

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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1 P R O C E E D I N G S

2 (8:30 a.m.)

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

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

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

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

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

1 studies as a reference.

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

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

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

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

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

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

22 Persistence of disease can vary among

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

7 So, Rich.

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

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

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

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

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

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

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

1 that are generally applicable.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 I also wanted to talk about the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 transplanted each year.

2 So, the non-processed are mostly fresh,
3 meaning the blood are still in them. If you just
4 include the osteochondral grafts, it's less than
5 percent. If you include the mesenchymal
6 stem cells, it's about less, or close to 3
7 percent; but I just used 1 percent because these
8 are the main orthopedic grafts, at least.

9 Osteochondral grafts are used in knee cartilage
10 reconstruction -- people we don't want to put a
11 joint replacement in -- only about 1500 grafts
12 used in the U.S. annually. This area is
13 increasingly very popular now, and these grafts
14 are kept in culture for several days; obviously,
15 treated in antibiotics but not sterilized.
16 Someone else among our speakers may speak on
17 mesenchymal stem cells, but there you can see
18 there are about 50,000 of these grafts used a year
19 now, mostly by spine surgeons. So, the other
20 fresh grafts not processed accounts for a small
21 number but, nonetheless, significant at 50,000, I
22 think.

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

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

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

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

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

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

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

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

7 Thank you.

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

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

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

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

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

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

18 We're learning a lot about the genetic
19 basis of congenital heart disease. Around about
20 percent of babies today are found to
21 have copy number variants verses 5 percent in the
22 non-congenital heart population; and there are a

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

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

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

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

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

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

1 was in the 1940s. In the 1960s, following the
2 introduction of the heart and lung machine in the
3 1950s, valve replacement first came along and the
4 aortic allograft was initially used in this
5 application, though it's rarely used to date. The
6 commonest options used today, certainly in adults,
7 are so-called mechanical prostheses, like this
8 pyrolytic carbon St. Jude Medical cardiac valve,
9 or a

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

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

22 So, the sort of procedure that does

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

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

1 ventricle to pulmonary artery conduit.

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

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

1 introduction of echocardiography for non-invasive
2 diagnosis.

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

12 So, here we are reconstructing the
13 aortic arch as part of this Norwood operation.
14 And this is the first stage. As I said, the
15 neonatal stage, with two subsequent stages at six
16 months, and at 2 years. Rather remarkably, these
17 kids -- this was a miraculous operation in the
18 1980s. Today, these kids can go on, go to school,
19 play sports, do regular things.

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

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

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

9 Thank you very much.

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

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

1 follicles.

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

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

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

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

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

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

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

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

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

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

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

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

6 So, we look at the burn patient and the
7 risk factors for susceptibility to disease and
8 disease severity. There are actually some that
9 are related to the burn injury itself. There's
10 first of all, as I said, loss of a skin barrier,
11 changes in local skin flora. We have to remember
12 the skin isn't sterile. There are also changes in
13 pulmonary and GI tract flora and wound ischemia
14 because the skin -- largest organ of the body --
15 gets the least amount of blood supply after injury
16 due to the basic constriction that occurs; and
17 there are also patient-related issues as well.
18 There are pre-existing morbidities, primarily in
19 the case of adults, extremes of age; and I can
20 tell you many burn surgeons aren't comfortable
21 taking care of a two year old with a
22 or 80 percent burn, even though it's an

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 Thank you.

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

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

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

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

1 wide range of indication and recipients for these
2 tissues.

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

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

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

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

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

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

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

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

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

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

1 elderly population.

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

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

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

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

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

1 keratoprosthesis on the surface of the eye.

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

6 Thank you.

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

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

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

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

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

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

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

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

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

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

1 reproductive tissue banks, at least, approaching
2 this consistently.

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

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

1 We do have more and more cryopreserved oocytes
2 available. The 2014
3 (inaudible) data of 30 percent of
4 donor oocyte cycles were from
5 cryopreserved eggs. So, the market
6 is definitely moving in that
7 direction for many reasons.

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

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

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

22 On the egg donor side -- very different;

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

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

1 the seminal fluid removed; the white blood cells
2 -- the majority of them are removed -- and you
3 have a dose that's about 0.5cc, and hopefully
4 greater than 10M motile sperm upon thaw. An ICI
5 specimen is simply added to cryoprotectant -- so
6 you have a raw sample added to cryoprotectant --
7 it's unwashed semen, a 1.0cc dose, and you target
8 15M motile sperm. The reason why you're targeting
9 more sperm on an ICI processing is because you
10 typically will wash it before it's used in an IVF
11 lab, and so you're trying to have more sperm to
12 start with.

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

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

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

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

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

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

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

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

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

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

18 But for allogeneic blood, the risk of
19 infection per transfused unit is in the 1 in 1M to
20 1 in 2M range at least for these four agents
21 listed here. And, I was reminded of this paper as
22 I was putting together the talk -- this is from

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

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

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

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

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

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

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

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

6 Thank you.

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

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

1 Risk Science and Public Health at George
2 Washington University. Dr. Gray also has
3 experience on the government side of this. From
4 2005 to 2009 he served as the assistant
5 administrator for the Office of Research and
6 Development at the U.S. Environmental Protection
7 Agency and he has also served as the past
8 president and fellow of the Society for Risk
9 Analysis. So he has a very well rounded view of
10 these kinds of risk analysis issues. He's going
11 to talk about how we apply these kinds of
12 assessments to decision making. Thank you very
13 much, Dr. Gray.

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

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

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

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

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

1 intervention that we might make.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 by FDA approved package inserts?

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

6 DR. EASTLUND: Thank goodness.

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

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

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

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

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

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

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

4 DR. FORSHEE: Are there other questions.

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

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

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

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

1 with precision.

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

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

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

1 273 recessive conditions and they're all performed
2 with full Exome sequencing. So the actual
3 sensitivity, the analytical sensitivity of the
4 assay is very, very high. It is 98, 99 percent.
5 When you actually apply that to populations and
6 you really adjust for ethnic background, the true
7 residual risk is person dependent and background
8 dependent but it is still very, very high. So I
9 think that when you're looking at these sorts of
10 very precise mutations you can estimate residual
11 risk for a paired potential couple quite well and
12 it will only get better. But what you touched on
13 is what

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

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

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

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

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

14 DR. FORSHEE: Any other comments
15 regarding risk communication.

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

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

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

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

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

14 DR. FORSHEE: Thank you for that.

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

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

22 DR. FORSHEE: Yes I think that is a very

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

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

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

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

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

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

1 excessive.

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

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

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

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

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

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

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

22 I think we have to recognize in terms of

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. KAGAN: Yes, Kagan, Cincinnati. The

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

1 DR. FORSHEE: Other comments from the
2 panel?

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

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

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

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

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

22 DR. GRAY: Hi, George Gray. I sometimes

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

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

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

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

1 the data is there.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 When building on that, the Project

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

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

22 DR. FISHMAN: There is an issue and it

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 who happens to be a physician hemophilia patient.

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

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

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

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

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

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

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

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

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

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1 CERTIFICATE OF NOTARY PUBLIC

2 COMMONWEALTH OF VIRGINIA

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

17

18 (Signature and Seal on File)

19 Notary Public, in and for the Commonwealth of
20 Virginia

21 My Commission Expires: November 30, 2020

22 Notary Public Number 351998

