issues as well. There are pre- existing morbidities, primarily in the case of adults, extremes of age; and I can tell you many burn surgeons aren't comfortable taking care of a two year old with a

or 80 percent burn, even though it's an

(inaudible) experience in the area. Pregnancy, obviously, causes a lot of difficulty; and there's also the altered immunocompetence that occurs after a significant burn injury; and I've outlined a few of those facts here.

So, these patients become rapidly immunosuppressed as a consequence of their extensive injuries; their decreased natural killer activity; decreased T-helper cell activity; and increased inhibitor cells, and the like, in decreased complement activation, macrophage activation. There's decreased immunoglobulin production that takes sometimes in the area of two to three weeks for recovery to occur; decreased neutrophil chemotaxis and phagocytosis; and altered antigen presentation processing. It's essentially as if you gave them agents that we would give after a transplant.

So, the most common microbes that we see after burn injury are actually those that belong

to the patient -- the gram-positive cocci, the staph and strep, which normally inhabit or colonize our skin, are the first to appear when we are doing the wound cultures after burn injury. Beginning in the second week it becomes water borne bacteria because these patients are laying in bed. There's a lot of moisture, and they begin to get colonized with a bacteria primarily from their GI Tract because these are not mobile patients. They're using the bed as a bed pan, if you will; and you really cannot sterilize these wounds; and then there's the enterococci, more recently. The fungi -- primarily, we see candida, although on occasion, we see aspergillus and mucormycosis -- would actually alter the immune system of the surgeon because it scares the you-know-what out of us when we see those types of fungal infections that are very invasive.

And lastly, the viruses which, while present, rarely alter the course of mortality or even length of stay as been shown in a number of studies. Cytomegalovirus, when found, rarely

causes systemic disease; and when we do see herpes simplex, it tends to be localized skin lesions and nothing is systemic.

Historically, Dr. Bill Monafo first described transmission of bacteria, pseudomonas in particular, back in 1976, when I think nobody knew anything about skin banking and efforts to decrease transmission. Since that time, I'm not aware of any reports of a bacterial transmission from a cadaveric donor to a burn patient; and, quite frankly, from the burn surgeon's perspective, I wouldn't want the bacteria that are on the burn patient to go to anybody else because the ones that have been exposed to antibiotics, and the like, and much more severely ill, and much more lethal. There was one report in the Lancet by Clarke about HIV-1 transmission; however, that was later proven to be false as the recipient had never been tested and had more risk factors for HIV than did the donor. So, that report was largely discounted; and there's one report from Pat Kealey from Iowa in which he had some patients

who were CMV negative who received allografts who converted to CMV positive; although it's much more common that it's a reactivation of latent virus. But, again, that has been shown to have very little consequence in the care of these patients.

A little bit about skin donation and some of these numbers are estimates. I think the numbers regarding number of donors of skin has pretty much plateaued in the 10- to 12,000 range, although we're hoping that the AATB will be able to provide us with some data as to that in the future. The best news is as more agencies have become involved in recovering skin, they've gotten better at it, and the yield per donor has gotten much better. What we do if there is the unavailability of these HCT/Ps; and I'm talking specifically about allograft. We would need to use a less effective temporary skin substitute which would (inaudible) decrease wound adherence; increase wound contamination, need for more operative procedures to replace that skin substitute, which means every time they go, more

anesthesia, more consequences of another operation; it increased overall cost primarily through extended length of stay. So, we would have a greater likelihood of wound infection, potential increase in both morbidity and mortality; and, obviously, huge increases in healthcare costs which is already pretty astronomical for patients with a 60 to 80 percent burn -- sometimes in excess of $1 million per acute hospital stay.

So, some of the alternatives to HCT/Ps would include porcine xenograft, not commonly used by most, although it's fairly inexpensive, it's just not very effective; and the variety of synthetic dressings; Integra, which is more of a partial skin replacement because it replaces the dermis with the neodermis; Epicel, which is actually not a skin

(inaudible) alternative, it's actually a skin replacement, but its only epithelial cells in the history with that is that the take

is extremely poor and results in extremely fragile skin that requires numerous repeated operations. And I won't go through the whole list because, actually, the list could take up about four slides.

So, years ago I tried to put into context in terms of either per square foot or approximately per thousand square centimeters what these things cost. Allograft is currently in the range of about $2,000 per 1,000 square centimeters; but if you look at things like the amnion, 16,000; Integra, close to $14,000. You know, if these products fail, you don't get a rebate from the manufacturer; you just have to take care of the infection, try to start all over again; and, again, here you are perhaps with an infection, more hospitalizations, greater length of stay.

So, in conclusion, allogeneic skin substitutes have been an important part of the

burn surgeon's armamentarium for more than 50 years. Their successful use in the care of the burn patient has been well documented for both partial and, primarily, full-thickness burn injuries. Transmission of infectious disease is extremely rare and has not been clinically significant even in immunocompromised thermally-injured patient. And, lastly, the benefits of the HCT/Ps, in my opinion, far outweigh the risks of potential infectious disease transmission when the tissues are recovered and processed in accordance with FDA and AATB guidance.

Thank you.

DR. FORSHEE: Thank you very much; and our next presenter is Dr. Jennifer Li from the University of California Davis Eye Center; thank you.

DR. LI: Hi, Good morning, again. I was asked to talk about, again, the characterization of infectious disease risk to ocular recipients. I have no financial interests.

As we heard yesterday from Dr. Marian Macsai, the reality is with ocular tissue the evidence of transmission of communicable disease is rare. It has been demonstrated for rabies, HBV, CMV, HSV, CJD; but the reality, again, is it's uncommon. To date, there is no evidence of any ocular donor recipient disease transmission for a whole host of diseases, and as we heard yesterday, there are cases where there have been donor recipient disease transmissions through other tissues, but the ocular tissue recipient did not seroconvert. So, there is some sense that perhaps we have some immune privilege with the ocular tissue, especially being fairly avascular.

To understand a little bit more about some of the risks or lack thereof for our ocular tissue recipients, I think we have to understand a little bit about the diversity of ocular donor tissue recipients. In the U.S. almost 50,000 corneal transplants are performed annually. Eye banks from the U.S. supply about 80,000 donor tissues across the world; and, again, there is a

wide range of indication and recipients for these tissues.

In terms of the types of tissue that we primarily transplant, I would categorize it as three different types. One is something called penetrating keratoplasty, which is a full-thickness corneal transplantation; the second and third are types of tissue that we are transplanting that are partial-thickness corneal transplantations, there's endothelial keratoplasty and anterior lamellar keratoplasty. These surgeries are becoming more and more common as our surgical techniques are improving where we are able to decrease surgical risks and post-operative risks by performing these partial-thickness corneal transplantations which target specific layers of the cornea that are diseased as opposed to replacing the entirety of the cornea.

In general, our ocular tissue recipients are not systemically immunosuppressed. For the most part, they're very healthy. The exception of this, of course, are our keratolimbal allograft

patients -- the limbal stem cell transplant recipients. These patients are systemically immunosuppressed due to the fact that tissue is highly vascular, and without the systemic immunosuppression, there is a much greater risk of having a graft failure, graft rejection.

In terms of our patients, again, the vast majority of these surgeries are elective procedures. As a corneal surgeon, I have the luxury of scheduling a surgery on a given day and really expecting that there will be tissue, adequate tissue quality, adequate tissue for my surgeries, and for my patients. As you can see, there are very few tissues that are distributed for corneal emergencies annually. About 4-500 tissues a year are distributed for true corneal emergencies; and, again, a corneal emergency are things like corneal ulcers that are already perforating; a corneal perforation related to perhaps an underlying autoimmune disorder. These are issues for the patients in terms of ocular salvage. We are doing these surgeries in order to

preserve their eye. The potential for some of these patients to regain vision may be relatively low, but, again, not life-threatening types of emergencies.

In terms of our ocular tissue recipients, again, penetrating keratoplasty used to be the gold standard for virtually all corneal transplantations; and it's in recent years, about the last 5 to 10 years, the numbers of corneal transplantations that are done via penetrating keratoplasty, or full thickness, have been declining. However, there's still a role for full-thickness corneal transplantation in our patients. The most common indication, as you can see up here, is for keratoconus. Keratoconus is a disorder in which patients develop a progressive thinning of their corneas which leads to a progressive decline in vision. These patients typically are younger. This disease starts to present in their early 20s, into their 30s; and, typically, these patients, if they're going to need a transplant, will be in their 30s or 40s at

the time of their transplantation. The other indications for penetrating keratoplasty include cornea swelling after cataract surgery. Fuchs' Dystrophy, which I talk about a little bit later, these patients may be on the older side.

I mentioned how in this day and age, more and more we're going away from full-thickness corneal transplantation into a realm of partial-thickness corneal transplantation; and one of the most common procedures that's being performed now is something called endothelial keratoplasty. This is surgery which transplants just the back two layers of the cornea, about 20 microns of tissue is being removed, and somewhere between 20 to 120 microns of tissue are being transplanted into the patient's eye. The most common reason for this is something called Fuchs' Dystrophy. This is a disease more of the elderly. It is a disorder of the corneal endothelial layer, which ultimately leads to corneal edema. Again, the second most common indication for endothelial keratoplasty is also after cataract surgery,

swelling of the cornea after surgical trauma; and these patients are typically older.

Again, what you must remember about these surgeries is that as our techniques get better, our threshold for performing these surgeries becomes lower and lower. Nowadays, for our patients who have things like Fuchs' Dystrophy, we're looking to try and provide them with a quality of vision to allow them to do the things that they normally want to do, things like driving. So, for my patients a lot of time the indication for surgery is when their vision drops below 20/40 which is usually the level of vision required for driving in most states. And, so, you can imagine these patients; although these are not life-threatening, per se -- as some of my colleagues have presented, very life-threatening types of conditions for their recipients -- for our patients, it's very much a quality of life to be able to see and do the things, and to have the independence to do the things that they want to do is, obviously, very important, even for the

elderly population.

So, in general, in summary, for ocular tissue recipients on the whole, we do really have a low-risk population. For the most part, there's usually no systemic immunosuppression, again, except in the case of keratolimbal allografts, or limbal stem cell transplantation.

We talked a little bit yesterday about some of the concerns that we have as corneal surgeons with bacterial or fungal keratitis occurring after corneal transplantation; and, I suppose, from that standpoint, there is local immunosuppression in terms of topical corticosteroids that may increase their risk of developing an infectious keratitis.

Our recipients may be elderly, although that is not always the case; particularly in the case of penetrating keratoplasty or our full-thickness recipients. Those patients tend to be a little bit younger, but are healthy. The vast majority of our surgery is elective which does give us, in some ways, a little bit of

luxury; and we do have a healthy excess of tissue, I think, in the U.S. at least. But one of the big things to remember about corneal tissue is there really is no good alternative to corneal allograft tissue. There really is no artificial corneal tissue that's being utilized. It's been difficult to develop tissue that is artificial tissue that allows for the clarity of corneal tissue, and that is able to be bio-integrated without sort of melting on the surface of the eye.

We do have keratoprosthetic devices which are artificial corneas that are made out of PMMA plastic. Those are utilized, although not as frequently as a standard corneal transplantation for a multitude of reasons. The keratoprosthetic devices have a tendency to extrude; they have a tendency to develop infections, and other complications that can lead to loss of vision in the long run. Additionally, with our keratoprosthetic devices, most of the devices that are used in the United States do require corneal tissue as well as a carrier device for the

keratoprosthesis on the surface of the eye.

So, again, to summarize in general, a low-risk population, the recipients may be elderly, but there really is no alternative to corneal tissue at this time.

Thank you.

DR. FORSHEE: Thank you very much; and our next speaker is Dr. Shamonki from the California Cryobank.

DR. SHAMONKI: Good morning. I'm the Medical Director of California Cryobank, and I'll tell you, despite our regional sounding name, we actually provide probably 50 percent of the frozen donor sperm and donor eggs in the U.S., and that's approximately 70,000 natural and ART cycles per year that are dependent upon donor gametes.

A side note: really regional. When the company was founded in 1977, the founders were considering calling it Century City Cryobank. They really weren't thinking that big. From a branding perspective, much less sexy; so, I'm grateful for the California.

So, who are the recipients of banked reproductive tissue? Donor sperm recipients have evolved over the years. In the late-70s when the Cryobank was established, we were just sort of coming out of the dark ages of donor sperm, and the majority of clients were heterosexual couples with male-factor infertility. Of course, with the advent of ICSI, the progression of technology, as well as some social progress, we now see most of our clients are actually lesbian couples and single women. On the donor egg side, most of our recipients are still heterosexual couples with female infertility, but I expect that we'll see some progress there as well.

All things said, generally speaking, the recipients are healthy immunocompetent individuals; but we need to keep in mind that, of course, there is intention to conceive. And, so, with a successful transplant, if you will, we have an offspring created. So, we have potentially vulnerable recipients, as well as infants that are affected. And, for that reason, when I think

about risk mitigation through these recipients, I'm also very much considering not just the infectious disease consequences but the genetics consequences; and I say that despite the fact that our emphasis today is upon infectious disease because it is virtually impossible for me to uncouple the two when I am performing a risk mitigation in qualifying a donor.

So, another note, just to keep in mind, is that donor options range from, of course, the typical anonymous donor which also we have open ID donors; but they're the same category. But we also have directed donors and that's important because when you're looking at risk benefit ratios, you might have a little bit of a different calculation for a directed donor -- somebody has clearly decided they want to utilize this person's DNA. There's also contingent directed donors and the context of sexual intimate partners in autologous, and so, again, the risk benefit ratio can be quite different depending on who the donor is.

I said that our recipients are generally immunocompetent and healthy but there's one specific population that I'd like to consider separately, and that's a CMV-negative sperm donor recipient. So, the guidance is really pretty general. We understand that we do not want somebody who is CMV negative to acquire CMV during pregnancy. Of course, the risk to the fetus of inquiring congenital CMV are potentially quite morbid; and so, we are all intending to prohibit the banking of a donor who is actively infectious for CMV. But the only guidance is to make sure you test a specimen from donors of viable leukocyte-rich HCT/Ps semen, in this case, to adequately and appropriately reduce the risk of transmission and establish a procedure in order to reduce the transmission.

So, generally speaking, most banks, they will do a total antibody screen. If the total antibody is positive, they'll reflect test for IgG and IgM-specific antibodies. It's not an entirely perfect test. I think that we have great clinical

outcomes from many, many years of data showing that it seems to be effective; but with the advent of PCR being available, we actually have a test where we can directly measure the presence of CMV in a tissue. There is a lot of discord within the reproductive endocrinology community about whether or not we can really trust a CMV result for a donor. Whether or not it's appropriate for somebody who's CMV negative to receive a CMV positive sperm donor; and by that I mean somebody who is been remotely infected, has recovered from the infection from a serologic perspective is not at risk, but if you do test the semen, you can often find CMV shedding in the semen. We don't really know what the clinical significance is of CMV nucleic acid in the tissue. I would venture to say that it's not that significant given the fact that we have years of clinical data or observation, I should say; but it would be nice to have a consensus amongst the users. Particularly, because it leads to a lot of confusion in the treatment of patients and I would like to see the

reproductive tissue banks, at least, approaching this consistently.

Some other clinical considerations -- CMV can drive you crazy. We often see isolated sporadic total antibody positive. We believe they're false positives. This specific antibody would be consistently negative -- that leads to great confusion. We see some donors that have persistent IgM production, albeit lower than you would expect for somebody with an acute infection; but, nonetheless, we try to reflect those with a PCR test just to show that there is no shedding. Again, it makes for your SOR to be very confusing. And then there's a new consideration that has been raised and that is what if somebody is re-infected with a novel CMV strain.

Okay, so, reproductive tissue we think of as one thing; of course, sperm and eggs are very different; and even the preparation of those gametes is quite different. On the oocyte side, traditionally, we've only had fresh oocyte donors. There's obviously no opportunity for a quarantine.

We do have more and more cryopreserved oocytes available. The 2014

(inaudible) data of 30 percent of donor oocyte cycles were from cryopreserved eggs. So, the market is definitely moving in that direction for many reasons.

On the sperm side, we, obviously, only cryopreserve sperm, and there's two preparations. There is the intrauterine insemination preparation and an intracervical insemination preparation. ICI, I believe, is really a hold out from the old days. It's the perfect specimen for an at-home insemination. I'm not a fan of those as you might imagine. At California Cryobank we actually require all of our patients to have a physician attesting that they're under a physician's care to hopefully discourage at-home inseminations. But, nevertheless, depending on how the sperm is processed, I believe it has a slightly different risk profile. In turn, how these specimens are used also would have a slightly different risk

profile. So, an intracervical insemination verses an intrauterine insemination, the big difference is the presence of seminal plasma and white cells, or not. And then, of course, as you move down into IVF and ICSI, you're dealing with really just gametes, and ICSI being a single sperm cell and a single egg.

A cryopreserved ICI vial could be used for any of these procedures. It's, obviously, meant for ICI; although most of our clients that purchase an ICI will subsequently have it washed at their IVF center, and there it will be used for either intrauterine insemination, or it will be used for IVF or ICSI. The majority of the vials that are produced and sold in the United States are IUI vials. We'll get into some of the differences and how they're processed in a minute; but, suffice it to say, you can thaw an IUI vial and immediately use it for an intrauterine insemination or you could wash it further and use it for IVF and ICSI.

On the egg donor side -- very different;

we're dealing with single cells or half cells, if you will, at a time. So, a fresh oocyte could be used for an IVF cycle, it could be used for ICSI, and the cryopreserved oocyte because of a hardened zone of (inaudible) following thawing could only be used for ICSI. When you think about the utilization of these tissues -- the way they're prepared -- I tend to think that an ICSI procedure would be the lowest risk in terms of transmitting an infectious disease, all the way to an ICI which, albeit, very small risk, would carry the highest.

So, how do we prepare these two vials? An IUI vial, as I said, is the most commonly prepared vial, and the important thing is that it's spun through, or washed through, a high-density gradient. So, you have a percoll gradient. The purpose of this is to separate the high quality sperm from the seminal fluid, the white blood cells and any dead or immotile sperm. Subsequent to that washing step, cryoprotectant is added, and so you're banking healthy sperm with

the seminal fluid removed; the white blood cells -- the majority of them are removed -- and you have a dose that's about 0.5cc, and hopefully greater than 10M motile sperm upon thaw. An ICI specimen is simply added to cryoprotectant -- so you have a raw sample added to cryoprotectant -- it's unwashed semen, a 1.0cc dose, and you target 15M motile sperm. The reason why you're targeting more sperm on an ICI processing is because you typically will wash it before it's used in an IVF lab, and so you're trying to have more sperm to start with.

So, in terms of conducting a risk benefit assessment, there is the obvious direct assessment that we're all familiar with, very comfortable with the infectious disease testing that we can perform now. We also, as I mentioned, are very concerned with mitigating genetic risks. And you can never mitigate all risk, particularly, when you're dealing with genetics; but we can directly measure karyotypes; we can do genome sequencing for recessive traits; we do a

hemoglobin electrophoresis and a metabolic panel. It's the indirect assessment that makes us all a little less comfortable; and, interestingly, the diseases that are on the right are the ones that our clients are very concerned with. So, looking at HSV I/II and HPV -- these are, obviously, ubiquitous -- and many of our clients have been exposed to many different strains of HPV; but, nonetheless, there is a lot of concern about how are we screening our donors. And it's difficult because of the ubiquity; there's not necessarily a clinical value in directly measuring for HPV. What we try to do is we take a social history. We have recurring social history that's taken at every donation -- physical exams, of course, are quite frequent and focused on these findings. And other social risk factors we actually get from a psychological assessment, and we even do criminal background checks.

So, we try to mitigate risks by finding the lowest risk donors we can; but we can't directly measure these to any utility, I would

argue. Obviously, emerging diseases, Ebola and Zika -- the best we can do is take a travel history; and, unfortunately, without direct test for Zika, in particular, which, as you can imagine, is very significant to our recipients -- we're stuck with what is really a sort of a cursory surrogate marker right now for mitigating this risk; and it's very concerning to all of us, and very much so to our clients. So, you know, it remains to be seen sort of how the disease emerges within our country and how we can accommodate from a travel risk assessment; but I have been advocating for and hoping for a more direct measurement of Zika in reproductive tissue for almost a year now.

The other, of course, travel risks for CJD have been part of our procedures for some time. And then, I will mention again, multifactorial genetics -- you can tell I really care about this -- we do conduct three generation family medical screening and we have very robust processes in place to try to assess donors who

from the public health perspective and look at the individual because when you're selecting a gamete donor, it's nothing like selecting a blood donor where you simply need a negative donor. There's no replacement, they say, for an individual donor. And when you are subjecting donors to the scrutiny that we do, and you're really trying to find these altruistic donors, and at the same time lowering vial limits year after year because the efficiency of infertility treatment has gotten to the point where we can only distribute so many vials in order to reach what we feel is a comfortable offspring limit per donor, the pressure to find novel donors that also meet our high standards and criteria is getting more and more difficult.

I think the market for using gamete donors is continuing to expand; so there's definitely a push-pull there. And every person who is unnecessary eliminated due to a false positive screening test is potentially very significant. And, so, we always say there's no substitute for the individual; and when you're

I was asked to focus on some aspects of the recipients; and so, who are these patients? These are really, you know, infants to elderly -- the full spectrum of pediatric and adult patients. Most often, these are patients being treated for hematolymphoid malignancies, and less frequently there are other diseases, like very severe non-malignant hematologic diseases, like sickle-cell disease, Thalassemia. Also, some immune deficiency diseases, inherited metabolic disorders, and other more rare tumors, like germ cell tumors and neuroblastoma. But really it's very much in large part leukemias, lymphomas, myelodysplastic syndromes, myeloid proliferative disorders. And this group of patients has a greater susceptibility to infectious disease, and/or increased severity of infectious disease, and that's in part due to the extremes of age, but also to the nature of their disease for which they're being treated. These patients are going to be receiving, or will have received, chemotherapy and radiation, or often radiation

with the chemotherapy; and then, just prior to receiving the cells, they are going to undergo a preparative regime which is often myeloablative or, at least, partially myeloablative; and this is dependent on a few things like age, and disease, and things like that.

Now, my background is also in transfusion medicine; although, for the most part, I probably do like 95 percent in cell therapy, but I tend to try to lean on blood for kind of cues for some of these types of issues -- like infectious disease transfusion, transmitted disease. And, so, really the screening and testing is very much equivalent to a blood donor. And I have up here just four infectious agents. There are certainly others that are tested we saw yesterday.

But for allogeneic blood, the risk of infection per transfused unit is in the 1 in 1M to 1 in 2M range at least for these four agents listed here. And, I was reminded of this paper as I was putting together the talk -- this is from

Zou, Stramer and Dodd at the National American Red Cross. This relates to estimating disease incidence and prevalence in the HPC donor population. Again, it's relying on blood, but, I think, at least -- my colleagues in transfusion medicine -- we seem to think at least for the non-emerging diseases that probably first-time blood donors is where we should assume HPC donors are without more data. And risks -- it's generally at least thought -- that risks may be higher in the related setting as there's definitely an impetus to donate to a family member and sometimes the donor screening questions may not be answered accurately.

And this paper is from Transfusion Medicine Reviews, 2012 and, I think, it just kind of nicely shows at least, minus West Nile, that first-time donors present positive is going to be a fair amount more positive than repeat donors, or like a pedigree donor; and you can see the group -- I'm going to try to point in this column -- here is a ratio of prevalence in the first-time

donor to the repeat donor, it's really just taken that divided by that; and you can see for many of these diseases or markers, the risk is higher with those first-time donors. And, I think, this was actually based on NAT, HIV/HCV. It was still, I think, looks like, obviously, from the table (inaudible) HBV, but I think it probably reflects nicely the current situation for most of these diseases, or entities.

And as John Miller, and others, maybe pointed out yesterday, you're really looking for a perfect HLA match, if you will, in 8 out of 8, or a 10 out of 10, or at least a partially matched product; and so, it really becomes a one product, one patient scenario because, as John showed, I think, with some of his diagrams that the HLA match really correlates with outcomes.

Alternatives are limited, as he showed in another one of his slides. You know, you can always go to a less desirable match, like a haploidentical transplant; but, again, the outcomes are going to be worse. So, alternatives

are truly really limited and shortages of any type would be potentially catastrophic for these patients. And so, at least my perception is that the benefits of a life-saving potential hematopoietic progenitor cell transplant greatly outweighs the risks of death due to their terminal disease and the relatively lower risk of infectious disease.

So, this is in no way meant to be flippant -- as I put this, and I was like, oh, people are going to think I'm just like not being serious here -- but, I've been to other talks where people do kind of -- maybe Mike Busch from BSRI, I think, had a slide showing kind of the daily activities we do and the risks or the odds of bad things happening -- and so, I wanted to kind of pull a couple things that kind of fell into that range of 1 and 1 to 2 million. This sounds awful, by the way -- and then, you know, some other things that we, you know, not to be morbid or anything -- but we know we can get in our cars every day and drive to work, or what have

you, and so, just kind of putting things maybe in perspective, a little bit, I don't know. This is from Time so it's not peer reviewed and, I don't know, I think they're a legitimate entity, I think at least; and I think that's it.

Thank you.

DR. FORSHEE: Thank you to all of the preceding speakers. One thing I would like people to consider is think about how all of these unique considerations for the different types of tissues that were just discussed would affect any sort of benefit risk assessments that we would try to put together. That was part of the idea behind putting these together was to reflect the diversity of benefits and risks and how that would affect any more formal benefit risk assessments that would be done.

Our final speaker for this session and for the workshop today, we still have the panel session so don't go anywhere. But the final formal speaker for today is Dr. George Gray. Dr. Gray is a professor and director of the Center for

Risk Science and Public Health at George Washington University. Dr. Gray also has experience on the government side of this. From 2005 to 2009 he served as the assistant administrator for the Office of Research and Development at the U.S. Environmental Protection Agency and he has also served as the past president and fellow of the Society for Risk Analysis. So he has a very well rounded view of these kinds of risk analysis issues. He's going to talk about how we apply these kinds of assessments to decision making. Thank you very much, Dr. Gray.

DR. GRAY: Thanks Rich and good morning everyone. You guys really have some interesting problems to think about. I will confess, I have spent a lot of time looking at risks benefits trying to think about ways to characterize and quantify them and balance them and the problems that you're thinking about, the applications that you're thinking about are, to me, some of the most interesting things that are out there. They are

very real, they are very tangible and they are really hard questions to think about. I appreciate the time that the previous speakers took to give us some background and remind us of what are the benefits of these technologies, who are the people that are going to benefit, what are the risks and what do those mean for us. What I'm going to do is step back like Rich did early on and say if we're going to think about doing these analyses, if we want to be formal about the way we weigh this, a lot of us have intuitions about whether the risks outweigh the benefits. One of the things that I've learned in a career of doing analysis is a lot of time our intuitions aren't very good. And it really does help us to take the time to do some formal thinking about problems. What I want to do is talk about how things that we have to think about when we want to do a good job of balancing risks and benefits.

So I just want to start with a little bit of a plug for why we really want to do formal analysis, why the kind of modeling that Rich

talked to us about this morning is something that can help us make better decisions. But I want to spend some time about what makes it hard to do. Some of these things have been touched on, some of them haven't so far, and then talk about where things might go as we try to bring the tools of risk benefit analysis into these kinds of technologies.

I really think about what we're calling risk benefit analysis as a broader type of analysis that is really helping us to focus on the consequences of decisions we make. And these decisions can be to use a particular technology but the decision can also be not to use it. Each one of those has consequences. The closest analogy in the world of public health that I work in is something we call looking at with tradeoffs or sometimes health-health analysis where most of the time we're trying to look at the consequences to people's health from making a choice or not making a choice. And what we want to do is understand the consequences of a particular

intervention that we might make.

So one of the most important things about actually talking about risks and benefits is remember that's the way the world works. That there are consequences to either side of a decision that we might make. There are consequences to the health of individuals, there are consequences to the quality of life of people and those consequences can happen on both sides of this. So if we can do a better job of thinking about these benefits and risks and I think this is something that Rich touched on, we can do a better job of communicating with people and that is communicating not only broadly with the public as say FDA might think about doing or communicating with the practitioners but also communicating at the level of the individual patients.

One of the most important things, I think, that can come from this is helping us identify mitigation options. One of the things that formal modeling and formal analysis can help us do is look for places that we might change the

consequences in ways that we hadn't thought about before. What we're hoping to do is to somehow maximize the benefits of a technology while minimizing the risks and carefully thinking through the quantitative implications of different choices helps us to find that maximization. So lots of us use these kinds of pans as a way to think about how we compare risks and benefits and the idea is that one of the things we'd like to do is to have a situation in which we maximize the benefits and minimize those risks.

I want to talk just very briefly and at kind of a high level about some of the challenges in actually trying to do this. And this is drawing on and in many ways we can generalize from a number of the discussions that we've had this morning and things that were learned yesterday. I want to talk about three different things. I want to talk about the problem in actually doing the quantitative estimation of risks. So we might talk about we're aiming for something like one in a million but a question is how well can we

actually estimate what is going to happen. There is discussion yesterday about how well we understand prevalence, how well our testing procedures work, how well we understand what the likelihood of transmission of a disease is. So I want to focus on two particular things that are just inherent properties of the problems that we're dealing with, uncertainty and variability. I want to talk a little bit about assumptions that are made and in many cases they're hidden from us. These are things that we may not acknowledge as assumptions that we make as individuals or as a field or as a profession or that maybe assumptions that are made by others that we have to take into account. And then I want to touch on a couple of others.

But first, risk itself arises because of uncertainty. If we knew what was going to happen we wouldn't talk about risk. Things would be forgone conclusions and we would know what is going to happen. So when we're talking about risk benefit analysis and we're thinking about those

risks that are out there, we have to think about what could happen and then we have to think about even causality. Does this really cause this to happen. And then we have to think about the likelihood of it happening. This is the thing where we often spend a lot of time. What are the chances of a disease being transmitted in a product. We also have to recognize that the consequences differ and this is something that several of our previous speakers have talked about, the consequences of the technology or not using a technology compared to the consequences of the potential risks that are going along there. We also want to know what we can do to manage these risks. Again, one of the things that careful analysis can help us do is potentially sometimes find new ways to manage risks that we might not have thought about before. But in all these cases we've got to recognize that we're using imperfect information because it is what we have at the time to forecast the future. What will happen if we increase the use of this,

decrease the use of this, what are the things that are going to happen and it is an uncertain future.

So when we talk about uncertainties, let's look at the bottom part. The bottom first, uncertainty is situations in which we just don't know what is going on. Sometimes we may not know if there is a causal relationship between a particular vector or infectious agent and an outcome. Or we may not know the dose response. What level of that agent being present in a product is likely to cause disease. So these are things that we genuinely do not know. One of the hard things about this, sometimes we can learn more about uncertain things with further study. So this is one of those places we're saying more research is needed may actually make sense.

Variability on the other hand, is the basic heterogeneity that exists in the world. It is something that many of you deal with every day and that each patient, each person you see is different and they are different for a number of different reasons. Biological reasons, behavioral

reasons, things that are going to influence the potential say, success of an intervention. The thing about variability is it is not reducible it is the state of the world. Sometimes we don't know it as well as we would like to and variability is prevalence of the presence of an infectious agent in the population. Somewhere underlying that there is a true distribution of that prevalence and sometimes we know it well and sometimes we don't know it as well as we would like.

So when we're talking about uncertainty, causality is an important situation. I'm going to show you in a minute an example of this. It is just a reminder of how difficult that can be. One of the other things that we always have to do is generalize from situation to another. And generalizing may be that we've got studies that have been done in one population and we're interested in applying our technology to a different population. We've got observations of rates or prevalence's in one population that we

have to generalize to another. Sometimes we might have situations where we studied a particular factor or particular outcome in animals and we want to generalize it to people. And then another thing that is an important source of uncertainty that goes to the kinds of models that Rich talked about is sometimes we don't know the right way to look at the relationship between two factors. A place that is obvious here is think about dose response. What level is the presence of one virus in a material likely to cause disease. Do you have to have ten do you have to have fifty, how does the probability of disease transmission change with that. That's a really important part of trying to understand risk and a lot of times we don't know the right model for making that prediction. That can be really important and a really hard to deal with source of uncertainty.

There are a lot of sources, variability in these assessments as well and we know that there are biological differences between individuals, their behavioral differences, lot of

things that can matter. So these hidden assumptions that I've talked about are situations where we have to make an assumption about whether there is, for example, a causal relationship. And these can have a big influence on the way things are done and we may not know about them. And this is quoting from EPA, this is an agency I know better than FDA, they actually tell us they deliberately bias some of their assumptions. And if you don't know about this and just use that information it can mislead you. So here EPA says, as an agency policy when they're doing risk assessment, in the absence of data the contrary should be health protective. So the idea is they sort of assume the worst when they're faced with uncertainty. Use of health protective assessment procedures means that estimates while uncertain, are more likely to overstate rather than understate the hazard and the risk. So here's an example of a situation where what we want to be concerned about when there are those hidden assumptions is whether we're putting our thumb on

one side of our scale and a thumb being we are giving more weight to something either on the risk side or the benefits side of our balance that we're trying to strike. Are mobile phones a cancer hazard? This is scientifically investigable. There have tens of millions of dollars poured into this. The data are out, they are available. Anyone who wants to can look at the results of things like the interphone study that did epidemiologic investigations in a number of different countries in Europe, we've got investigations that have been done in the U.S. and lots of other places. This should be something that is a straight forward answerable scientific question. The Food and Drug Administration says it is not. This is a fact sheet that the FDA has put out. There is no evidence linking cell phone use to the risk of brain tumors. Exactly the same time, looking at exactly the same data, the International Agency for Research on Cancer which is part of the World Health Organization who has as their mission, judging the cancer risk of

various exposures says they think it is possibly carcinogenic to people. And they site the fact that there are some epidemiologic studies that do find a positive relationship between extent of use of mobile phones and gliomas. The U.S. National Cancer Institute has looked at exactly the same data and they also say there is no evidence from studies of cells, animals or humans that radiofrequency energy can cause cancer.

If you start off with an assumption of causality that is based on someone else's judgement, something like this, you don't know necessarily how they're interpreting the data. The people IARC aren't smarter than the people at FDA or NCI and vice versa, they are just different interpretations of scientific information. If those kinds of interpretations aren't apparent to you or aren't known to you when you're doing your assessment, you could be systematically biasing your analysis.

Here is another example of this. A question is something carcinogenic. This is

tetrachloroethylene is a compound that is an industrial solvent and is also used in lots of dry cleaning so it is something that all of us exposure to. The EPA says it is likely to be carcinogenic to people. The National Toxicology Program of the United States says it is reasonably anticipated to be a human carcinogen. Another group, the American Council of Government Industrial Hygienists who promulgate standards for workplace protection from chemical exposures says it does not suggest that the agent is likely to cause cancer in humans except under very unusual circumstances. These kinds of judgements are present in many of the assessments that we'll want to do and it simply tells us that we've got to look very closely and really objectively at the evidence that is in front of us.

A couple of other of other challenges that we face and try to do a good job of this risk benefit analysis, differential uncertainty means that we will often know more about one set of risks than another. We may know more about the

risks of the infectious disease then we do in any quantitative way of the benefits of actually using the technology. If we have differential uncertainty on both sides in our assessment we've got to be careful that we're not simply going with the thing that we think we know best and not spending time characterizing acknowledging the other side of that balance.

A really hard thing to do is to have some kind of units or some way to compare risks and benefits because we're talking about very different things. We've talked about improving my vision versus risk of a transmitted disease. We've talked about things that would save the life of a baby compared to a transmitted disease. All of these comparing these things is really hard. People have different preferences and different utility for this. There are tools and I've been involved in analysis and a variety of agencies have done analysis where we use tools like quality adjusted life years and other sorts of measures that can quantify morbidity, mortality and even

quality of life issues for both sides of our balance so we can get closer to a way to compare apples to oranges. It is one of the hardest things we have in risk benefit analysis is comparing very different and often incommensurate outcomes on either side of our balance.

Something that I don't quite know how to handle is that I'm used to doing these sorts of analysis with a social perspective. This may be more like the way that FDA thinks about these. We're looking at a broad population, we're looking at many decisions being made, sort of a portfolio of decisions that are out there. One of the things that struck home to me today from a couple of our speakers was this notion of the decisions that are made at an individual level. Where it is an individual, each intervention is made at an individual level. Is this the right person, what is the intervention for this person, what is available to me, all of those things and making risk benefit analysis that we're very comfortable with on a big scale, think about how to use it on

a smaller scale is just a challenge. And then a really hard thing to do is, Rich brought this up is the question of how do we communicate this well, how do we communicate to people in an accurate and a fair way and an informed way what we know about the benefits that they might see but also communicate to them appropriately about the risks that they're facing.

So looking forward, this tool can actually help us all do a better job of maximizing health and that's what we would like to do. These analyses are hard. They are subject to uncertainty and variability but those things are real, they're out there. We can either kind of go with a gut feeling about what is better or worse or we can be more formal and more analytic about how we're going to approach that. That happens to be the point of view that it thinks, that's my point of view.

Being transparent is really important. We've got to make sure that people understand whether these are the people who are going to be,

who are developing or making these interventions that people are using them or the people who are receiving them. One of the things I will say is we can look to other fields that have been thinking about these kinds of things for a long time. To find new approaches, new tools and advances that can be applied in this particular setting.

With that, I'd like to thank you all for giving me an opportunity to talk to you, thanks.

DR. FORSHEE: Thank you all very much. We're going to go ahead and take a break now. We'll let people think about any questions they have for the speakers during break and then come back. So we're going to take about a 15 minute break if people could be back here at 10:45 we'll resume at that time. Thank you very much.

Okay we're going to go ahead and resume for the question and answer and the final panel session. We have a rather big panel set up for this because we wanted to have reflections from both the sessions yesterday as well as what was

discussed this morning. We have most people sitting around the table up front. We have a couple of panelists in the front row. Everyone has been introduced before but I'll just quickly give everyone's name. We have Dr. William Tomford, Dr. Richard Jonas, Dr. Richard Kagan, Dr. Jennifer Li, Dr. Shamonki, Dr. McKenna, Dr. Gray, Dr. Strong, Dr. Kuehnert, and Dr. Fishman, all participating in this panel.

We have a few prepared questions but before we get into those I'd like to open this up for questions and answers. Let's start with anything relevant to the discussions today but since we do have representatives, actually before I get to the questions and answers I'll ask the panel if they have any opening comments that they would like to make. So let's start with opening comments with people on the panel. We'll start from the far right. Dr. Shamonki, do you have any opening comments? Okay great then Q&A it is. Any questions and again let's start with things from today's session and then we'll open it up to

anything from yesterday. As with yesterday, please remember to introduce yourself so that gets into the transcript.

DR. EASTLUND: Ted Eastlund. Dr. Forshee, I have a question. For many new drugs and biologics, it can take five years or more for the rare but extremely serious complications to develop. Many examples from Albumin to Ciprofloxin. I am aware that the FDA participates in post-market surveillance passively through reacting to reports of complications, say MedWatch. Does the FDA have any standard active post-market surveillance that would routinely apply to new drugs, devices, blood or human tissue and if so, can we look forward to this in tissue banking? I have a second question. Pertinent to post-market surveillance and severe reactions you developed black boxes on package inserts to warn me about ruptured Achilles tendon from the Ciprofloxin I took. Will there ever be a time that tissue allografts, cord blood, corneas are treated like blood, drugs and devices and benefit

by FDA approved package inserts?

DR. FORSHEE: So let me start by saying, what I'll be saying during the panel discussion is an informal communication that represents my best judgement but does not bind the FDA.

DR. EASTLUND: Thank goodness.

DR. FORSHEE: Let me start with the question of active surveillance, actually a very timely question because this time last week, I was at the 9th Annual Sentinel public meeting and then last December I participated in a meeting that my office sponsored looking at how we were using the sentinel prism component which focuses on vaccines to develop active surveillance. For anyone who is not familiar with the Sentinel system, the Sentinel system was developed in response to a congressional mandate to develop active surveillance to compliment the passive surveillance that we've used for many years. Depending on how you count the numbers, we're in the range of 100 million or so lives that are included in the Sentinel system. This is

primarily monitored through health claims data. There is a coordinating center that is currently run by Harvard Pilgrim that manages the communication between FDA and I believe we've got about 15 data partners now and we have tools that we can use to submit queries to the data partners, again primarily private health insurers, to find out about either just use of products or whether there are associations between people who have used that product and adverse events. We also are developing some data mining capabilities. I wouldn't say that this is fully integrated into the regulatory environment yet but it is being regularly used and it has provided very valuable information in a number of cases. So I think the answer there is we've been investing a lot to develop active surveillance capabilities and we've come a long way and I think that that is going to continue developing and people who want to know more if you just search for 9th Annual Sentinel meeting you could get more information about that program.

I'm sorry could you just quickly remind me of the second question.

DR. EASTLUND: Will we ever benefit in the tissue bank profession by black box complications in a package insert as they do in blood and drugs and biologics?

DR. FORSHEE: So I think I'd rather have some of the people from OTAT to see if they want to make any comments on that because they are the ones most responsible for the product communication.

DR. MCFARLAND: So reviewer of labels is tied to, oh, Richard McFarland, OTAT. So the way the risk-based framework works is that premarket review and black box warnings and what not on labels review is part of premarket review. There are some HCT/P that are subject to premarket review and some that aren't. That's the current status and current policy. I've learned being the associate director for policy it is hard to say what we're going to do exactly until you hear it is being signed but it is a risk-based approach.

Do you have an idea of how that might work in terms of, I mean I'd be glad to hear it in the discussion.

DR. FORSHEE: Are there other questions.

DR. FINK: This is Donald Fink. This is sort of targeted for Dr. Shamonki but anyone at the panel who would like to give some opinion is welcome too. Back in 2000 we organized a workshop like this, an advisory committee meeting on stem cells when there was keen interests and early development. One of the issues we spoke to clearly was about donor determination, who would be the best and most appropriate donors from starting material from which you could use to make a product. One of the things we touched on at that time even was genotypic analysis or genotype testing to look for markers or indications that the material might not be really well suited for an intended purpose of which would be to have a product. So in that conversation, there was a lot of discussion about if you identified some feature through the genotypic analysis, how would you then

use that information, A for product assuredness but B, what would be your obligation to share finding results of concern if they were with the donor or the individual that you attested? So I was curious as to how you sort of instituted that in your practice which certainly is something we've thought about and if anyone else has a comment about it I would be interested in hearing it.

DR. SHAMONKI: So my philosophy and approach is full transparency. I know that is somewhat evolved from earlier days maybe in practicing but I feel like we have an obligation to donors and to recipients to provide them with all of the information we have and supportive education. Obviously I don't just drop news on them and say, okay, go follow up with your doctor. It is hard because you're walking the fine line between tissue banking and practicing medicine but what we try to do is be very transparent and provide donors, whether it is an infectious disease result or whether it is a genetic finding.

In the way of genetics though, it is interesting because what makes a suitable donor is also evolving. So in the past we had much more crude instruments and we could really only exclude people based on you have sickle trait or an abnormal carrier type or now you're a carrier for CF and so there were certain findings that would just automatically in our eyes make somebody ineligible as a donor. But with sequencing and expanded carrier screening we are now moving more towards compatibility with recipients rather than exclusion of donors and so with that, you actually have even more education that is required and you really need to bring in the recipients' physicians in the conversation because we will screen for a certain number of diseases, most of which are of no actual clinical concern to you because you're likely just a recessive carrier for this disease and we want to make sure that a recipient has received compatible paired testing and then will also receive the education that he or she needs to find a suitable donor pair. So it is evolving

with precision.

DR. FORSHEE: Do other people on the panel want to comment on that.

DR. STRONG: Mike Strong, still retired. One of the interesting things in terms of risk analysis it seems to me with the genetic testing is now when you go do your family history and you do 23 and Me and Family FT DNA you get a whole battery of potential things that might be wrong with your inheritance. So you have a six percent chance of having Tay Sachs or whatever disease that might be there. So in terms of the risk benefit analysis, this seems to be getting to be quite complicated. At what point, would you accept a risk, what percentage of a risk would you accept for anyone of those genetic diseases that comes up in a battery of tests like that?

DR. SHAMONKI: Well, you hit on something that is really interesting. So as I mentioned, there's a movement towards expanded carrier screening. And that specifically is looking at, currently the largest panel is about

273 recessive conditions and they're all performed with full Exome sequencing. So the actual sensitivity, the analytical sensitivity of the assay is very, very high. It is 98, 99 percent. When you actually apply that to populations and you really adjust for ethnic background, the true residual risk is person dependent and background dependent but it is still very, very high. So I think that when you're looking at these sorts of very precise mutations you can estimate residual risk for a paired potential couple quite well and it will only get better. But what you touched on is what

and Me talks about which are really interesting, very enticing. I've done 23 and Me. I found it to be very entertaining. But I think that genomics is moving us in a direction where we're going to start to understand more about this multifactorial inheritance. So diabetes is obviously not a point mutation. Your likelihood of developing something in your forties or fifties is so multifactorial and way too complex at this

point. But I do think that in the next years in particular, particularly with the data we're collecting from companies like 23 and Me and actually Mt. Sinai's genetics and genomics department is doing amazing things, we'll have a lot more information and then it is just going to be up to, there will be a first level of a computer estimation of residual risk in a paired couple and then from there it is going to come down to individuals having conversations with their physicians and saying how much risk do I accept.

DR. FORSHEE: So I'd like to broaden this question just a little bit because one of the things it made me think of is all of the issues that come up with trying to effectively communicate highly technical information to diverse audiences that may not have the same background that we have. So I wonder if anyone on the panel would like to talk about some of the challenges with that, some of the ways to do that better. Any comments regarding this risk

communication aspect. We also have the table mics by the way.

DR. TOMFORD: For patients that we operate on it is based upon the, Bill Tomford, Boston. Patients that we operate on it is between the surgeon and the patient at the time of the consent. So our surgeons will tell the patient, yes I'm going to use bone graft or whatever the risks are. If they don't know the risks they ask me about them but most of the time they are, I think, hopefully all the time the patients are told about what the risks are even though they are negligible.

DR. FORSHEE: Any other comments regarding risk communication.

DR. KUEHNERT: Matt Kuehnert, CDC. There had been some discussion at a blood and tissue safety advisory committee a couple of years back on the need for some sort of template for recipient informed consent for blood transfusion and I think they discussed a little bit about tissue transplant, too. Because there is a pretty

wide variability in how clinicians convey the risks. But I think the conclusion of it was that well we actually don't really know what to say either. So I think that's something that we really need if not a template just some sort of basics on how to break the risks down and then how to best to convey the risks. CDC has been involved in the organ transplant arena in terms of working with groups on how best to convey risks of disease transmission through organ transplant to both clinicians and patients and it is a lot more difficult than it might seem at the outset to try to convey that in a way that compares to being struck by lightning or some of these other events that people can relate to.

DR. FORSHEE: I think someone in the audience has a comment.

MS. GRAY: This is Sarah Gray with the American Association of Tissue Banks, Director of Communications. I just wanted to make a comment on that which is after the advisory committee requested it, the AATB's communications committee

put together a new brochure that is designed to help physicians communicate with their patients, the risks. I did notice, Matt, on your slide yesterday that was the number from 2007, Srinivasan I think was his name. Yes, to it uses his number so I was going to ask if we could borrow your slides we can update our number for the next version of our brochure. But we want to be distributing next month, at the American Association of Orthopedic Surgeons conference. If anyone would like a copy my email address is grays@aatb.org, I'd be happy to share it with you through email or hard copy.

DR. FORSHEE: Thank you for that.

DR. FISHMAN: Just a comment on that and to build on what Matt has already said. So if you take some piece of factual data and to extrapolate from that. So somebody has been incarcerated and then they become a tissue or organ donor and you say the risk is.00 something percent of transmission it really depends a lot on your recipient. So if they need a heart transplant,

they're going to say yes. In fact, they will say yes if it comes from somebody who is known to be infected with a variety of things. If you say it is a voluntary issue, cosmetic surgery something of that nature, if they are smart they say no. So a lot of it depends on the context that we're providing. But I think what I was most struck by this morning is we have no data. So the idea that we're providing useful information to convey and I think comes out of your talk this morning which is, you can't have transparency, you can't convey information in the absence of data. So we don't really have that. I think it focuses our research on at least common scenarios where we should be able to provide better data. We've provided scripts for surgeons to follow to informed consent so that the basics are covered. But again, it depends on the patient. If you're doing informed consent on somebody who is desperately ill or needs a skin graft, that kind of informed consent is meaningless.

DR. FORSHEE: Yes I think that is a very

helpful point. There has been a lot of work describing how someone's risk tolerance very much depends on what their current situation is. When you're comfortable and healthy and safe you don't have very much risk tolerance. In other situations, you're much more willing to accept risk. Are there other, yes please.

DR. SCHULTZ: Yes, Dan Schultz from AATB and LifeLink. Although surgeons will give informed consent and they'll say, just as if you were getting surgery for anything, they'll say you may have bleeding, you may have infection, you may have these sorts of things. The bottom line is the AATB brochure is an example and one can clearly say to an individual, look, there is a risk of infection but I can tell you there have been zero transmitted infections in processed tissue in these decades of use. So the point is, it is exceedingly low. So for a person that needs an ACL repair that may, in fact, because of the immobility get PE's and other things, I would hope that would be an unreasonable response to say

there is a risk of infection that is significant for an allograft made in the United States from an AATB accredited bank.

DR. FISHMAN: I find your assurance a little disconcerting. Because I don't think we know quite as much as what we think we know. Our sterilization procedures, I show a slide periodically of the drunk under the lamppost. We know to look for the things we know about. I think there are a lot of things we don't know about, we don't have assays for that we haven't been challenged on that FDA doesn't require and we're going to keep going into those, xenografts is a perfect example, where we don't know the field we're going into. Although the rate of transmission is very low, the notion that in an individual nothing bad will happen I find unacceptable.

DR. SCHULTZ: No, that's not --

DR. FISHMAN: I would just say, that you can transmit that information but any degree of assurance as a physician I think would be

excessive.

DR. SCHULTZ: I would simply to say to, number one, there is no number to assign at the present time but I think if you were to indicate that with processed tissues there are no current, the risk is exceedingly low, I think that is a fair statement for processed allograft.

DR. FISHMAN: I would say only that we haven't detected them.

DR. FORSHEE: Are there comments from the panel on that?

DR. STRONG: I've been involved in the last several years with a World Health Organization project called, Notify, which has brought together all of the various fields related to medical products of human origin. One of the interesting byproducts of that gathering, which includes actually a lot of people that are in this room, has been what we're experiencing here today which is bringing together experts from a variety of different transplant fields. We have to admit that for the most part, we don't talk to each

other, even within the organ transplant field. You have kidney transplanters and heart transplanters and maybe they'll see each other at an annual meeting but actually sharing the information that is pertinent to their practices is not always the case. And to bring together, for example, ART, was a whole new experience because that is a field that is relatively new even though it has kind of been around for a long time but not well recognized as one of the products of human origin. And now, of course, that definition is expanding quite substantially when we talk about fecal transplants and the like.

The benefit of having everybody together is that we recognize that everybody has taken a very different approach to these various issues that we're discussing today. For example, donor consent, I mean the donor consent forms of each of these fields is quite variable. And we have been collecting publications on risks and transmissions, adverse reactions that have occurred in each of these fields with panels of

experts in each of those fields and it includes to collect information on donor risks as well. On the donor side, the informed consents have just been alluded to vary tremendously from one group to another, and the reports that are included in this library of adverse reaction events includes the near miss events. Those things that might have caused a problem if they hadn't been caught which is a very large group in the blood field. The biggest risk you have in transfusion medicine of actual mortality is a mislabeled tube. That has been around since the beginning of blood banking and we have really not yet addressed it. We've done a great job with testing, we've spent a trillion dollars or something on developing nucleic acid testing to test agents that are there in one in five or ten million. Whereas, if you look at the risk of being transfused with the wrong unit, it is something less than one in a hundred. So our risk assessments sometimes are off the mark.

I think we have to recognize in terms of

what has just been commented on is terms of do we really know what the risks are. We don't have a good mechanism for collecting what we call biovigilance data. Reports that come to us about things that have happened. The Europeans have done a tremendous job with that and it all stemmed from the risks that they recognized back with the dentist in New York who distributed a lot of tissue to banks that were processed and went worldwide. Even in the City of London there were something like 8000 grafts they couldn't trace. That stimulated the European Union to start up projects both EUSTITE and SOHO projects that ended up with new documentation of how to report and suspect and identify events and reactions that occur as a result of medical products of human origin. They now have reporting systems with their regulatory offices for adverse reactions and events that have been picked up in hospitals and systems around in each of the 26 European countries. They are identifying things that people didn't really even recognize before.

So I think we have to be real careful about claiming what the risks really are because we don't have a good mechanism to capture those events. Now in each of the fields there have been better attempts at that. In the organ transplant field, you have DTAC which actually came about as a result of CDC's attempt to establish a Sentinel network. They are capturing information that they didn't even recognize before and they are studying and understanding imputability of some of the things that have happened, for example, the loss of organs in the transport system. A lot of these errors are human errors. They are not the presence of an infectious agent going into somebody else but the fact that somebody didn't label the box right and so the kidney sat on the loading dock at the airport for 48 hours and was lost. Those are the kinds of events that cause real harm and we're not even capturing.

Now, in the U.S. we are way behind on hemovigilance, the reporting of blood related transfusion errors and donor errors. CDC now has

a system so we're finally beginning to capture those. We have a health system that is quite divided and split among different states and different jurisdictions and a lot of these things that we're beginning to understand, there are other places in the world that have done a much better job with.

So I think this is a good start because it offers us the opportunity of all these different fields getting together and sharing information. It has been great for me because I get to see some old friends that I haven't seen for like 20 or so

years in all of these fields. I think we have to just recognize that we haven't done a great job in capturing all the thing that might happen as we transplant organs, tissues, cells, reproductive gametes et cetera to patients. And on the donor side, that is another issue that needs to be addressed. The living organ donor informed consents vary quite dramatically from place to place and clearly there have been

misinformation to donors in terms of the risks that they have. So there is just a huge amount of work to be done that we all need to recognize and I commend the FDA as this is a good start.

DR. FORSHEE: Thanks Mike and I just want to link that back to some of the discussions from yesterday, particularly yesterday afternoon. We did have a conversation during Q&A about how we could facilitate, we being the community, facilitate more information sharing and I think your comments just show the importance of that even more. I do also want to acknowledge that one of our participants talked about some work that had been done on improving and standardizing some of the donor questionnaires and perhaps that's some work that people could continue to build on. So I just wanted to make some links back to some of the things from yesterday.

DR. TOMFORD: Tomford, Boston. I just wanted to add to Michael's talk. One of the slides presented yesterday about transmission of HCV was due to a clerical error. The bank that

knew that it was HCV positive and it was a clerical error that allowed all these grafts (inaudible) so what is the risk of a clerical error. Are we putting those into our models?

DR. FORSHEE: So what I can say is in some of the blood safety world, we have included quarantine release error as one of the factors in our risk assessment models and we did have some reasonably good data on the quarantine release errors. So those sorts of things certainly can be built into models, you have to have the data first. You can make assumptions but it is best to have the data first to get a truly accurate representation of what is going on there.

I think I'm going to use my prerogative and move on to some of the prepared questions now. So the first question that we had for this session, and we've already started touching on some of this both in the presentations and the discussion, but what information should be considered for a benefit risk assessment and how can this be applied broadly for all HCT/Ps or what

portions of information that we have can be applied across this. This goes to, I was laying out what a theoretical model might look like and the question is, how do we start getting the data that we need to fill in some of those boxes for the risk assessment. So anyone on the panel want to start with this question.

DR. MCKENNA: Dave McKenna, Minnesota. So I think some of the obvious things, I guess I'll speak to the obvious, are the severity of disease, the prognosis, the best available infectious disease data for risk. Like you said, we probably don't have that and alternatives to treatment, in my case alternative graft sources. As far as application broadly, I don't mean to be negative, I don't know if it can be broadly applied, I think it is certainly perhaps a framework or kind of a logarithm or something to at least provide a framework for discussion. I think clearly we saw from the people speaking up here today that your patients range from very healthy and young to extremes of age and

malignant, terminal disease. So I guess those are all obvious things but maybe to get the discussion going.

DR. FORSHEE: Well and I think that moves right into the sub question (a) on this and that's how given I think we've all seen that there is enough diversity in the use of these tissues, the risks of these tissues that it is certainly hard for me to imagine some universal model that could be applied to all of them. I think there is lots of elements that are common across off of them that could help in terms of building a modular program. But let's move into the second question about given all of this diversity in tissue types, uses, benefits, risks how should we go about factoring some of this into benefit risk assessments. Any thoughts about that?

DR. FISHMAN: Just to build on what was just said. When we do stem cell transplants a large percentage of them develop fever. We make a diagnosis in less than 50 percent of those individuals and there are all kinds of reasons for

that. One of the things we're starting to do is apply high next generation sequencing to try to at least raise the bar a little. How often are these donor derived versus nosocomial infections versus anything else. We don't have those data. In the absence of those data it is very hard to make a risk assessment but in most of those patients we have no choice, this is the only therapy that is available, so we live with it.

In a conference that was organized in part by Scott, I hate to say it was a long time ago, the notion is reporting is so hard with tissue grafts. Something turns red they tend to give antibiotics and they don't tend to have a high rate of recovery of data. So we don't actually know what the incidents of infection transmission is for most of these grafts. So unless we have a blame free reporting and we get some increased data, we can't change the analysis I don't think very much. Filling in the model therefore, becomes very difficult.

DR. KAGAN: Yes, Kagan, Cincinnati. The

burn patient is extremely different from most of these situations. Nobody anticipates that a loved one or a child is going to have a life threatening burn injury so no parent has had an opportunity such as somebody, perhaps, undergoing elective operation to go on the internet and do a search and try to find out what the general risks are, what has been reported et cetera. So in my case, when I'm treating patients, quite frankly the parents look to me and say whatever you think is best. They don't talk about what kind of autologous graft I'm going to do. They care first about survival, second about functionality and third about cosmetic outcomes. And so while I do obtain the consents the use of allograft skin and for the use of blood, which they get a lot more of then they actually get skin in the course of their care, they are so focused on do whatever it takes for my child to survive or my loved to survive, that these questions really don't get posed by them. So essentially, it is runway issuance of information because they don't have questions.

DR. FORSHEE: Other comments from the panel?

DR. STRONG: Mike Strong again. We have a very basic problem which is in order to assess risk you have to have both numerator and denominator data. For many of the things that we're talking about today, we don't have those. That is a pretty basic thing to start with.

DR. FORSHEE: Any comments from the audience on this question?

MS. DEAN: One thought is like with that, oh sorry, Debbie Dean, MiMedx, is that I think there is really a tier in structure and risk. Just like you do, you know how you have the flow chart for adverse reactions or adverse events, there is a tier also with allografts and types of tissue and how it was processed. For example, some of them are terminally sterilized as we saw some presenters said yesterday, that obviously reduced the risk. Some of the additional processing steps depending on what they are reduced the risks. So maybe there is a

categorization not just similar to how you have a log reduction, risk factor that you use a flow chart similar to that and categorization by tissue type and processing elements to determine what the risk level ratio is. Then everyone contribute data to a repository of some sort so it is tracked and measured over time and then you can come up with statistical significance that is meaningful.

DR. FORSHEE: And just building on that comment, one of the things that I had shown in the little toy model that I presented was the probability of transmission and how processing might affect that. I think based on everything we've heard in the last day and a half, it sounds like there are things that we know about that but it may not have all been pulled together in a way that everybody knows and everybody can think about how to factor it in. So again, just building on that, I think this general idea of probability of transmission has come up time and again in the last day and half. Yes, please.

DR. GRAY: Hi, George Gray. I sometimes

worry when we're all sitting down here and talking about how we don't have any data it is kind of discouraging. It is like, oh my gosh, we've got to know everything before we can move. But that is not actually true. I think one of the things that the kind of analysis that we're talking about can do is in the case of Rich's example model, all of those little circles that interact with each other are uncertain, we don't know how much, we don't prevalence's, we don't know the reduction in processing perfectly. But if reflect the fact the uncertainty that is there and we have some idea of the range could be between here and here over the prevalence or something like that. The really cool thing is there are actually tools that can be applied, analytic tools. One of my favorites is something called value of information analysis that can actually tell us which of these bits of data that we don't know as well could be most important to us in making our decision so that we're not just waiting until we know everything there is to know but, in fact, we can prioritize

and focus on getting the kind of information that is going to make the biggest difference in our decisions. So in some ways this kind of thinking can help us prioritize and focus the gathering of the data that is going to help us do a better job of making choices.

DR. FORSHEE: We have a question or comment in the back.

MS. LEWIS: This is Michelle Lewis with AATB. I think the biggest difference that you're talking about that you have data collection and med device, you have MAUDE, you have the MDRR system. But with HCT/Ps regulation only requires reportables if there was a likelihood of causing disease transmission. So all of these banks do have that data they just don't send it to anybody and they may or may not talk amongst their friends about near misses that they've detected which could have led to a disease transmission but the problem really is, is what MiMedx was talking about, there isn't a repository and there isn't a standardization to report that information. But

the data is there.

DR. FORSHEE: Thank you. The last comments lead very naturally into sub point (b) here. I'm actually going to tweak this just a little bit because I think we've already talked a little bit about how to characterize the uncertainty of the estimates. Within the field of risk analysis, we've got very good practices for doing this. We can use probability distributions to represent the uncertain inputs, those probability distributions can be more precise if we know a lot about it. They can be very diffuse if we don't know much about the issue and we also use, as I mentioned in my presentation, a lot of sensitivity analyses and testing of assumptions in order to characterize the uncertainty of estimates. In some ways, that is the easy part. We can go to the risk manager and say the likely risk is somewhere between m and n but that might be a pretty big range. I think the more difficult point is how do you go about making decisions in light of that uncertainty. I'll just kick off

that discussion by saying, part of that making decisions under uncertainty involves being clear about what your decision criteria are and what you're trying to maximize and what sorts of things you will tolerate. But I think I'll open it up there if anyone want to add anything to my comments on the first part of the question or wants to drill down a little bit more about making decisions where there is a lot of uncertainty.

DR. SHAMONKI: I would say that making those decisions has a lot to do with the quality of the information that you collect. And one thing that bothers me, is that I see a wide range of practices within gamete donor banks. So in the sperm side, of course, it has evolved over years and I'd like to think that our processes are really industry leading and I know that there are a lot of banks that meet the standards, meet the requirements I should say, but they don't necessarily have on site medical directors. They don't necessarily elicit the same type of quality information from donors. And it makes it very

difficult, I would imagine, to do a really quality risk assessment without that kind of information. So I know that I made a statement about how the individual needs to be considered and how day to day, I do concentrate often times on how can I help this one individual person. But truthfully, my job really is all about mitigating risks on a large scale. Forty thousand vials of sperm a year, obviously I'm not looking at each individual vial. But I do think that we do need consistency and we need to set an example for the industry to say these are the types of information you should really be collecting and you should be asking somebody's updated social history every time they come in to donate.

The same thing is true on the egg donor side. It is traditionally a very fragmented industry. They've grown out of IVF clinics. And only because of the availability now of frozen donor eggs are we seeing a little bit more of a tissue banking orientation coming into the field. But truly, these are doctors that will recruit

donors from Craigslist and they may have a really awesome third party team in place and be totally dedicated to just qualifying donors or they might be doing this as just a very small part of their practice and there is absolutely no oversight other than whatever that physicians sort of position is that day. So I think that orientation towards standardization and moving the field in that direction and also providing an ability for people to report their data is absolutely necessary to make those assessments.

DR. FORSHEE: Other comments from the panelists? Any comments from the audience about this issue of making, okay yes please.

DR. JONAS: I guess there are plenty of statistical methods for characterizing risks. I mean we really have to do this constantly in our field. It is often related to inadequate numbers. If a center has a mortality of 3 percent and they've done five operations in the previous year that doesn't really tell you anything. So we work very hard to try to characterize risk in an

extremely uncertain environment because of a very small number of procedures. I have to have conversations pretty much daily with families trying to help them understand a risk benefit. And when there is uncertainty of risk which is pretty much every case, what I'll often say is if you look in the books or look on the internet you might find that the risk of this operation is five percent. However, your child instead of being a full term neonate weighing 3.5 kg is a 28 week preemie who weighs 1.2 kg. and there are no data to help us understand what the risk is for you. All I can tell you is that the risk is more than five percent, it is a lot more and the risk is probably high. On the other hand, the alternative is certain death. So most families don't have any difficulty understanding that characterization of risk and are prepared to accept that.

I think in terms of disease transmission, it seems to me from my perspective as a clinical surgeon that what I really need to know is what is a catastrophic risk. Is a child

going to get HIV and die a miserable death in a few years from receiving an aortic allograft or are they going to simply get a strep infection that we can treat with antibiotics and they spend an extra week in hospital. So that to me is what I would want to know from the FDA and the tissue banks is what is a catastrophic risk that I can tell a family is really life threatening. That balances out the lifesaving benefit of the operation I'm doing.

DR. FORSHEE: Thanks very much and just a follow up on that from the modeling perspective where I spend a lot of my life, that goes to some of the characteristics of risks that I tried to mention how serious are the risks, how likely are they to occur and in general, when we're modeling, we start with the notion of saying we want to understand what is the probability that something bad is going to happen and if it does happen what are the consequences of that. That is sort of where we start and then we also have to think about all the uncertainty around that but I think

that is the sort of generic approach for modeling that we think about probability and consequence that links up to the very nice specific examples that you were talking about.

Other questions or comments from the audience? Okay we'll go ahead and move on to the next prepared question. This next question, under what circumstances should a new assessment be performed, for example, when a disease switches from emerging to endemic. It really gets at the iterative nature that I think both George and I got at in our presentations. But in the specific world of thinking of thinking about doing benefit risk assessments for HCT/Ps, what are some of the considerations that would trigger going back and taking a new look at a previous risk assessment that was done. Again, I'll start giving anyone on the panel an opportunity to think about what are some of the things that might trigger that.

DR. KUEHNERT: This is a bit of a hard question to answer but, you know, with sort of obvious answers. So something seasonal, makes

sense to do it every year. If it is not seasonal, it is going to depend on, again, going back to how much data there is, how much epidemiologic data. So if there is good data out there that is new, it makes sense to reassess it. The problem is it is sort of a vicious cycle because if there is not enough interest in the pathogen there is not enough data, you don't have any new information so there is no updating. So with that I think there needs to be some sort of an intervention to say sort of like neglected pathogens to stimulate some sort of collection of data so you don't get into that endless cycle. That's what I would suggest.

DR. FISHMAN: There is a very interesting field of emerging pathogens which you probably all know better than I do but where people look at primates and other species worldwide to see what is coming next. I find it fascinating because the yield hasn't been that good in terms of predicting even things that we know are coming like influenza. But it is out there in terms of a scientific discipline where we

can start to think about what the next Dengue is going to be or the next Ebola or something of that nature.

There are other groups and I referred to this yesterday, I think, where you can look in certain populations as Sentinels for what is coming next and we do this every year, to build on Matt's comment, for influenza. I can tell you how much influenza and how severe it is going to be by looking at the rate of disease in October or November in immunocompromised patients and it pans out every year in February and also how well the vaccine works each year. So there are certain sub populations where you could potentially look as reservoirs or as indicators or as Sentinels. And then there is the odd events, the transmission events and unfortunately, they are often missed because there is too much noise. The question is as with Project Notify or others, should we somehow, I say publish, I'm not sure what the format is, those events so that there is a Sentinel or somebody else knows you've had that.

I think the perfect example was, from the organ realm, was the lymphocytic choriomeningitis virus where the donor unfortunately bought a pet hamster and transmitted it. And it turned out that similar events had occurred several years earlier but had not been published and eventually they were all published. So the ability to publish data transparency, those kinds of things, so that people know that it is out there I think is very important. But otherwise, we won't see the signal, it often doesn't come above the noise in the background.

DR. FORSHEE: One thing I'd like to add to your point about attempting to anticipate what is going to come next and the difficulty with doing that. Obviously, we try to anticipate as much as we can. One of the things that we have tried to do and we've presented some of this publically already, while we may not know exactly what the next emergent infectious disease is going to be, we have a pretty good idea of what kinds of questions we're going to ask about any one of

those. And to the extent that we can build the capability to get that data quickly and one of the things that my team does is we built modular risk assessment programs based on our prior experience. We know we're going to need these pieces. We may not need them for everything that comes up but we know we need to have these pieces available and so we've tried to build some of those that can be quickly put together. I think when Mark Roberts spoke yesterday about the FRED model for framework for replicating epidemiological dynamics. When he was speaking about that model yesterday I think that is another example. It is a general agent based model that to the extent you can quickly put in new data on it, it can help you start understanding the spread of the disease. So that is just to build on in addition to try to anticipate what is coming next, having a tool box available to get the data and put it together in the right way is something we found to be helpful.

DR. KUEHNERT: One thing I just wanted to add were, my comments were related to things

that we know and how often to reassess on things that you know. Dr. Fishman brought up the thing that I think is much more interesting to people is how do you look for things you don't know about and that gets into horizon scanning. Of course, we have an HES group that meets periodically on emerging infectious diseases but historically it has been more related here is what I saw in a journal, is this something we need to worry about with blood, organ or tissue. But we don't really have a way to do routine horizon scanning. Not only doing a literature search but also just looking at things that are unpublished and that really is a challenge that I think has to be an effort beyond government. Because there is so much work going on now with next generation sequencing and searches for new pathogens that are going on so I think that is a whole different collaboration but one which is absolutely critical.

DR. FISHMAN: And just to comment, to build on Matt's comment which is the big data

issue. How you recognize a signal. We're doing incredible science now but how do you recognize an important signal amongst all of those data might be something that an algorithm might help that is focused on the public health aspect as opposed to an individual experiment or an individual diagnosis. So I don't know if those algorithms exist in the public health sphere but we're generating tons of data that we don't know what to do with.

DR. FORSHEE: I mean what I can say with regard to that sort of data mining aspect that you're saying, there is a great deal of interest in using both the passive surveillance data that we get through things such as the FDA adverse event reporting system. We've had data mining capabilities in place for the FAERS and the vaccine adverse event reporting system I think for decades at this point. I mentioned Sentinel earlier, we're in the earlier stages of getting systems in place for doing data mining in the active surveillance with health claims data. It

is hard but we are trying to find ways to do that and then build it into a system so that we also know, what do we do next. So we find something that is an alert of some sort, we need to have a process in place for once we find an alert, what are going to be the next steps. The epidemiologists across FDA have done a lot of work in terms of laying out what to do at the various stages of here is something that says there might be an issue, how do we then characterize that further and get to the point where we can act on it. So again, it is hard but what I can tell everyone is that it is something that we think about a lot within the federal government and certainly within FDA to try to

(inaudible) on that but we can always do better. Is there a comment in the audience?

DR. BIGGERSTAFF: Thanks, Brad Biggerstaff, CDC. With respect to number two, I would suggest two instances that make sense to do a new assessment. One is if it is determined that

uncertainty is sufficiently high for adequate risk assessment or actually adequate decision making that continued assessment should be undertaken. And the other is when it is thought that as with the example there that the risk is sufficiently different that it would impact decisions and simulations can help with that.

DR. FORSHEE: And I would just tie that back into Dr. Gray's comment about the value of information analysis. That all ties in about when is the, on the one side you can do simulations to say which data would be most valuable for informing our decisions. You can also flip it around and say when new data comes up on this area is it likely that that is going to change the decision that we make. So I think those are very good points about when you would consider revisiting the risk assessment. And again, you should always be looking at that it doesn't stop when you publish it.

Other questions or comments on this point two regarding when to revisit risk

assessments? Okay this is the final prepared panel discussion question that we had and it really goes to the question of communication. In the field of risk analysis, risk communication is its own special part of the field and in an ideal world it permeates the whole process and we're typically not talking about communication as just being, for example, from the FDA out to all of the stakeholders but communication really as an active exchange of information among all of the stakeholders in the process. So this last question is about what can we do to help improve this sort of communication between the people who are doing the risk assessments and those who are either making decisions or may implement the results of those decisions. So first, again as always, I'll open it up to people on the panel who may want to make a comment or to an audience member.

DR. GREENWALD: This is Melissa Greenwald from HRSA. I certainly have thoughts about communication. I would begin, actually this

is an interesting question because it is asking how you improve it. I would say you would start by having communication between the risk assessors and the decision makers and the various communities. Because when it comes to some of these types of assessments that are being made formally and informally there is actually not a lot of communication that is happening right now. And one of the things that I've heard over the years and Matt and Jay from some of the projects they've done they can speak to this even more than I can, but it is really, but I've heard this also from the transplant community in the past few years. People spend a lot of time reporting things to CMS, to FDA, to whoever and they never get information back on the results of what they're reporting. What are you learning from this, what can we learn from this and how can we use this information. I think that would be a really great place to start.

The other thing to think about is when FDA is doing something that is a regulatory issue

there is a very formalized process, everybody has to be communicated to at once and putting out that information has to be done in a certain way. But when it comes to some of these things about evaluating risk and then thinking about how to deal with it and how to process that in getting information, it is what you just said, an information exchange. I think it is really important to think about who the different stakeholders are and to reach out to them where they are instead of expecting everybody to read an FR notice or to hear about things that are only in very specialized areas when the clinicians are not going to be spending their time noticing those things come out. That is something that we're struggling with, with some of our projects at HRSA right now is doing a better job of getting that two way communication going even at multiple levels. I'd like to ask the panelists to think about specific ways to reach out to the various stakeholders because we've got a lot of stakeholders in the room.

DR. GRAY: This is George Gray. Something along those lines that the Environmental Protection Agency has started doing really only recently is actually having public meetings as they're starting assessments. And they're doing it with the stakeholder community and it is a combination of letting people know what is going on, that something is going to be happening that we're looking at this, but also having that opportunity to exchange information, to learn. In many cases, the stakeholder community has more expertise about the specifics of some kind of an issue than sometimes is present in an agency that has a generalist's approach to doing these kinds of assessments. So just choosing to actively have outreach kind of at the beginning and even during a process is something that can really begin to help this. It has been pretty successful, I think, for EPA.

DR. KUEHNERT: The comment about feedback, I think, is really important because we have a voluntary system and a national healthcare

safety network that CDC operates for patient safety. Now it is a little bit less than voluntary now because it is tied to CMS reimbursement but for transfusion reactions it is still completely voluntary. So you think, well why would anyone do that. At the hospitals, it actually takes a lot of work and the reason they do it is they get the information back. They get information on how often transfusion reactions occur, errors occur not only for their hospital but also blinded nationally so where they stack up against other facilities. But also, just how often it occurs. It is just so important to them, you know, back to risk communication, knowing what's the scale of what we're dealing with here. If there were something like that for tissue, you know, I think it would be valuable. We don't have a tissue module, we have a biovigilance component so it is sort of waiting there but for right now it is only hemovigilance for blood. It is something to think about in terms of trying to engage facilities and clinicians, they want

feedback. They want to know both where they fit in with other facilities but also just in general, the frequency of the events which are all too infrequent for them to see it themselves. If they know it is happening elsewhere, it gives them perspective.

DR. STRONG: Well, I can't let that one sit. There are so many lessons to be learned. When the hemovigilance module went up it was kind of a hard sell, not many hospitals really wanted to participate for the very reasons that Matt mentions which is it is a lot of work and we already do that in our hospital. But those who signed on, it gave them a different perspective on how to look at those kinds of events that were occurring in their hospital and the testimonials that we heard shortly thereafter was really encouraging because it was like, wow, I didn't know that was going on in my hospital and we had to change everything. So it was really educational events.

When building on that, the Project

Notify has been working on building tool boxes to assist people with these problems. One of the real additions to the library has not only been the published papers, some of which get rejected because they weren't properly reviewed by the editorial boards and imputability was highly questionable. That was mentioned actually this morning about the transmission of HIV in a skin donor. What has been very valuable is that the biovigilence systems in the various countries of the EU have been sending their annual reports into the system and there are just amazing things to be learned from that. We don't generally publish our errors, it doesn't really benefit it us that much to publish that we screwed up. So those papers don't get into the literature like the find of a cryo freezer in Italy where several hundred embryos were lost because of an accident that they let the freezer thaw. Nobody is going to publish that except for the newspapers which, as Matt had in one of his slides, that is not where you want to have your problems resolved. Or the throwing

away of a living donor kidney accidentally instead of the bad kidney. Those are things that show up sometimes in the newspapers but we ought to be able to fix those before they happen. So the reports that are coming in from the regulators of adverse reactions and events that they have picked up or that have been reported which are now required in most of the EU countries, has been a valuable resource in identifying problems and helping people identify, wow, if that happened there can that happen in our place and we just don't know about it and in many cases that turns out to be the truth. So once again, just sort of shining a light on something often makes people realize that maybe they have some issues that they can resolve and really improve safety. It is a logical term that all quality assurance managers know about when they're tracking down adverse reactions and events but just shining a light on the information and recognizing that there is an issue, often can be very valuable.

DR. FISHMAN: There is an issue and it

came up before in terms of tissues that were terminally sterilized and others of scope and scale, which is, as a clinician, you want feedback in hours regarding epidemiologic events. The example, again I'll take from the organ community is, I have a patient, don't know what is going on, just got a transplant. You call the organ procurement organization, how are the other recipients of organs from the same donor doing. It should be automated, it is not, Matt tried. Those things happen but it is a very facile system and everybody participates even though it is an informal kind of system. Therefore, you would expect as a clinician that the timing on those responses would be real time, if not hours than certainly days. That doesn't occur and so you file a Med Watch form, you get a whole series of questions back about your Med Watch form and then it goes someplace. I know there is a lot of them but it doesn't help in terms of taking care of the acute event. Conversely, if you're talking about epidemiology or a tissue graft that has been split

fifty ways and distributed then you can do a different kind of analysis and a different kind of communication. So I think the communications modules have to be scaled to the nature of the event and are much more effective if you know the needs of the community, and again, it is about maintaining lines of communication, if people don't know how to do this then it doesn't occur. I think a lot of it is, you have an event, who do I call. Do I call FDA, do I call CDC, do I call all of the above, do I call the Boston Globe and see whether that works better and it does. So just some thoughts.

DR. FORSHEE: Other comments from the panel? It looks like we've got an audience question.

DR. PELTIER: A comment/question. Linda Peltier, McGill University Health Center. I think the communication has to be evaluated upon the needs. If it is cord that I need to infuse into a patient, the cord has been frozen three months, three years, ten years ago and there is a new

endemic disease that is found now, it doesn't impact me. So I think there are different levels but if it is a fresh PPC that I will collect for somebody who is traveling and there is Zika that just popped up, I need the information before Zika gets there. But if it is the influenza that will come back in six months, these are the different levels and depending on the product that I will infuse if it is bone or bone tissue that has been frozen for years that I will distribute, it is really different on the impact. So I think that there are different level of communication depending on the impact on the type of donors that we have and at the time of the transplant that we need it.

DR. FORSHEE: Other questions or comments from the panel or the audience, if not I'm going to inject one more dimension to this but I want to make sure anyone else who has a comment. The other dimension that I will put into this is patient engagement. I've been involved in a number of meetings recently with patient

engagement. The FDA has held a series of meetings on patient focused drug development where patients and patient representatives have come in to talk about specific diseases and exactly the kinds of benefit risk tradeoffs that we've been talking about here. So I what I want to ask is what are we currently doing in the tissue community to elicit from the people who are using these products, how they think about the benefits and the risks and are there ways that we can, certainly there must be ways that we can do better about that but I'll open it up to the panel.

DR. STRONG: I think that is a valuable asset. In the blood world, of course, where the hemophilia community has been very active in participating in discussions about risk assessment and safety because they are at the highest risk in terms of blood transfusion. In the tissue community, I think it varies from organization to organization. I know that in ours we had a patient representative on our board who had input into policy decisions and discussions. I think

that certainly could be expanded. I don't know if we have AATB representatives here, if you have a patient representative on your board or any of the other organizations that might comment on that.

MR. WILTON: This is Frank Wilton from AATB. The answer to the question is we do not, but that is an interesting idea. I was unclear about the original question when you said the people who use the allografts are you referring to the clinicians who use them or the patients who receive them?

DR. FORSHEE: Well they are both important groups in what we're talking about. In this latest comment, I was thinking more about the recipients.

MR. WILTON: Yeah so as I think my colleague Sarah Gray mentioned, we did produce a brochure designed to clinicians and we're going to take that and produce one that is more focused towards patients, helping them understand some of the risks but also where the tissue came from and other factors that are involved. So that is one

aspect of it but having a patient representative, somehow, is an interesting idea.

DR. FORSHEE: It looks like we have another question or comment.

MS. DEMATTEO: Jennifer DeMatteo from EBAA. Currently we do not have a recipient, a member of the community on our EBAA board. However, I know that many of our eye banks do. In fact, they generally have a corneal recipient as part of their boards. As far as recipient information and communication, I think corneas are a little different because of the fact that the transplant happens generally within two weeks and we do do follow up, we do know the outcomes. The corneal surgeons are very involved in eye banking. They are medical directors, they are part of our association so we do have data, it may not be perfect but we do have reporting and we do know outcomes of those patients.

DR. FORSHEE: It looks like we have another comment from a panelist.

DR. MCKENNA: I was just going to add, I

don't want to call out John Miller from NMDP but I do know that National Marrow Donor Program does have recipient representation on a variety of committees. I don't know if you can elaborate.

DR. MILLER: Yeah, thanks Dave. John Miller from NMDP. We actually have recipient and donor representatives on our board and various committees, so thanks.

MS. GRAY: I'm Sarah Gray with American Association of Tissue Banks, Director of Communications again. I just wanted to mention that we do have a speaker's bureau website on our site where we invite tissue recipients to register and typically we get requests from the tissue banks around the country who say I need help finding a tissue recipient. Some of the feedback I hear is that sometimes the tissue recipients are not aware that they're tissue recipients because their physician has implanted something and they didn't know what it was anyway, and maybe they didn't care, they were in a coma, whatever, and so we've learned through different ways that they're

a tissue recipient but include them in the community. We do have people, I'm sure as you guys have this in your organizations, people who are passionate about this cause because of their personal reasons. I know Emman Fattahi was here yesterday, he is a cornea recipient and he works at WRTC. My son was an organ and tissue and cord blood donor after he died and I also became a tissue donor when I just had a baby, we donated placenta a couple of months ago so there's that.

DR. LI: I'm just going to add from the eye banking perspective or a from a clinician perspective, my eye bank is very good about reaching out to recipients. I find as a clinician, the more my recipients know about the process the more likely they are going to be compliant as well with their post-operative care. So from my standpoint, that has been huge, the connection that my bank has made with my recipients.

MS. GRIFFIN: I'm Deb Griffin, I'm from the International Society of Cellular Therapy. We

don't currently have patient representatives on our executive board, that is part of our three year strategic plan to start incorporating patient places.

DR. SCHULTZ: Dan Schultz, AATB. Actually, as Sarah brought up, I'm a recipient of demineralized bone matrix. There are a variety of individuals certainly within AATB that are recipients. In terms of our own agency that I work for, yes, we have recipients and donor families that are involved with the foundational level board. But it is almost ubiquitous these days, there are people who have gotten various grafts. My own case is interesting because when the surgeon talked to me he didn't actually use my bank's DBM. I said well look, I don't want you shifting gears here. The point is did it come from a bank that is accredited, yes, fine and dandy I'm getting DBM.

DR. TOMFORD: I think as something to bear in mind when thinking about patient representatives, people can be extremely

passionate about their cause but not necessarily have an in depth understanding of the complexity of the risk benefit analysis that we're all grappling with here. In the congenital heart community, we've certainly endeavored to involve parent panels and so on but I have to say, having observed some of the discussions that have gone on in terms of panel discussions about risks involved with specific surgeons or specific hospitals. Having extremely passionate lay individuals when the topic really does require an in depth statistical understanding can raise some pretty difficult emotional dilemmas. I think it is something that we all need to be cognizant of. It is obviously very PC in this non PC environment right now to say that we have to have patient representatives. But let's have qualified patient representatives who have some educational background in terms of statistical analysis.

DR. STRONG: It is another risk benefit analysis level. I know in Hema Quebec blood system there they have a patient representative

who happens to be a physician hemophilia patient.

DR. FORSHEE: So I'd just like to build a little bit on that comment. One of the big topics of discussion in the patient engagement field right now is about how to get information on patient preferences that better reflects the whole community not just the self-selected community that choose to be patient representatives. There has been a lot of work done on how to better select a broader cross section, how to make sure that they have enough information that they make informed choices, how to use valid instruments. This is not the place to get into that discussion but I just wanted people to be aware that there are a lot of smart, dedicated people that are thinking of ways to address that problem of only hearing from those who speak up when you're thinking about these issues. Yes, please.

DR. SHAMONKI: I was just going to say that we put a lot of value in learning of outcomes of insemination and also, of course, from egg donor recipients. Most notably because we want to

be able to track these people over time but we also track our sperm donors and egg donors over time. In fact, we have teams of people that reach out to donors for health updates and developments in their personal or family genetic history and it is very important to emphasize to recipients prospectively that please let us know what happens with you or your offspring and also so we can get in touch with you in the future. So we put a lot of effort into incentivizing people to report the outcome of their insemination.

DR. MILLER: John Miller from NMDP. Following up on the patient and donor representatives, one of the things that we have that I think really helps with that issue, because I agree it is a two edged sword, is we have a donor patient safety monitoring committee. So we've got donors, we have patients, but we also have independent physicians and other healthcare professionals on that committee so that when we're trying to assess risk in a very complicated patient and donor population, we're getting an

independent outside of our own potential bias in, oh I don't think this is related, and there might be a transplant physician who would say, oh, I think it probably is and we actually do that imputability as part of our analysis. So if you're thinking of some of these complicated things, actually expanding that to include the other professionals in your community I think helps.

DR. FORSHEE: I know Dr. Tomford needs to leave momentarily. Bill, do you have any other comments before you need to depart? Any other questions or comments from either the panelists or the audience. I know we're getting toward lunchtime at this point. Did any of the other workshop organizers want to speak? Michelle, did you want to say any last words? Okay well, first of all just thank everyone for coming today and for the whole workshop.

We really appreciate your participation. I thought the discussion was wonderful. Thank you all very much. Again, as was mentioned earlier

there will be a transcript prepared from this meeting, so thank you, safe travels and enjoy the rest of your day.

(Whereupon, at 12:13 p.m., the PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

COMMONWEALTH OF VIRGINIA

I, Carleton J. Anderson, III, notary public in and for the Commonwealth of Virginia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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