

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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U.S. FOOD AND DRUG ADMINISTRATION

WORKSHOP

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APPLICATION OF ADVANCES IN NUCLEIC ACID  
AND PROTEIN-BASED DETECTION METHODS  
FOR MULTIPLEX DETECTION OF  
TRANSFUSION-TRANSMISSIBLE AGENTS AND  
BLOOD CELL ANTIGENS IN BLOOD DONATIONS

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THURSDAY

APRIL 11, 2013

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The workshop was held in the Main  
Auditorium at the Natcher Conference Center,  
Building 45, National Institutes of Health  
main campus, Bethesda, Maryland, at 8:00 a.m.,

Andrew Kasarskis, Moderator, presiding.

PANEL FOR SESSIONS IV AND V:

ANDREW KASARSKIS, Ph.D., Mount Sinai School of  
Medicine, Session IV Moderator

TOM SLEZAK, Lawrence Livermore National  
Laboratory, Session V Moderator

SUKANTA BANERJEE, Ph.D., BioArray Solutions,  
Immucor

ELENA GRIGORENKO, Ph.D., Diatherix  
Laboratories, Inc.

JEFFREY LINNEN, Ph.D. Hologic Gen-Probe

KEVIN McLOUGHLIN, M.S., Lawrence Livermore  
National Laboratory

MATTHEW MEYERSON, M.D., Ph.D., Dana-Farber  
Cancer Institute, Harvard Medical School

PEJMAN NARAGHI-ARANI, Ph.D., Lawrence  
Livermore National Laboratory

EDWARD NOTARI, M.P.H., American Red Cross

VAHAN SIMONYAN, Ph.D., CBER/FDA

CLARK TIBBETTS, Ph.D., TessArae LLC

RAYA ZERGER, MT(ASCP)SBB, Beckman Coulter,  
Inc.

PANEL FOR SESSION VI:

MICHAEL BUSCH, M.D., Ph.D., Blood Systems  
Research Institute, Session VI Moderator

MELISSA GREENWALD, M.D., CBER/FDA

JOHN PEYTON HOBSON, Ph.D., CDRH/FDA

PAUL MIED, Ph.D., CBER/FDA

PETER SCOTT, M.B.A., AdvaMed, Immucor

SUSAN STRAMER, Ph.D., American Red Cross,  
Biomedical Services

MAJOR CHARLES DiTUSA, Ph.D., USAMMDA

PANEL FOR SESSION VII:

SANJAI KUMAR, Ph.D., OBRR/CBER/FDA, Session  
VII Moderator

HARVEY ALTER, M.D., NIH

JAMES BERGER, M.S., OASH/HHS

MICHAEL BUSCH, M.D., Ph.D., Blood Systems  
Research Institute

CHARLES CHIU, M.D., Ph.D., University of  
California San Francisco

SIMONE GLYNN, M.D., NHLBI/NIH

ORIEJI ILLOH, M.D., CBER/FDA

LOUIS KATZ, M.D., America's Blood Centers

MATTHEW KUEHNERT, M.D., CDC

HIRA L. NAKHASI, Ph.D., CBER/FDA

UWE SCHERF, Ph.D., CDRH/FDA

PETER SCOTT, M.B.A., AdvaMed, Immucor

TOM SLEZAK, Lawrence Livermore National  
Laboratory

SUSAN STRAMER, Ph.D., American Red Cross,  
Biomedical Services

CONNIE WESTHOFF, Ph.D., New York Blood Center

ALSO PRESENT:

STEVEN BINDER, Bio-Rad Laboratories

KHATEREH CALLEJA, J.D., AdvaMed

ROGER DODD, Ph.D., American Red Cross

JAY S. EPSTEIN, M.D., CBER/FDA

SUSAN GALEL, M.D., Stanford Blood Center

JERRY HOLMBERG, Ph.D., Novartis

STEVEN KLEINMAN, M.D., AABB

BEN MARCHLEWICZ, Ph.D., Abbott Laboratories

BRIAN McDONOUGH

SAYAH NEDJAR, Ph.D., CBER/FDA

## A-G-E-N-D-A

Session IV. Highly Multiplexed Technologies  
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P-R-O-C-E-E-D-I-N-G-S

8:01 a.m.

DR. KASARSKIS: We're going to go ahead and get started here. This session as on highly multiplexed technologies for blood donor screening. We're going to hear about a combination of different technologies, both sequence-based, next-generation sequencing and other. And then after the related discussion on bioinformatics data analysis and management there will of course be a panel discussion right before lunch.

So I'm Andrew Kasarskis. I'm chairing this session here. And then our first speaker is Pejman Naraghi-Arani from the Lawrence Livermore National Laboratory. I'm going to seek to keep the introductions brief because you've got the complete biographies.

But the interesting thing about Pejman is that he has been working in the molecular assays and virology group at Lawrence Livermore National Laboratory for

1 some time. And he actually comes to us from  
2 a plant background which I actually think  
3 leads to a lot of very valuable background  
4 because plants are different than animals in  
5 that they cannot change their environment.  
6 And I've actually started studying some plants  
7 at Mount Sinai Medical Center solely because  
8 of the breadth it forces us to take.

9 So with that, Pejman, why don't  
10 you come up here and tell us what you have to  
11 say.

12 DR. NARAGHI-ARANI: Thank you very  
13 much. I don't know if you guys are very  
14 familiar with Lawrence Livermore National  
15 Laboratory but we're a Department of Energy  
16 laboratory mainly focused on developing  
17 nuclear weapons. But as part of that there  
18 has been a very large investment in science  
19 and technology for everything from computation  
20 to chemistry to biology.

21 Biology started at Lawrence  
22 Livermore actually in trying to understand the

1 effects of radiation on biological systems and  
2 later it developed into the human genome  
3 sequencing project. And since about 2000 with  
4 the help of the bioinformatics group which  
5 we'll be hearing from later on today we've  
6 been doing a lot of assay development  
7 targeting biothreat agents, mainly Category A,  
8 B and C pathogens. And that's mainly the work  
9 that we've been doing in developing assays for  
10 pathogens.

11 So there's going to be two things  
12 that I'm going to talk about. One is an  
13 expression profiling system applied to virus  
14 detection and inflammation response profiling.  
15 And the other is multiplex molecular assays  
16 for pathogen detection that we've developed.

17 So I'm going to describe the  
18 nCounter Analysis System. I don't know if any  
19 of you are familiar with this but it's  
20 developed by NanoString Corporation in  
21 Seattle, Washington. It allows multiplexing  
22 of up to 850 analytes simultaneously. It's



1 quantitative. It's direct hybridization  
2 process so no enzymatic reactions are  
3 involved. And it has a dynamic range of about  
4 5 logs. And with a single instrument you can  
5 have a throughput of about 36 samples in a 24-  
6 hour work period.

7               So I'm just going to quickly  
8 describe the technology and then go into some  
9 of the results we have. So, this is the  
10 instrument. This is a liquid handling  
11 station. This is essentially a slide reader  
12 that uses microscope objectives to look at  
13 nano bar codes that have been tagged with  
14 fluors that are able to then hybridize using  
15 a piece of RNA to your target molecule.  
16 Obviously this instrument is not something  
17 that would be placed at a point of care kind  
18 of a setting.

19               So it enables simultaneous  
20 measurement of anywhere from 2 to over 800  
21 targets per sample. It's digital detection  
22 analysis. As I said there's no enzymatic

1 reactions.

2 One of the nicest things about  
3 this system is its ease of use in that someone  
4 who has really not even trained in molecular  
5 biology can learn how to use the system in a  
6 single day. And we've actually shown that we  
7 can do that with some students that we've had  
8 in the lab and get valid results.

9 The simplicity of data analysis is  
10 also another high point in that basically you  
11 get very large amounts of data that actually  
12 can come out in an Excel format. And the  
13 system actually does a lot of the  
14 biostatistical analysis for you.

15 It's highly sensitive and it gives  
16 you reproducible data. And it gives you a  
17 flexibility in sample type in that you can use  
18 -- you can detect DNA, you can detect RNA, you  
19 can detect non-coding RNA and microRNA. And  
20 we've done some -- pretty much all of that.  
21 And it enables up to about 81,000 data points  
22 in 24 hours.

1                   So basically the system relies on  
2                   two probes, each of them about 50 bases of  
3                   RNA. One has a biotin that is called a  
4                   capture probe. The other is the reporter  
5                   probe. So the reporter basically has a piece  
6                   of DNA that is non-reactive that is attached  
7                   to the RNA that has multiple different fluors  
8                   incorporated into it. The fluors essentially  
9                   produce a bar code. So in this system you're  
10                  not looking for fluorescence intensity, you're  
11                  just looking for the fluorescence as a bar  
12                  code to determine which analyte you had.

13                 The only thing that connects these  
14                 two probes is your target. So this is your  
15                 target nucleic acid. Your capture probe binds  
16                 to one part. Your reporter probe binds to the  
17                 other part. And there is no covalent  
18                 interaction between the two probes. The only  
19                 thing that connects them is your target  
20                 nucleic acid.

21                 So basically when you order the  
22                 reagent you get a little thing like this which

1 comes with tubes that have all of your  
2 reporter and capture probes mixed in to a tube  
3 that you can actually add directly your  
4 samples to.

5 The amount of sample needed for  
6 each run is about 100 nanograms of total  
7 nucleic acid. We've actually found that we  
8 can go down to about 1 nanogram of total  
9 nucleic acid and still get valid results.  
10 Below 1 nanogram of total nucleic acid you  
11 really start losing detection ability.

12 So the process basically is a 5  
13 minutes hands on on day one to essentially add  
14 your target nucleic acids to your reporter and  
15 capture probes, and put it on a thermal cycler  
16 to hybridize at a specific temperature.

17 And then the liquid handling  
18 station removes the excess reporters after the  
19 probes are hybridized. The probe  
20 hybridization takes about 17 hours for the  
21 more sensitive assay. You can go down to  
22 about 3-hour hybridization but you lose quite

1 a bit of sensitivity if you do that.

2 You then bind the reporters to a  
3 surface that is coated with streptavidin that  
4 binds the biotin. Then an electric field is  
5 applied that orients all the probes in one  
6 direction. And then the other machine that I  
7 showed you basically images all of the  
8 targets.

9 The only thing that the machine  
10 sees is the reporter probes. So if your  
11 reporter probe bound but your capture probe  
12 did not everything is washed away. You don't  
13 see it.

14 If your capture probe bound but  
15 your reporter probe didn't bind you still  
16 don't see it even though it's on the surface  
17 because there was no specificity. So it takes  
18 advantage of two levels of specificity by two  
19 separate probes which is quite nice, actually.

20 And then the instrument basically  
21 collates all the different probes that it  
22 counted and it says, okay, I saw this code

1 5,000 times, I saw this code once, I saw this  
2 code 200 times. And then you also can always  
3 compare to a healthy sample to be able to  
4 determine statistical relevance of the data  
5 that you found. And as I said there's an  
6 Excel output for the results.

7 So I'm just going to give you some  
8 preliminary results that we have from an NIAID  
9 Partnership in Biodefense grant that we have  
10 been working on with Charles Chiu at UCSF and  
11 Alex Freiberg and David Beasley at UTMB.

12 The grant was basically to develop  
13 a highly multiplex assay that would be able to  
14 detect all Category A, B and C pathogens in a  
15 human sample and simultaneously do  
16 cytokine/chemokine profiling to give you an  
17 idea of whether or not the patient is showing  
18 signs of illness.

19 So I'm only showing you some of  
20 the data that comes out because if I wanted to  
21 show you the actual graph of all the data you  
22 wouldn't be able to see anything. And you

1 will actually see what I mean a little bit  
2 later.

3 So essentially here are uninfected  
4 samples. These are the average counts of the  
5 uninfected samples. This is standard  
6 deviation of those counts. So basically you  
7 see that you get about counts of anywhere from  
8 42 to about 7 for uninfected samples.

9 For the infected samples, in  
10 Nipah-infected samples your Nipah probes give  
11 you counts of anywhere from 193,000 to 538  
12 depending on this probe specificity. The  
13 other advantage of the system is that because  
14 you have multiple probes you actually get some  
15 information about the strain that you have.  
16 So you can compare sample to sample to try to  
17 understand potentially differences in strains  
18 that were infecting the individual.

19 And of course these are the counts  
20 from other non-target pathogens that were in  
21 the original code set. So the way we designed  
22 the code set was we used the bioinformatics

1 capabilities at Lawrence Livermore to find the  
2 specific targets that we wanted to identify  
3 that were unique to the different viruses.  
4 The original code was for about 35 different  
5 Category A, B and C viruses. And then we went  
6 ahead and had NanoString design the probes for  
7 us to detect those unique signatures that we  
8 had already identified.

9                   So this is another sample. This  
10 is a hendravirus. These are housekeeping  
11 genes. This is some of the genes that are  
12 used to do normalization of the data because  
13 as you can imagine it's very hard to add  
14 exactly 100 nanograms with an assay this  
15 sensitive. Even very tiny differences in the  
16 amount of RNA that you add can cause changes  
17 in the responses you get. So there are  
18 normalization signatures in the assay in order  
19 to make sure that you have added the same  
20 amount of targets to all of the different  
21 wells.

22                   So I don't know if you can see the



1 numbers here but it goes from 100,000 to 1  
2 million. And so these are the responses. I  
3 always like to tell the people in the lab, I'm  
4 like oh, look at the signal to noise ratio.  
5 So that for me as someone who's developed a  
6 lot of PCR assays it's one of the most  
7 impressive things about the system.

8 And so these are, again these are  
9 -- I'm sorry, I also failed to mention these  
10 are cultured samples. So basically we took  
11 100 nanograms of total nucleic acid from viral  
12 cultures supernatant and spiked into the  
13 reactions. We've been doing some other work  
14 where we've been doing titrations and we have  
15 found that we can actually go down without  
16 addition of carrier RNA.

17 We can go down 2 logs and not lose  
18 any -- and not lose detection capability. The  
19 work where we're actually titrating with  
20 carrier RNA is actually ongoing now so I don't  
21 have any information on that. But I expect  
22 that we will be able to get much better than

1     2 log dilution -- ability to detect the  
2     viruses at greater than 2 log dilution.

3             So the yellow fever signatures,  
4     these are the responses for them. For Junin,  
5     Nipah, West Nile for instance which is a near  
6     neighbor of yellow fever you see that there's  
7     no response. Now this is not necessarily  
8     always true. So again for Guanarito these  
9     were the counts that we got and these were the  
10    counts for the near neighbor agent. And these  
11    are the uninfected samples. As you can see  
12    there's a pretty large difference in the  
13    signal to noise.

14            And these are two different  
15    isolates of Junin virus. And I'm basically  
16    mainly showing you this to demonstrate that  
17    two different isolates of Junin will give you  
18    two different responses for the various Junin  
19    probes that we had which essentially gives you  
20    an idea of the genotype of the virus.

21            And these are dengue viruses,  
22    three different isolates. And you see the

1        responses for the different probes. I  
2        apologize about the lack of clarity on the  
3        scales but essentially this is about 10,000  
4        and this goes up to about I think 50,000 is  
5        the count up there.

6                    And these are with three West Nile  
7        isolates. Interestingly, Japanese  
8        encephalitis virus also lights up with the  
9        West Nile virus template. Because of the fact  
10       that you have multiple probes for West Nile  
11       virus showing up and only one of the Japanese  
12       encephalitis virus probe showing up, you can  
13       essentially be able to tell that it is West  
14       Nile and not Japanese encephalitis.

15                   Now, the second iteration of the  
16       code set we basically used the original codes  
17       that we had developed. And additional codes  
18       that we received from Charles Chiu from some  
19       of their microarray studies that had  
20       demonstrated the ability to detect the viruses  
21       for the various Category A, B and C viruses  
22       that we're interested in.

1                   So those were pre-tested on  
2                   microarray. We basically took those  
3                   signatures, put them on the NanoString  
4                   instrument, added signatures for -- I believe  
5                   it's about 179 different signatures for  
6                   cytokine and chemokines from humans. And made  
7                   a new code set that's about 765 different  
8                   probes simultaneously affected.

9                   And basically this is again just  
10                  to show you the responses that we get. So  
11                  this is actually from patient samples with the  
12                  BASV rhabdovirus that was recently discovered  
13                  in Dr. Chiu's lab. And this is cDNA that they  
14                  had amplified from serum samples. So this  
15                  isn't just the RNA, this is cDNA that had been  
16                  amplified. And the counts are quite large,  
17                  the largest one being 182,000 counts. These  
18                  are basically the positive control probes to  
19                  show you kind of the responses that you see  
20                  there.

21                  Now here, directly from serum  
22                  samples for two different dengue-infected

1 patients, one patient is in blue, the other  
2 one is in red. Again because of the scaling  
3 it's hard to see but this is 5,000 counts. So  
4 you can clearly see that there is a signal for  
5 dengue without any amplification, without any  
6 other manipulation directly from serum.

7 Now this is a total of about 1  
8 nanogram of nucleic acid that was added. The  
9 reason there's only 1 nanogram as opposed to  
10 100 nanograms is because that's essentially  
11 what you're going to get in a serum sample and  
12 we believe that the real strength of the assay  
13 will be when we test whole blood samples.

14 And as you can imagine whole blood  
15 samples are a bit hard to come by but one of  
16 the reasons that I wanted to present this work  
17 was that I believe that because of the way  
18 that the assay works that whole blood testing  
19 would probably work better than serum because  
20 of the large amount of nucleic acid as present  
21 in whole blood.

22 We have demonstrated in previous

1 work that there is no interference from the  
2 host. So for us the more host nucleic acid  
3 you have actually the better the system works  
4 because of the liquid handling system needing  
5 carrier RNA to be able to complete the process  
6 and not lose signal.

7 So basically we have demonstrated  
8 that we can detect at least two different  
9 isolates of dengue from an actually viremic  
10 patient.

11 I'm just going to show you very  
12 quickly some of the work that we did at UTMB  
13 with trying to understand the  
14 cytokine/chemokine responses of mice outbred -  
15 - after mice 2 West Nile virus infection.  
16 These are volcanographs of different tissues  
17 from multiple mice that were tested multiple  
18 days after infection.

19 Basically anything that is above -  
20 - that has a p value of 0.05 or better is  
21 counted as a positively correlated difference  
22 with the presence of virus. And we actually

1 found about 114 genes differentially expressed  
2 in lung, some that were reduced in their  
3 expressions, some that were increased in their  
4 expression. Forty-one genes for spleen, 61  
5 genes for liver and 9 genes for brain. We're  
6 about to be publishing this data soon in  
7 Journal of Virology.

8 What's really interesting for us  
9 was that noone -- we never expected to see  
10 huge changes in gene expression for cytokines  
11 and chemokines in the lung for a flavivirus.  
12 That was quite exciting for us.

13 These are the various genes that  
14 were detected to be differentially regulated.  
15 And these are the types of genes, cytokine  
16 ligands, chemokine ligands and receptors,  
17 cytokine ligands and receptors, genes involved  
18 in the complement response, signal  
19 transduction, et cetera.

20 And this is a graph showing you  
21 the correlation of expression changes in  
22 different genes with pfu of virus detected per

1 gram of various tissues in mouse. This is for  
2 lung and this is for spleen and these are the  
3 different genes that are being differentially  
4 regulated. Only for those with a p value of  
5 0.05 or better.

6 So basically I just wanted to give  
7 you a little taste of what I believe is the  
8 suitability of the system. As I said the  
9 system enables direct, simultaneous detection  
10 and quantification of quite a few different  
11 targets. So one can imagine that you can look  
12 for all of the various pathogens that are of  
13 concern for blood and be able to do some level  
14 of blood antigen typing using the system.

15 It takes very little labor, only  
16 about 15 minutes of hands-on time for each of  
17 the samples processed. The simplicity of use  
18 is quite nice. It's not susceptible to  
19 enzymatic inhibition by heme of the materials.  
20 Fractionated samples such as formulin-fixed  
21 paraffin-embedded samples can be analyzed with  
22 no loss of sensitivity or selectivity. And as



1 I said it's amenable to whole blood analysis.

2 And people have actually, not us  
3 but others have demonstrated and we are hoping  
4 to demonstrate soon the ability to directly  
5 detect from blood that has been put into  
6 PAXgene tubes.

7 And it is unlikely to miss new  
8 viral variants if you're looking for viruses  
9 because up to 8 percent nucleic acid sequence  
10 changes in that 100 bases that you're  
11 targeting can be tolerated without significant  
12 loss of signal. After that you're going to  
13 see a loss of hybridization efficiency but we  
14 believe that you can still see the signals as  
15 you saw with some of the Junin samples.

16 Some of the drawbacks. The system  
17 is expensive, it's about \$250k per instrument.  
18 I don't really see this as becoming a system  
19 that can be used routinely in labs for typing  
20 unless the cost comes down quite a bit. We've  
21 been talking to the company about potentially  
22 engineering a smaller version of the system

1       that would be more amenable to a smaller  
2       number of code sets but still would give you  
3       robust results and we'll see how that goes.

4               The reagents can be expensive on a  
5       per-sample basis, \$80 to \$500 per sample for  
6       100 to 850 target analytes. But the nice  
7       thing is that the labor costs are quite a bit  
8       reduced. And as I said it's really not  
9       amenable to point of care.

10              As I was listening to the talks  
11       yesterday it struck me that potentially some  
12       of the work that we've done with Luminex  
13       analysis might be of value. We've been using  
14       the Luminex xMAP system for a few years now to  
15       develop multiple multiplex assays for various  
16       government agencies including the CDC and DHS  
17       and USDA.

18              And I'm just going to give you a  
19       little flavor of some of the work that we've  
20       done and why I think the Luminex might be more  
21       amenable to the kinds of testing that we've  
22       been talking about here.

1                   So these are just some of the  
2                   various multiplex panels that we have  
3                   developed so far. The largest multiplex we've  
4                   developed is the 41-plex influenza RT-PCR that  
5                   simultaneously detects and subtypes influenza  
6                   A. And we've also been recently working with  
7                   the FDA for detection of agents in food  
8                   matrices.

9                   So I think yesterday there was a  
10                  very good presentation on how the Luminex  
11                  technology works. Essentially you do an  
12                  offline PCR or RT-PCR with a biotinylated  
13                  forward primer. Your pre-sterile product has  
14                  a biotin on one of the strands. You hybridize  
15                  that to probe-coupled beads. Each probe is  
16                  able to be differentiated on a modified flow  
17                  cytometer and then the flow cytometer tells  
18                  you which beads had green fluorescence  
19                  associated with them with  
20                  streptavidin/phycoerythrin. And then you can  
21                  basically quantitate how many different  
22                  targets were in the sample.

1                   So the 41-plex H-typing assay,  
2           these are the different number of signatures  
3           present for the different H types in the  
4           assay. We want -- for Luminex we've found  
5           that we really do need more than a single  
6           signature for any single target because of the  
7           robustness that gives us. So that if you have  
8           for instance a false positive rate of 1 in 500  
9           which is what we usually try to target for our  
10          analyses, for each signature if you have three  
11          signatures and you need three signatures to  
12          really make a call you'll have a very, very  
13          low false positive rate to the level that  
14          would be acceptable in the kinds of regulatory  
15          environments such as blood.

16                   So this is basically an actually  
17          titred H1N2 virus that was tested at 2,000 egg  
18          infectious doses. As you can see the median  
19          fluorescence intensities for all the H1's is  
20          quite robust. For all the H's this is quite  
21          low. And these are the three -- this one,  
22          this one and this one are the three FluA, Pan-

1       FluA assays.

2                   The other nice thing about the  
3       assay is that has multiple controls in each  
4       reaction. There's a positive control, there's  
5       a negative control, there's a fluorescence  
6       control and there's even a user control. And  
7       that's for each tube, each of the reactions.  
8       So you can run 96 reactions in a 4 and a half  
9       hour work cycle.

10                   And so essentially we can run  
11       three plates per -- if we work hard three  
12       plates per instrument per user in a single  
13       work day which translates to almost 300  
14       samples, each of them with multiplex analysis.

15                   This is basically a titration of  
16       the -- of H5N9 by egg-infectious doses. And  
17       this is the median fluorescence intensities.  
18       And as you can see the sensitivity of the  
19       various signatures is anywhere between 1 and  
20       10 copies -- I'm sorry, 1 and 10 egg-  
21       infectious doses of the virus.

22                   This is basically a similar kind

1 of a plot using an H4 virus. There is no H4  
2 probe in our assay so there is no H typing  
3 that is able to be done. So only the three  
4 pan influenza A signatures lit up. And this  
5 is basically just to show you if we were to  
6 plot all the data points this is what it would  
7 essentially look like. And so again your data  
8 comes out as an Excel sheet.

9 And we've developed algorithms  
10 where we can actually tell the instrument to  
11 flag assays that have had problems with their  
12 controls which would require a retest and also  
13 to flag ones that are positive with red and  
14 ones that are negative with green that don't  
15 require retest.

16 So this is -- and these are  
17 actually clinical samples. Animal and human  
18 samples that were tested using the multiplex.  
19 As you can see for H1, H2 and H3 because these  
20 are mainly animal samples that were tested we  
21 don't get a very good correspondence. That  
22 was because all of the H1, H2 and H3 probe

1 sequences that we used were derived from  
2 humans because there isn't a whole lot of  
3 animal samples that had the sequences in the  
4 databases for H1, H2 and H3.

5 But H5, H7 and H9 which are animal  
6 viruses gave very good correspondence. This  
7 is initial results. And then for the pan flu  
8 positives we got 100 percent correspondence.  
9 So essentially your assay is always as good as  
10 the data available to make your assay from.

11 We've actually been developing --  
12 actually Tom's group has been developing some  
13 rapid selection of signatures, some processes  
14 for rapid selection of signatures to put into  
15 a multiplex. So the idea is how many  
16 different signatures do I need to put into a  
17 multiplex assay to be sure to detect 90  
18 percent, 85 percent, 50 percent of all the  
19 genetic diversity that is in a population.

20 So here's an example of one of  
21 these tests where this is the phylogenetic  
22 tree of Crimean Congo hemorrhagic fever virus.

1 Each box -- each colored box represents a  
2 different signature that would be able to  
3 detect that particular strain.

4 So as you can see by using just  
5 two signatures we are able to detect about 50  
6 percent of the genetic diversity of CCHF. We  
7 also have found out from collaborators at CDC  
8 that most of these other strains are ones that  
9 are historic in refrigerators and are not now  
10 circulating.

11 So this gives you a rapid tool to  
12 be able to discriminate and identify which  
13 signatures you want in a multiplex to capture  
14 a specific amount of diversity of samples that  
15 you want to detect.

16 For the avian influenza test that  
17 I showed you results for we actually found  
18 that when you do the genetic tree of influenza  
19 of the four signatures that we have for H5,  
20 signatures 1 and 2 are specific to the  
21 Eurasian strains and signatures 3 and 4 are  
22 specific to the North American strains. This



1 kind of typing would be of great value because  
2 as you know the North American strain of H5  
3 has not been associated with human disease  
4 yet. They have all been the Eurasian strains.  
5 We've been able to actually do this for all of  
6 the various pathogens that we've been  
7 targeting in our work.

8                   And we've also developed PriMUX.  
9 It's a new process for identifying target  
10 signatures. And instead of doing whole genome  
11 sequence alignments what PriMUX does is it  
12 basically says give me all of these seven  
13 primers in the world that would be specific to  
14 influenza A and not specific to anything else.

15                   By using that process, I'm sure  
16 that the bioinformatics guys here can explain  
17 that much better, you can scale the assay  
18 development process much better so that you  
19 don't need as large of memory space and  
20 computational strain in order to be able to  
21 develop very robust assays.

22                   And basically here are some of the

1 more recent results that we have for the  
2 multiplex developed for the FDA. These are  
3 titration curves with actual template spiked  
4 into water for *Francisella tularensis*. Each  
5 of the different signatures has a specific  
6 response curve and for each of the different  
7 strains.

8 And one of the other things that I  
9 wanted to emphasize is that you can set  
10 thresholds for each signature independently  
11 because these are independent reactions in a  
12 multiplex. That really helps us to be able to  
13 set robust thresholds that enables us to be  
14 able to differentiate between false positives  
15 and false negatives.

16 These are some of the results for  
17 salmonella. And for *Brucella* this Bru9958 is  
18 specific for *Brucella abortus*. That's why it  
19 does not respond.

20 So basically going through some of  
21 the advantages and disadvantages. The  
22 sensitivity and selectivity of the multiplex

1 we've demonstrated with over 500,000 tests now  
2 from environmental, clinical and animal  
3 samples to be equivalent to qRT-PCR. If  
4 anyone disagrees I would love to talk to you  
5 about it later but I'm sticking to the facts.

6           Commercially available assays are  
7 available through -- these are FDA-approved  
8 assays. I only looked mainly at the pathogen  
9 detection assays. So the system has been able  
10 to clear FDA before.

11           The system is flexible. It can be  
12 used for nucleic acid or antigen antibody  
13 detection. Some groups are actually now  
14 trying to do that simultaneously in the same  
15 reaction. I believe that a better process  
16 would be to have one plate of nucleic acid  
17 detection, one plate for antibody or antigen  
18 selection and be able to get the results that  
19 you need.

20           So you can do 1 to 384 multiplex  
21 assays per instrument per day. The reagents  
22 are relatively inexpensive and very stable.

1 And the cost per run for a 25-plex is about  
2 \$12 bought in bulk whereas TaqMan costs of the  
3 equivalent multiplex is about \$75. This is  
4 only for reagents, by the way.

5 The system is open and manual.  
6 The nucleic acid detection requires pre-  
7 amplification which can be a difficult issue  
8 unless you have automated robots to do the  
9 extractions. And the assay will likely miss  
10 novel pathogens because if you have large  
11 changes in the sequences the primers won't  
12 work. That's all. Thank you.

13 (Applause)

14 DR. KASARSKIS: Okay, so I am  
15 going to just go ahead and get started here.  
16 So the title I initially I had I talked about  
17 evolving sequence-based approaches for  
18 pathogen and blood cell pathogen detection.  
19 But I think actually this supplies the blood  
20 cell antigen as well so we're going to -- I'm  
21 going to try and cover both here.

22 Just to summarize some of the

1 problems that I heard discussed yesterday as  
2 related to the blood supply there are  
3 difficulties in finding rare traces of a  
4 pathogen in a sample. It's difficult to know  
5 exactly what you have. That could be a strain  
6 of a virus or a bacterium that's contaminating  
7 things, or it could be the haplotype of donor  
8 and recipient blood, or donor blood and  
9 recipient tissue.

10 It's important to be sensitive  
11 enough for routine use at blood banks.  
12 There's a point made that any test is a good  
13 test but to displace the existing test you  
14 have to have an incredible-looking ROC curve.

15 And then being able to detect new  
16 pathogens is important. And there's sort of  
17 three phases to that that I heard. One is  
18 monitoring for new pathogen emergence, the  
19 kind of thing Nathan Wolfe discussed.

20 Then there's this tricky thing  
21 about actually finding out if this new  
22 sequence or new thing that you've detected is

1 actually pathogenic, you know, the Koch's  
2 postulates and all.

3 And then there's this question of  
4 a quick transition from, okay, now we have a  
5 new emerged pathogen, how do we actually  
6 identify that in the blood supply? How do we  
7 work through it?

8 And what's interesting to me is  
9 that in theory conventional, next-generation  
10 sequencing should be able to address almost  
11 all these problems. Because DNA sequence is  
12 actually for a pathogen, the ultimate in  
13 specificity. You know exactly what it is.  
14 And NGS of course is inherently multiplex so  
15 it should in theory be cost-effective if  
16 you're trying to cover a large number of  
17 things.

18 The one place where it really  
19 wouldn't would be this one here because to do  
20 that you're going to need to actually have  
21 good information about what the phenotype of  
22 an organism infected by an infectious agent

1 would actually happen to be.

2 So what's interesting though to me  
3 is that a lot of what we have in biomedical  
4 work today is not unique. There's a lot of  
5 data you can generate with next-generation  
6 sequencing but if anything the biomedical  
7 field probably lags many others in effective  
8 use of rich data sources to make decisions.

9 If you think about it the weather  
10 forecasts when you were growing up were pretty  
11 poor. Sometimes they didn't get it right.  
12 But now they're actually pretty accurate much  
13 of the time, at least for temperature and  
14 whether or not we're going to have cloud  
15 cover, things like that.

16 Similarly, you know, logistics  
17 firms are infinitely better now than they used  
18 to be. No one thought about managing supply  
19 chains that included 30,000 parts across 5  
20 continents when trying to build things 30  
21 years ago. Now people do that routinely.

22 So one of our objectives at Mount

1       Sinai is to actually try and take some of the  
2       big data analytic techniques that have been  
3       developed in other fields and start applying  
4       them to biomedical data which is historically  
5       very fragmented and also hard to access  
6       because of concerns with privacy that need to  
7       be addressed.

8                       How big is the digital universe?  
9       It's currently measured in zettabytes. A  
10      zettabyte is a lot bigger than a gigabyte, 101  
11      trillion gigabytes get created -- were created  
12      in 2011. That gets big. 1.8 zettabytes is  
13      enough to stack -- if you think about  
14      visualizing this it would be a stack of iPhone  
15      5's going to the moon and back. So a lot of  
16      information is out there that can be accessed.  
17      And some of that's relevant to almost any  
18      decision you want to make today.

19                      We have this in biology as well.  
20      You've gone from terabytes of data, now  
21      petabytes and exabytes and onto these  
22      zettabytes.



1                   Everyone's seen this sort of  
2                   graph. You can get this from the NHGRI  
3                   website. If you look at this right now this  
4                   is the introduction of next-generation  
5                   sequencing, cost of a full human genome right  
6                   now in our CLIA facility is just under \$6,000  
7                   for a decent whole human genome. So the cost  
8                   has come down and continues to go down.

9                   And what's interesting about this  
10                  is that means that a whole genome sequence is  
11                  starting to become less and less of an  
12                  esoteric test and more something that you  
13                  might continue to do regularly. And that's an  
14                  insight I credit to David Dimmock at the  
15                  Medical College of Wisconsin.

16                 Parallelism's increasing with  
17                 these technologies. Speed is actually  
18                 becoming relevant. That used to be one of the  
19                 big digs against these. And new technological  
20                 innovations are coming all the time. So how  
21                 best to exploit them and how to actually deal  
22                 with that when one is trying to develop a

1     stable, reliable platform for assaying  
2     anything leads to this interesting question.

3             So why can't we just sequence  
4     everything with second-generation -- next-  
5     generation sequencing technology and be done  
6     with it? There are a lot of problems.

7             One we heard about yesterday is  
8     the reads are too short so you can't go across  
9     repeats. If you've got a genome that's  
10    complicated, be it a bacterial genome or a  
11    human genome those things get confused and  
12    sometimes that structure is important.

13            Trying to phase polymorphisms to  
14    figure out if it's actually on the same  
15    infectious segment of influenza, if it's on  
16    the same bacterial chromosome, if it's on --  
17    you know, in a human if you've got mutant  
18    alleles on the same chromosome or different  
19    ones they're going to translate differently.  
20    They're going to have different functional  
21    consequences.

22            Not all sequences can actually be

1       sequenced. Second-generation sequencing  
2       technology from Illumina has a hard time with  
3       high GC content sequences.

4               Crucially, the cost of sequencing  
5       huge genomes is great because these things are  
6       very parallel, it's very efficient. But if  
7       you have to sequence lots and lots of little  
8       samples and small portions of them it becomes  
9       cost -- very, very difficult. Because the  
10      cost of sequencing doesn't have a curve like  
11      the one I showed you before.

12             The cost of sequencing has been  
13      flat or increasing over the past 15 years when  
14      it comes to the sample preparation. So the  
15      sequencing itself, yes, it gets cheap. Sample  
16      preparation is often manual, often  
17      complicated. These fancy technologies if  
18      anything are more demanding about what kind of  
19      sequence you have to put in there. It gets  
20      hard to do.

21             And also we have limited material  
22      in samples. The sample preparation can be

1       difficult. The time to get sequence can be  
2       improving but it's still going to lag some of  
3       these later, faster assays.

4               And crucially there's frequently  
5       insufficient phenotype data to actually  
6       interpret what's there. So even if you do a  
7       great job of coming up with a list of variants  
8       from your bioinformatics pipeline you will end  
9       up with hundreds of thousands of variants of  
10      unknown significance that nobody really can  
11      opine upon other than to say that they exist.  
12      And that is a degree of ambiguity that is  
13      difficult for physician providers as well as  
14      for people receiving information, and it's  
15      probably relevant to the questions about how  
16      we screen blood supply. Some of that came up  
17      yesterday.

18             Complementary highly multiplex  
19      technologies can be an answer to that. I'm  
20      taking an example that I'll be hitting on  
21      throughout because I'm familiar with both  
22      these technologies but it could also apply to

1 NanoString and next-generation sequencing or  
2 other things. Some combination of  
3 technologies can often be useful because  
4 they're going to have different error  
5 modalities and you can use one to correct for  
6 the errors in another.

7               So the example I'm using here is  
8 that if you take Illumina and you've got short  
9 reads. And this actually came from a  
10 metagenome experiment. We have a bunch of  
11 Illumina reads and they were unknown function  
12 because they were so short they didn't map to  
13 anything in any database.

14              We had some Pac Bio reads which  
15 were really long but didn't map to anything  
16 because they have a high error rate. And the  
17 various sorts of alignment algorithms that you  
18 would use standard to screen against GenBank  
19 databases don't do you any good in those cases  
20 because the things don't match.

21              However, if you combine these two  
22 and use the errors in one to correct the other

1       because all the errors in Illumina are  
2       essentially mismatches and all the errors in  
3       Pac Bio are essentially insertions and  
4       deletions, you end up with a hybrid read which  
5       is pretty darn good.

6               And that actually you can run  
7       through a TblastX and hit databases and find  
8       out that these sequences came from an RNA  
9       polymerase. That's just one simple example  
10      that happens to use these two technologies but  
11      that is probably true for almost any two other  
12      combinations of technologies.

13             So rather than working like a dog  
14      trying to optimize one technology and make it  
15      better and better, frequently it's a good  
16      exercise to go ahead and try and combine two  
17      technologies with different error models to  
18      get you to where you actually have the data  
19      where they agree and can say that that's  
20      actually probably real, and the rest of it,  
21      who knows.

22             So I'd mentioned that sequencing

1 technologies continue to evolve. Third-  
2 generation sequencing technologies are  
3 basically characterized by processive  
4 inspection of single molecules. I'll talk a  
5 fair bit about specific biosciences but  
6 there's also looking at sort of technologies  
7 where you stretch out DNA and then use a  
8 scanning tunneling microscope to actually just  
9 inspect it and see what's there.

10 Oxford Nanopore keeps threatening  
11 to come out with an actual product that will  
12 be allowing us to sequence DNA by clipping off  
13 little pieces of nucleotide and running them  
14 through a pore.

15 The folks at IBM actually have got  
16 some interesting technology where in theory  
17 you could use the entirely solid-state system  
18 to look at the electrical disturbances in a  
19 solenoid if you run a molecule through it.  
20 All of these that are great technologies that  
21 might come into fruition and actually be  
22 really good commercially viable things down

1 the road or not. But some of them will  
2 eventually.

3 And the Pacific Biosciences  
4 technology is one we use routinely so that's  
5 the one I'll talk about right now in terms of  
6 how it complements the next-generation  
7 sequencing technology.

8 So, one of the challenges with --  
9 we wanted to really look and watch what an  
10 enzyme does. They're great machines. They  
11 sequence DNA beautifully. If you had just  
12 watched what they did you'd be able to know an  
13 awful lot about what they're sequencing.

14 The problem is that they work with  
15 high concentrations of nucleotides and so how  
16 can you watch that. This represents a DNA  
17 polymerase here. This is the concentration of  
18 nucleotides you need for that thing to run at  
19 its natural processive rate of a couple of  
20 nucleotides per second.

21 You are labeling each nucleotide  
22 with a different color. And if you were to



1 use a conventional confocal microscope you  
2 could see nothing because you've got this  
3 nasty background problem when you're wanting  
4 to observe what the enzyme is doing right now.

5 In all these slides I'm going to  
6 show that there's a template strand in purple  
7 and a new DNA strand being synthesized in  
8 gold.

9 The innovation that Steve Turner  
10 and Jonas Korlach at Pacific Biosciences had  
11 many years ago back when they were at Cornell  
12 was to realize that if you were to illuminate  
13 just the enzyme you could have high  
14 concentration and you wouldn't get any  
15 background. So if you could just observe a  
16 very small volume here that would work they do  
17 that using a technology which is the same way  
18 that the microwave oven works actually.

19 If you shine light or in this case  
20 microwaves through a solid barrier they get  
21 attenuated if their wavelength is wider than  
22 this hole. So if you use a 100 nanometer hole

1 the most visible light is not going to make it  
2 very deep in there. It illuminates just the  
3 enzyme. You're going to have these things at  
4 high concentration.

5 And if you have a way to detect  
6 fluorescence down here and shine some light in  
7 from below, voila, you can actually watch this  
8 enzyme as it adds base by base by base by  
9 base.

10 And these enzymes are designed to  
11 replicate your DNA, my DNA, viral DNA very  
12 quickly. They're designed to do it without  
13 making a mistake because otherwise we wouldn't  
14 have managed to survive as organisms. And  
15 they managed to do it for thousands and  
16 thousands, hundreds of thousands at base  
17 periods without falling off. Which means if  
18 you wanted to get long, correct DNA sequences  
19 it should be able to work.

20 The Pac Bio RS is a machine that  
21 actually does this. We have one at Mount  
22 Sinai. We're actually getting another one.

1                   And this is just to give you a  
2                   flavor for what the actual data looks like.  
3                   And sometimes this actually works on here.

4                   So each one of these little holes  
5                   represents one of these guys there. So those  
6                   flashing lights is a polymerase adding a base  
7                   pair. So each one of those little points  
8                   there has a well like this and each one of  
9                   them is generating a trace that looks like  
10                  this.

11                  This is actually realtime. The  
12                  modern enzymes actually run about twice to  
13                  three times faster than this but you see this  
14                  is time in seconds and it's seeing an A, G, G,  
15                  G, G.

16                  There's a lot of information here  
17                  that I don't have time to talk about right  
18                  now. But you'll immediately see that you're  
19                  getting long reads. Obviously this goes on  
20                  quickly.

21                  And interestingly you're getting a  
22                  population of reads from individual molecules

1 here. So if you aren't amplifying you're  
2 actually sampling the real DNA with its  
3 modifications and everything like that from an  
4 organism or from an environmental sample which  
5 has a lot of advantages in terms of sample  
6 preparation.

7                   It also means that you get to do  
8 statistics on the actual DNA that you got from  
9 your isolates. You don't have to rely on an  
10 instrument and a manufacturer's algorithm to  
11 tell you exactly what's going on. You can  
12 actually inspect the data and work with it  
13 yourself which actually is a very good thing  
14 for discovery, perhaps less so for a buttoned-  
15 down diagnostic test although there are ways  
16 you can package software to do that.

17                   So an interesting problem though  
18 is supposing you've got enzymes that can  
19 sequence 20,000 bases of DNA can you tell me  
20 how many molecular biologists out there are  
21 really good at preparing 20,000 molecular base  
22 pair chunks of DNA? Not many, especially not

1 without nicks or damage or things like that  
2 that polymerases tend not to like.

3 So a standard challenge in  
4 preparing DNA for this new technology, and  
5 it's going to be true for a lot of other  
6 sequencing technologies. We already see that  
7 there's substantial sample prep for any  
8 sequencing technology that's come on the  
9 market.

10 You have to take the DNA sample.  
11 You need to cut it. You need to repair the  
12 end so it looks decent. This is usually  
13 mechanical shearing. Add some adaptors.

14 And for this technology we  
15 actually tend to use these little hairpin  
16 adaptors to make what is called a smart bell  
17 structure. You can stick a primer on here.  
18 You can sequence it around and around. And  
19 what that means is that you will eventually,  
20 if you have a really, really successful  
21 polymerase and an awfully short fragment  
22 you'll sequence around here and you'll start

1 to sequence the other strand.

2 This is fairly standard technology  
3 at this point. It works pretty well.

4 There are two ways you can use  
5 this. You can put it in really long inserts  
6 and you can basically just get sort of one  
7 strand, or you can have a relatively short one  
8 and you can sequence over and over and over  
9 again until you know exactly what that DNA  
10 sequence was.

11 And again, this is like doing  
12 Sanger sequencing on both strands to confirm  
13 something except you're dealing with a single  
14 unamplified molecule that was taken from an  
15 organism and you know exactly what was on that  
16 molecule. So you can look at populations and  
17 see just how different they are.

18 Just to point out that all is not  
19 lost sample prep is a difficult thing. And  
20 there needs to be new innovation in it.  
21 Fortunately the new innovation does come up.

22 This is some data that Bobby

1 Sieber just gave me a few days ago where using  
2 something called a BluePippin purification  
3 system. A BluePippin is essentially a really  
4 fancy agarose gel that happens to be done in  
5 a sort of microfluidics context.

6           The key point here is we took a  
7 library which was 10 to 20 kilobases and we  
8 told the BluePippin that we wanted to get  
9 things that were greater than 7, up to 50  
10 kilobases. And this input here was the input  
11 library. You see it's a log scale in terms of  
12 base pairs. And this is the number of  
13 megabases -- sorry, this is the number of  
14 fluorescence units coming off the instruments,  
15 how much is actually there. You can see it  
16 managed to get a very precise cut here right  
17 around 7,000. You lose this entire shoulder  
18 so you can actually focus on getting the long  
19 sequences of DNA if that's what you want to  
20 do.

21           And so you get the -- sort of the  
22 average read lengths that you get on this

1 system are just shy of 5,000 base pairs each.  
2 And the 95th percentile is a long tail. You  
3 can see the distribution here. It was about  
4 13,000.

5 You can see that 13,000 is, you  
6 know, that's pretty long. It's basically the  
7 size of a human mitochondrial DNA. You  
8 actually, we've been doing whole preps where  
9 you cut human mitochondrial DNA to sequence  
10 the DNA. That's interesting as you -- expect  
11 mitochondrial damage to the system as well.  
12 But that's for another talk some other time.

13 So what's the advantages of having  
14 these sorts of, you know, a new sequencing  
15 technology in the mix? This is the genome of  
16 the strain of cholera that led to the outbreak  
17 in Haiti. We had identified what that was  
18 using Pac Bio sequencing technology.

19 One of the things that eluded us  
20 in our initial publication because we were  
21 kind of in a hurry to get that news out was  
22 exactly what the structure of that genome is.



1 And the structure we did what was called a  
2 reference-based assembly. You took the  
3 standard cholera reference and you mapped  
4 reads to that and you said, okay, well we've  
5 got these alleles. We now know what the  
6 strain is. We've identified it so that's  
7 great. But you don't know and necessarily  
8 understand much about the physiology of the  
9 microbe until you actually know how the genes  
10 are arranged, and that's important for  
11 regulation.

12 So you can see here this is an  
13 assembly based on the Illumina sequence. This  
14 is one based on the slightly longer 454  
15 sequence. Each of these blue blocks is a  
16 separate contig, a separately assembled thing.  
17 And where they don't join there's a gap in the  
18 assembly that tells you how it doesn't quite  
19 fit together perfectly.

20 We actually managed to do a  
21 completely automated assembly of both colored  
22 chromosomes using solely Pac Bio reads. And

1       it's even easier if you go ahead and you  
2       include the other things.

3                   And so what that tells you is it  
4       gets to this question about how do we actually  
5       know what is in what. What is the order of  
6       things along a chromosome. How do we actually  
7       know exactly what you've got? Clearly it can  
8       be done as we're showing here. And that is  
9       potentially a very advantageous thing. It can  
10      also happen in a human context.

11                   So this is a problem with the  
12      question of whether or not the FLT3 gene with  
13      a certain mutation called an internal tandem  
14      duplication here is actually causing AML, a  
15      type of cancer of course, acute myeloid  
16      leukemia.

17                   And the approach on this one was  
18      basically the ITD sequence which is thought to  
19      be activating and leading to the FLT3 acting  
20      as the driver mutation in the cancer is about  
21      a kilobase away from various places -- this is  
22      not to scale -- various positions inside the

1 kinase domain of this kinase that were shown  
2 in vitro to evolve resistance to a FLT3-  
3 specific or relatively specific kinase  
4 inhibitor.

5 So if you get this duplication  
6 that actually activates it. And we went ahead  
7 and we sequenced a bunch of these things. And  
8 we counted the number of alternative codons in  
9 these different positions.

10 And this gets at the question of  
11 can you detect a phased molecule because we're  
12 looking at basically the question of over that  
13 1.4 kilobase region are there a combination of  
14 an ITD mutation -- is there a combination of  
15 this ITD duplication and one of these. If we  
16 see that then we know that this activated  
17 molecule is in fact under selection by the  
18 drug in the case of the cancer.

19 And this is actually in seven real  
20 patients. So here are the patients. This is  
21 work done with Neil Shah and Cathy Smith at  
22 UCSF. It's published so there's more people

1 involved obviously.

2 And we have the pre-treatment  
3 samples here. And you can see that there's  
4 some noise in the system. There's an  
5 alternative codon frequency observed but at  
6 very low frequencies. That's probably the  
7 error in the assays. The number of samples we  
8 looked at.

9 If you looked at people who then  
10 relapsed, these different subjects, you'll see  
11 that we start to see alternative codons that  
12 correspond to these resistance mutations at  
13 relatively high frequencies. And if you look  
14 at just a normal control individual you'll see  
15 that it matches the pre-treatment.

16 So basically when you select with  
17 a drug for these AML patients they derive  
18 resistant mutations that correspond with their  
19 relapse. That validates this as a target and  
20 it also shows that you can with reasonably  
21 decent precision catch phased molecules of  
22 long length in a mixture and understand what's

1 going on there.

2 So one of the things that was  
3 interesting was this F69L because this guy  
4 actually shows up in combination with some of  
5 these mutations here on the exact same  
6 molecules. And that's exactly the pairing you  
7 would expect because the mechanism by which  
8 these things are likely related to resistance  
9 is the ability of the drug to get in whereas  
10 this actually is a pi-stacking interaction  
11 between these two erratic structures there  
12 that would help to actually bind the drug in  
13 the pocket. So you would expect there to be  
14 some synergy in those kinds of things.

15 So this is an example of where you  
16 have to -- you can actually assay the nucleic  
17 acid as well. You can actually correlate it  
18 to the physiology of, you know, life or death  
19 phenotypes in humans.

20 What we're trying to do more  
21 broadly is kind of the following work flow.  
22 So we have a CLIA-operated genomics core

1 facility. We think that's a good way to go  
2 because CLIA is all about basically one thing  
3 and that is asserting for sure that the data  
4 that comes back from your instrument came from  
5 the sample that you put in. And you kind of  
6 want to do that anyway if you're running a  
7 good facility so we bit the bullet and made it  
8 an all-CLIA thing.

9 Of course we have a super computer  
10 do the analysis. And we also have a screening  
11 facility to help us deal with what these  
12 results mean phenotypically down the road.  
13 Our overall work flow is we've got patients  
14 coming in, giving us samples during clinical  
15 labs, seeing our clinic.

16 We've got a biobank where we have  
17 been doing some research on individuals who  
18 have consented to that sort of research. That  
19 information ends up in EPIC and data  
20 warehouses. EPIC is an electronic medical  
21 records system.

22 And then we go ahead and build

1     some disease models. We construct these, we  
2     interpret them and then we try and actually  
3     use these for operational feedback to  
4     influence the clinical process in the hospital  
5     and our outpatient clinics.

6                 So that's a great little vision.  
7     How do you actually get sequences into there?  
8     So of course it's never as easy as you might  
9     think but we've been trying to leverage these  
10    multiple technologies to do that.

11                So this is an example of trying to  
12    do this thing which is not cost-effective but  
13    is a good illustration of where the technology  
14    can go.

15                So NA12878 is a standard genome  
16    that's been sequenced an awful lot by an awful  
17    lot of people. You can order it and sequence  
18    it.

19                So we looked at a little  
20    combination of Illumina and 454. And that's  
21    shown graphically. The 454 read's about this  
22    long, the Illumina read's about that long and

1 the Pac Bio reads are much longer.

2 And we were going to try and see  
3 what you could learn about the structure of  
4 this incredibly well-annotated genome that's  
5 missed in both the standard HD19 reference  
6 assembly as well as other assemblies that  
7 people put together.

8 This is similar in spirit to  
9 trying to look at different platforms to try  
10 and cull single nucleotide variants. There's  
11 a lot of platform comparison lore that we  
12 could get into during the discussion if people  
13 are interested.

14 One of the things we're interested  
15 in since we do a lot of follow-up to newborn  
16 screening actually is can you actually screen  
17 for some of these things that we know have  
18 genetic disease consequences that are  
19 currently inaccessible. And all these  
20 trinucleotide repeat disorders fall in that  
21 category. Fragile X is one example,  
22 Huntington's disease is another. You wouldn't



1 screen for that probably in newborns because  
2 it's adult onset but it's the same kind of  
3 class of thing.

4 And so what's interesting here is  
5 that if you go ahead and you look at some of  
6 these genes you get reads that span all these  
7 repeat things. And again, the Illumina reads  
8 are going to have a hard time with that  
9 because these are trinucleotide repeats, CAG  
10 for instance, repeated many, many times. And  
11 sometimes they're going to be too long for a  
12 single Illumina read to span.

13 And so not surprising if you get a  
14 read that spans all of that then you can  
15 actually figure out exactly what the structure  
16 looks like and it can be an effective way of  
17 doing this that you otherwise would not with  
18 other technologies.

19 If you look at this particular  
20 region, this calcium channel here, there are  
21 two repeat regions I believe in separate exons  
22 actually, one exon here and one exon there.

1       These can expand and you can actually start to  
2       get the phasing from here to there.

3                       This is probably fairly relevant  
4       for thinking about what exactly is the  
5       antigenicity in the MHC or the HLA region of  
6       the MHC regarding a blood donation. If  
7       there's a lot of repeat structures, many kind  
8       of duplications we saw how complicated the  
9       haplotypes are, technologies such as this  
10      allow you to actually get across and say with  
11      confidence that there was a molecule that had  
12      a number of repeats here and a number of  
13      repeats here as well as certain single  
14      nucleotide polymorphisms in that area. So, it  
15      tends to increase the precision of what you're  
16      doing.

17                      So since we're kind of genomics  
18      people and we had a bit of genome coverage, we  
19      decided well let's look at all the other  
20      trinucleotide and bigger repeats across the  
21      genome. You can see there's a distribution of  
22      different repeats, lengths that are present in

1 the genome as well as in exons or at least  
2 predicted exons.

3 The overall upshot of this is if  
4 you compare the HD19 reference down here with  
5 the tandem repeats counts on this thing and  
6 the span of those there is a bias, this is  
7 sort of shown by chromosome here and aggregate  
8 over there, for essentially an increase in  
9 this sequence here which is probably due to  
10 compression of the standard HD19 reference  
11 because that's your repeats. If you don't  
12 have an easy way to span them they tend to all  
13 get piled up in one place and you  
14 underestimate the length of the repeated  
15 sequence. So I just covered that.

16 Just to give you some examples of  
17 what this looks like this is one from the MHC  
18 region, the major histocompatibility complex.

19 And what's neat about this is this  
20 is mapped to a standard reference sequence.  
21 And you can see that we've got a gap in these  
22 reads that just doesn't map. And there's also

1 a section here where -- so these are the 454  
2 reads. These are the Illumina reads.

3 There is a substantial difference  
4 between what we know to span this little  
5 region here. And there's a section which we  
6 don't see because it doesn't map to this  
7 assembly that's quite large that is  
8 essentially unknown to the Illumina and the  
9 454.

10 A somewhat more complicated  
11 example is this one here where clearly you've  
12 got some things. We've got reads that span.  
13 We've also got some that actually look like  
14 they map the reference. Perhaps this  
15 particular genome is part reference and part  
16 something different in this location.

17 And then I'm going to just go on  
18 and say that our overall work flow clinically,  
19 and this is one where the color is kind of --  
20 it renders better on my PC. But suffice it to  
21 say we've got a work flow which starts from  
22 whole blood or Guthrie cards, it goes through

1 two different sets of library prep, one for  
2 RNA, one for DNA.

3 We'd go ahead and try and  
4 understand gene expression. We try -- on the  
5 Illumina platform we try and look for standard  
6 sequencing and SNPs on this platform, on the  
7 Illumina platform. We'd complement that by  
8 targeted Pacific Biosciences sequencing and we  
9 would go ahead and analyze this at the end.

10 The overall goal though is to  
11 remember, getting back to that sort of big  
12 data slide I had at the very beginning, if you  
13 think about cancer where there is a rich  
14 amount of data. So you've got sort of cancer-  
15 specific data sets of various kinds. You've  
16 got phenotypic data, you've got things from  
17 the Cancer Genome Atlas (TCGA), you've got  
18 genotype information, you've got RNA  
19 information from both tumor and normal. Then  
20 you've got these reference things like various  
21 pathway databases, the ENCODE work, you know,  
22 of course the literature itself.

1           You'd like to make that all  
2       accessible when you're trying to analyze an  
3       individual patient. So how do you do that?

4           Well, one of the easy ways, it's  
5       not completely cheap but next to cancer  
6       therapy it might turn out to be cheap actually  
7       because that sure isn't and especially when it  
8       often doesn't work. You know, you can  
9       sequence germ line DNA, tumor DNA, tumor RNA,  
10      you can detect somatic variants.

11           You can try and model this in one  
12      way. We tend to use Bayesian networks for  
13      this although there are other ways. And you  
14      can try and make predictions of what might be  
15      constructive for individualized vaccines.

16           You can then try and actually take  
17      this information, analyze it in the context of  
18      standard networks for what normal tumors look  
19      like, quote unquote "normal tumors," what  
20      normal tissues look like and use that to try  
21      and construct xenograft mouse models, patient-  
22      specific fly models, or to screen in cells and

1 actually try and come up with personalized  
2 therapy.

3           So the overall strategy here is  
4 one of taking a large amount of information,  
5 organizing that in a statistically rigorous  
6 and computationally tractable way, frequently  
7 a network model, generating some rich  
8 information on an individual patient and then  
9 reflecting it on these network models to try  
10 and drive specific targeted approaches to what  
11 you might actually try and do clinically.

12           And of course this requires a lot  
13 of ways to interact with the data and these  
14 sorts of things that are complicated and  
15 interesting.

16           So as a vision for where we're  
17 thinking about trying to take sequencing, how  
18 we're trying to integrate it medically it does  
19 rest fundamentally on a rich foundation of  
20 public data that's already out there. It's  
21 messy, it's ugly but you can distill a good  
22 signal and learn good things from it,

1 generating a rich picture of the phenotype  
2 molecularly of the individual you're looking  
3 at as well as matching that to their clinical  
4 phenotype and using that to drive personalized  
5 decisions with the right sort of resources and  
6 the right sort of people looking at it.

7 I suspect that one can probably do  
8 something along those lines for blood as well.  
9 And I'll close by acknowledging people who  
10 were involved in that Pac Bio sequencing of  
11 the whole genome work which are right here.  
12 So I'll stop and take questions. Thanks.

13 (Applause)

14 DR. KASARSKIS: Actually, no I  
15 don't take questions. We take questions  
16 later. With that I should probably start by  
17 introducing our next speaker.

18 So Clark Tibbetts is our next  
19 speaker. He comes to us from TessArae and is  
20 going to be talking to us about that platform  
21 and how it can be used.

22 He has spent a lot of time doing



1 many things with regard to diagnostic  
2 development over the years and I expect we'll  
3 have a chance to hear from him both here and  
4 in the panel session.

5 DR. TIBBETTS: Thank you, Darrell,  
6 for your AV help and Andrew. Thank you to the  
7 FDA for organizing yet another workshop where  
8 it confirms my lifelong lesson learned that  
9 whether a speaker or participant there's a  
10 real risk here of learning some good things.

11 So let me jump right in. I don't  
12 want to dwell on the debate of the relative  
13 pros and cons, costs and benefits, risks and  
14 opportunities, threats, strengths, weaknesses  
15 of biomarker, short DNA signature PCR-type  
16 assays, or sequencing-based assays. It's very  
17 easy in the semantics to get mixed up between  
18 sequence-based which PCR certainly is and  
19 sequencing-based which goes to another  
20 dimension of information yielded by the  
21 assays. So I'm not going to go into this  
22 other than to acknowledge it and declaim my

1 bias to being a strong zealot of sequencing-  
2 based applications.

3 This started -- no credits to  
4 George Lucas for the title of this slide --  
5 this started in work more than a decade ago in  
6 the Defense Department where we were seeing an  
7 opportunity using high-density microarrays to  
8 bring a sequencing-based analysis into  
9 operations in a practical sense for worthwhile  
10 applications.

11 The store we have here is an array  
12 that we built that's similar to the blood  
13 array I'll be describing today. It was aimed  
14 at all sorts of respiratory diseases,  
15 bacterial and viral, all in one assay, one  
16 sample, next-day results.

17 And this particular array  
18 represented sequences for detection and  
19 reporting of all 16 hemagglutinin and all 9  
20 neuraminidase variants of influenza type A  
21 subtypes including many different clades of  
22 these that come from more or less related

1 groups of avian, swine, equine and human  
2 subtypes of flu.

3 It was designed in 2004. Every  
4 single year since 2004, almost a decade now,  
5 that array has correctly identified to the  
6 strain the H1N1 seasonal variant, the H3N2  
7 seasonal variant and the B virus seasonal  
8 variant of annual flu vaccines.

9 That means that strains that were  
10 totally unknown and in no databases anywhere  
11 in the world in 2004 were being detected and  
12 accurately reported with a diagnostic assay  
13 that was developed up to 10 years earlier. A  
14 diagnostic assay that can see into the future.

15 Similarly, since these are  
16 vaccines that are manufactured with master  
17 donor strains in every single case the  
18 interior non-HA, non-NA sequences of these  
19 viruses were correctly identified in each case  
20 as the 50-year-old master donor strain of the  
21 cold-adapted engineering strain for FluMist,  
22 the live virus vaccine, or the 75-year-old

1 strain from Puerto Rico of H1N1 that's  
2 engineered into the type A inactivated  
3 vaccines. So it can see almost a century back  
4 as well as decades forward with a static  
5 assay.

6 You can't do that with any  
7 conceivable PCR test. PCR requires a priori  
8 knowledge of the sequences, of the target, of  
9 the assay that is to be developed. And it  
10 really works well with the best-looking ROC  
11 curves when you test it against that strain it  
12 was intended to detect and report.

13 It fails when you have a PCR test  
14 that tries to detect natural variants of H1N1  
15 or H7N9 or whatever that don't quite match the  
16 primer-binding sequences upon which the direct  
17 reporting of a signal from a PCR probe may  
18 emanate.

19 So getting to the applications of  
20 transfusion-transmissible agents I do want to  
21 say thank you to Jerry Holmberg who introduced  
22 us to this array and to our colleagues now for

1 several years from the FDA/CBER/DETTD group.

2 We went through early discussions  
3 and a learning curve reviewing documents that  
4 were critical several years ago for looking to  
5 the future of screening the blood supply for  
6 greater safety for various pathogens,  
7 particularly pathogens that we aren't quite  
8 sure we're engaging yet or have not engaged at  
9 all yet.

10 And the outcome of that was a  
11 project of collaboration with the DETTD group,  
12 particularly Dr. Duncan and Dr. Hewlett and  
13 their lab groups to develop a prototype  
14 microarray that would use various strategies  
15 for various relevant pathogen targets in order  
16 to evaluate the capability of a single assay  
17 that in a single day would generate strain-  
18 and variant-specific information at the level  
19 of gene sequences and at a cost that would be  
20 comparable to a similar scale of multiplex PCR  
21 tests.

22 I won't go through the details

1 here but we'll just point out that we had a  
2 panel of experts including infectious disease  
3 groups from the Army and the Navy, the FDA's  
4 DETTD group, Harvey Alter's group at NIH and  
5 several folks from industry. And then we  
6 doubled the weight given to the FDA group  
7 since they were sponsoring the development of  
8 the chip and we ended up with a popularity  
9 poll of target pathogens for the first array.

10 We went through an extensive  
11 bioinformatics analysis through all known  
12 sequences of all the genes of all the target  
13 pathogens, selecting segments that represented  
14 different clades of variants of each pathogen  
15 type. And from those sequences we tried to  
16 identify primers that would generically  
17 amplify those target gene segments of those  
18 pathogens.

19 And the primers we select would  
20 fail in every conceivable PCR test because we  
21 used degenerate nucleotides at various  
22 positions to cover single-nucleotide

1 variations in primer binding sites. And we  
2 used an extraordinary relaxed amplification  
3 schedule that would litter a PCR test with  
4 false positives. We don't care.

5 This assay does not detect on the  
6 basis of what you can amplify and therefore we  
7 can amplify a much broader range of biological  
8 pathogen materials than a PCR test would.

9 What this test does is it looks at  
10 the sequences of those amplicons that are  
11 generated to determine if an amplicon that's  
12 relevant to the target of the assay indeed has  
13 been detected. And with that sequence we can  
14 identify it much more acutely at the level of  
15 strain and variant.

16 So this is the list of things that  
17 are on the smallest of the arrays that  
18 TessArae design and develops. It includes a  
19 large number of viruses, 25 different types  
20 and subtypes, bacteria of various types,  
21 eukaryotic pathogens and a leftover legacy of  
22 several biothreat pathogens that we've had on

1 all of the arrays since 2004.

2 This is the kind of results that  
3 are generated for just one of any of these  
4 pathogens that may be tested as a single  
5 target or as a blind mixture of targets. This  
6 happens to be a hepatitis type C virus that  
7 was spiked into blood and then assayed.

8 The array has 15 different  
9 detector tiles for the 5 prime genome  
10 sequences of different clades of hepatitis C  
11 viruses. There's a lot of diversity in this  
12 group.

13 And 12 of those clades responded  
14 to the particular hepatitis C template that  
15 was blinded into this sample extracted from a  
16 spiked blood sample. And those 12 sequences  
17 depending on how they were laid out as  
18 detectors matched more or less well to  
19 whatever the corresponding sequences were in  
20 the template. And they had very high to  
21 almost 50 percent of the detector tile  
22 sequence giving a read of sequence of the



1       template.

2                       And we took all of these 12  
3       sequences from different detector tiles all  
4       reporting from the same template and we  
5       aligned them. And I don't expect you to read  
6       much less memorize these sequences here that  
7       are aligned. They're in descending order of  
8       the highest quality reads of about 90 percent  
9       of the detector tile to the lowest quality,  
10      about 50 percent. And a consensus sequence is  
11      easy to derive from the alignment.

12                     And if you put that into BLAST you  
13      come up with a single strain in all of GenBank  
14      that as of yesterday matches the particular  
15      template we were given. And it's a particular  
16      2002 isolate.

17                     That's the closest match of any  
18      strain that's been known and reported. It  
19      doesn't mean that what we had in that tube as  
20      a blind sample was that strain, but it's the  
21      most similar strain.

22                     There are almost 60 similar

1 strains with only 1 or 2 nucleotides different  
2 from that particular strain that is the best  
3 match. So there's really an unequivocal  
4 result here that we have hepatitis type C in  
5 that sample and we have some insight as to  
6 what strain it may most closely resemble.

7 Now I'm going to go through a  
8 couple of anecdotes that are similar to what  
9 we have seen in our early development with the  
10 blood chip. In 2008 there was an outbreak of  
11 hand, foot and mouth disease in China. Anhui  
12 Province in particular is where it focused.  
13 And it was being caused by enterovirus 71.

14 An earlier array that had 40  
15 different detector tiles for different clades  
16 of enteroviruses, enterovirus or rhinovirus.  
17 Of those about a dozen picked up and reported  
18 sequences from multiple samples from that  
19 outbreak.

20 And every single one of these  
21 sequences that was reported best matched  
22 enterovirus 71 sequences in the GenBank at the

1 time. The interesting thing was none of the  
2 sequences on the array were enterovirus 71.

3 Now, I can't show the data that  
4 was generated by our Chinese colleagues so  
5 I'll show what we can reveal. The NRL as our  
6 colleagues went to the CDC and asked for a  
7 sample of enterovirus 71 to test. And the CDC  
8 graciously complied and sent a sample which  
9 was then analyzed to generate the results I'm  
10 showing here.

11 And the consensus of sequences for  
12 these tiles is shown here with a BLAST report  
13 of the most similar sequence found in GenBank.  
14 And when Dr. Stanger at the NRL got back to  
15 the CDC and said thank you, we had great  
16 results with the entero 71 sample you sent us.  
17 By the way, was that by any chance the strain  
18 1M/Australia/2012? And they said how did you  
19 know that.

20 Flu story one -- so this is the  
21 second movie in the series on flu -- is in the  
22 same time period as we are today, March and

1 April, 4 years ago. There had been a few  
2 outbreaks in Mexico associated with influenza  
3 with a very high mortality rate. There were  
4 feelings in Mexico at the time that the death  
5 rate was attributable to co-infections with  
6 respiratory bacteria of these flu patients.

7 A few weeks after those early  
8 reports the CDC got involved when there were  
9 more and more tourists coming back from Mexico  
10 with mild flu symptoms and some cases that  
11 suggested there was something going on  
12 different from flu.

13 We were fortunate to be able to  
14 access at the end of March a sample from a  
15 tourist returning to the Washington, D.C. area  
16 having been in Mexico during one of the -- in  
17 the region of one of the outbreaks.

18 And at the time, right about April  
19 1 the GISAID EpiFlu database released first  
20 genome sequences. There was nothing in  
21 GenBank matching the outbreak strain until  
22 April.

1                   We got four more samples from the  
2           Navy of presumptive atypical H1N1's and they  
3           had identical sequence reporting from our  
4           array assay. And then a few weeks later the  
5           CDC announced its hemagglutinin- and matrix-  
6           based diagnostic test for the novel H1N1 and  
7           the sequences then appeared in GenBank.

8                   So when we looked at GenBank at  
9           the end of March and the first of April to the  
10          sequences found on the RPM array they matched  
11          a whole variety of different avian gene  
12          sequences from matrix or NS or PB2 gene.  
13          That's what we could pick up and detect  
14          easily.

15                   When we looked at the GISAID  
16          database that published sequences from these  
17          outbreak strains about 10 days earlier than  
18          GenBank every single one matched perfectly to  
19          the sequences that were reported by the people  
20          who had sequenced the whole influenza genomes.  
21          So the array had satisfied the expectation  
22          that it would be able to look ahead and detect

1 and characterize an outbreak strain.

2 I'm going to skip ahead because I  
3 see we're getting close. Just to be ironic,  
4 the results of the last 2 weeks in China with  
5 H7N9 recapitulate exactly the story I just  
6 told you about the pandemic H1N1 flu. It was  
7 picked up in Beijing in Dr. Xue-Jun Ma's lab  
8 who was working parallel with the flu  
9 institute of the Chinese CDC.

10 In our laboratory with the  
11 collaboration of DETTD we have analyzed  
12 several different categories of pathogens on  
13 the array and determined that they correctly  
14 report genus and strain -- genus and species  
15 and strain when that information is available.  
16 And we've done a limited number of serial  
17 dilution assays to estimate what the  
18 sensitivity of the assay is. And most of the  
19 targets indicated here in red have shown what  
20 we've attained over and over and over again  
21 with high-quality templates in the RPM assay,  
22 that is, detection in the assay of 10 to 100

1 genome equivalents per assay.

2                   So we're looking ahead to further  
3 work. We want to expand the sensitivity and  
4 specificity studies. We know that the RPM  
5 because it's delivering sequence uses longer  
6 amplicons and so it does not work as well with  
7 degraded templates. We want to take extra  
8 care at looking at the preparation and storing  
9 processes that have been used by people that  
10 have provided templates for us to analyze.

11                   We want to expand the content of  
12 the array using peg-mounted arrays following  
13 the lead of our other FDA collaborators at the  
14 Center for Food Safety and Applied Nutrition.  
15 This will give us a chance to use longer tiles  
16 with somewhat greater specificity or more  
17 tiles representing greater diversity of the  
18 target pathogens that we want to screen.

19                   This is a picture of the FDA SAN  
20 assay. Right now food safety assays rely on  
21 MLST panels of seven or eight different genes.  
22 We've expanded that by a factor of 10 on this

1       array.

2                   And so far the preliminary studies  
3       are showing that all of the strains that we're  
4       following and sequencing with the array are  
5       matching to an extremely high level the  
6       quality of sequences generated by next-gen at  
7       our collaborating CFSAN laboratories.

8                   And then lastly we want to look at  
9       how we can take this prototype to more of a  
10      beta product and demonstrate its practical  
11      utility in a clinical application. Following  
12      a lead that we have been working on for the  
13      last year or so with a human carrier screen  
14      assay we're looking to automate the assay  
15      which allows an expansion of the number of  
16      multiplexes and the granularity of the  
17      resolution you can expect.

18                  It has an enormous contribution to  
19      reduce manual pipetting errors. The gene  
20      screening assay currently uses 384-well  
21      plates, 12 templates per plate, 32 multiplexes  
22      per assay with 360 different amplicons. It



1 looks at 500 different mutations associated  
2 with 92 different monogenic diseases.

3 That kind of technology and the  
4 new lower-cost, higher-throughput, higher-  
5 content arrays on peg technology that we're  
6 using in the food safety applications I think  
7 will enable us to take lessons learned from  
8 the study of the blood chip prototype and  
9 carry it to the next step where we can  
10 demonstrate practical applications in a  
11 clinical utility exercise.

12 I'll take it that you were  
13 listening and abandon the conclusions and say  
14 once again thank you very much, everybody. I  
15 look forward to questions coming up in the  
16 panel.

17 (Applause)

18 DR. KASARSKIS: Our next speaker  
19 is Elena Grigorenko, Diatherix Laboratory.  
20 She'll be speaking to on the Life Technologies  
21 open array platform for pathogen detection.

22 And she has a long history in

1 industry beginning back at Millennium  
2 Pharmaceuticals and Caliper. And of course  
3 she's spent a long time at Life Technologies  
4 as well. And she's a biochemist by training  
5 so we look forward to hearing what she has to  
6 say.

7 DR. GRIGORENKO: I'd like to say  
8 thanks to the organizers for the invitation to  
9 give a talk and to present the work that has  
10 been done at Life Technologies in the last 3  
11 years.

12 So the project goal when we  
13 started this project was to see if the  
14 OpenArray platform can be used as a tool for  
15 doing the profiling of the different pathogens  
16 in the high-throughput settings.

17 So the idea is that we can achieve  
18 the sensitivity for the detection as low as  
19 100 copies per ml in the high complex  
20 background. And the platform should be  
21 flexible enough so you don't really need to go  
22 through activation of the primer sets every

1 time you -- the new pathogen comes in. And so  
2 analytical performance of the platform will  
3 not be sacrificed.

4 And the platform will be pretty  
5 standard and reliable. So every time it could  
6 be used in a clinical setting, so in an R&D  
7 environment the answer will be the same  
8 regardless of the sample being used. And it  
9 will be at the end of the day using this  
10 platform people can generate -- can use it for  
11 profiling of large number of samples.

12 So a little bit of project  
13 history. So we started this project in  
14 collaboration with the FDA almost 3 years ago.  
15 So the goal of the phase I was to evaluate  
16 OpenArray platform and the TaqMan chemistry  
17 with the idea is that can this platform be  
18 used for the profiling of the blood-borne  
19 pathogens.

20 And at that point in time we had a  
21 small number of assays for the profiling in  
22 mind only for viruses, for bacteria and three

1 parasites. So to see can we use the same  
2 platform for profiling very variable targets,  
3 different targets that could be present in the  
4 blood supply.

5 And then later in the year as we  
6 expanded this platform we include not only the  
7 genes but also different species of the  
8 bacteria, the parasite and multiple subtypes  
9 of the viruses.

10 And we decided to create two  
11 different panels that will target bacterial  
12 and viral pathogens. And then this year the  
13 project is concluded for testing unknown coded  
14 samples on the panels where assays have been  
15 validated.

16 So for those who don't know what  
17 is OpenArray platform it's -- I think what was  
18 mentioned a couple of times yesterday in the  
19 different presentations. It's a realtime PCR  
20 platform that instead of using microtiter well  
21 plates it's using a stainless steel plate  
22 which has through-holes, open holes where the

1 assays for specific target could be spotted  
2 in. And when the sample is loaded on  
3 OpenArray plate using automated device which  
4 is shown here, assays are reconstituted in the  
5 media. And again, they use in the realtime  
6 PCR with the sample.

7 Now, advantage of this platform  
8 that as you can see here the -- it has a lot  
9 of wells on a plate. That means a lot of  
10 different assays can be deposited on OpenArray  
11 plate. Assays are spatially separated.

12 So there is no need for  
13 multiplexing and further activization of the  
14 multiplex reaction. And instead individual  
15 PCR reactions is running separately with the  
16 same sample in the separate well. So in a way  
17 you can see here it allows you to achieve a  
18 spatial multiplexing since assays are  
19 separated in a space.

20 So one can run 48 samples in a  
21 single plate. On a new instrument which is  
22 shown here, QuantStudio 12K Flex, you can run

1 four OpenArray plates which allow you to  
2 profile 144 samples in a single run. The data  
3 collected in a realtime PCR. So the quality  
4 of amplification can be assessed by looking at  
5 the amplification curve and the CT values  
6 generated.

7 So, here's the project milestones.  
8 For phase I and phase II we had very similar  
9 milestones which we had to achieve.

10 So first of all, it's starting  
11 with the target assay design. And some of the  
12 assays for this project has been used  
13 successfully in the laboratory of FDA. And  
14 some of the assays for the target has been  
15 designed by Life Technologies. So we use the  
16 specific TaqMan PCR assays for each individual  
17 target either from published sequences or  
18 designed internally.

19 Then assay has to be validated for  
20 specificity and sensitivity. And then once we  
21 validate assays for sensitivity and  
22 specificity we selected the best-performing

1 assays and prepared OpenArray plates for  
2 further evaluation using either spiked samples  
3 with specific nucleic acids, and then later  
4 use this platform for the coded samples.  
5 Because the last phase is basically, the  
6 optimum goal to see how this platform will  
7 perform when the sample identity is unknown.

8 A few slides just show you the  
9 assay performers. So here you can see two  
10 different targets. One is West Nile,  
11 Plasmodium falciparum and Leishmania. For the  
12 most part for most of the target you can see  
13 here when in the presence of other targets of  
14 other organisms there is no amplification is  
15 detected.

16 In case of Leishmania donovani and  
17 this assay specific for Leishmania you can see  
18 that there is some amplification with assays  
19 specific for T. cruzi. But this is not  
20 surprising because there is quite a similarity  
21 in the sequences between two different  
22 organisms.

1                   When the serial dilution of the  
2                   specific nucleic acid was made we were able to  
3                   achieve the level of sensitivity of detecting  
4                   15 copies per ml -- 15 copies per microlitre  
5                   or 100 copies per microlitre for different  
6                   organisms.

7                   Of course this level of  
8                   sensitivity using just straight nucleic acid  
9                   was not sufficient enough and in the latest  
10                  study we decided to use pre-amplification  
11                  step. So all the results that I will be  
12                  showing you later is -- describe when pre-  
13                  amplification step was used.

14                  But here's to show you how  
15                  reproducible the system is. When you spot  
16                  assays inside of the well you get very tight  
17                  standard deviation regardless of the target  
18                  that has been interrogated on OpenArray  
19                  plates.

20                  The top is showing you the --  
21                  where if you use -- regardless what target you  
22                  use, RNA or DNA, the reproducibility of the



1 system is very tight. And even pre-  
2 amplification step, and this is the graph on  
3 your right, showing you regardless if you use  
4 24 cycles of the pre-amp or going with the 40  
5 cycles which we use later in our further study  
6 the precision of the system -- doesn't really  
7 compromise the precision of the system.

8 So this just gives you an idea of  
9 our first steps of this study. So in the  
10 first phase we decided to put all the targets,  
11 all the assay that we have designed all in a  
12 single sub-array plate. And it does include  
13 DNA pathogens as well as RNA pathogens.

14 And in the list we have a variety  
15 of the subtypes of HIV viruses, dengue,  
16 Chikungunya, influenza, to include all  
17 potential emerging pathogens that could be  
18 tested for -- in the blood.

19 So once assays has been validated  
20 for sensitivity and then specificity we have  
21 more refined panel which is shown here. So we  
22 design two types of the OpenArray plates. One

1 is for working with the DNA target and another  
2 one for RNA target.

3 This is the example of the final  
4 panel that was used in the phase II study  
5 where we have a single assay for a species and  
6 an assay that can detect genesis. And this is  
7 an example of the viral layout panel where we  
8 have, as I said, we have assay that can  
9 differentiate different species as well as pan  
10 assay.

11 So once the panel has been  
12 designed and the manufacturing then next  
13 logical step is to see how this panel is  
14 performing when we use a sample that resembled  
15 real life samples. And in this case we used -  
16 - the pathogen was spiked in the whole blood  
17 and at the different concentration DNA was  
18 isolated, DNA or RNA was isolated. And then  
19 pre-amplification step was employed using a  
20 pool of the TaqMan primers at the different  
21 cycle number.

22 And in this table you can see that

1 using pre-amplification step we're able to  
2 achieve the level of sensitivity for detection  
3 of the 100 cells per ml for all different  
4 organisms with the exception of Plasmodium  
5 vivax. That for this particular target our  
6 best LOD was 1,000 cells per ml.

7 The same was true for testing  
8 limit of the detection of the virus spiked  
9 plasma. Again, in the -- for this case this  
10 target has been reverse transcribed and then  
11 pre-amplified using the pool of TaqMan-  
12 specific assays.

13 And if you look at this table our  
14 level of the detection limit for the detection  
15 for the viral target is ranging from 100 to  
16 500 PFU per ml if we use 18 cycles of pre-  
17 amplification. However, we were not able to  
18 achieve this low level of sensitivity for  
19 dengue viruses.

20 So when we test unknown, and this  
21 is a slide from phase I work. When we test  
22 the unknown viral spiked samples since our

1 assays are very specific and this is -- on the  
2 column on your left you see the coded sample  
3 that has been sent to us by FDA. And the  
4 results are generated with OpenArray panel.

5           You see there is only a single  
6 cell is colored. But it has been that there  
7 is -- we're not able to detect any other  
8 amplification with other assays. That  
9 confirms the panel we designed and I said it  
10 has been validated previously, a very specific  
11 and was able to detect only a specific target.

12           So based on these results we come  
13 up with the decision tree for cold calling to  
14 -- that could be used for identification on  
15 unknown samples if this system potentially  
16 could be used in any type of the clinical or  
17 diagnostic settings.

18           And what we've been looking for  
19 knowing the platform performance we'd be  
20 looking first at the quality of amplification  
21 plot. So, how steep the curve is, what is the  
22 CT values.

1                   Another advantage of OpenArray  
2 platform is it reports CT confidence value  
3 that tells you about the quality of  
4 amplification curve generated on OpenArray  
5 plate. And this parameter could be very  
6 useful tool when you assess the -- when you  
7 assess the quality of amplification.

8                   Another very important parameter  
9 is reproducibility of the performance of the  
10 plate. And it's related how many data points  
11 has been detected for each individual target.

12                   Precision is also very important  
13 since on OpenArray plate we've been able to  
14 spot a single assay three times that gives you  
15 information about the technical performance of  
16 the plate. So it's -- it also could be used  
17 in decision tree.

18                   So the last few slides just show  
19 you when we start testing unknown samples we -  
20 - using this decision tree that I described  
21 previously we've been able to identify  
22 correctly in terms for DNA target all except

1 two which is listed in red here.

2 For the viral pathogens our call  
3 rate also was pretty successful. We've been  
4 able to correctly identify all except three  
5 pathogens using OpenArray plate.

6 The last two slides just show you  
7 the results from the phase III which is not  
8 completed yet. We've been able to test only  
9 24 samples here. And what is most important  
10 when we tested repository donor samples, we've  
11 been able to correctly identify and call all  
12 24.

13 So saying that I think OpenArray  
14 platform, it's a novel multiplex platform that  
15 can be used for profiling of the blood-borne  
16 pathogen. It has all required parameters in  
17 terms of the sensitivity and the flexibility  
18 that require for the testing of the blood  
19 samples.

20 And I would like to thank my  
21 collaborators from the FDA, Dr. Duncan and his  
22 associate Carolyn Fisher as well as folks at

1 Life Technologies, Sunali Patel, Paco  
2 Cifuentes and Nancy Toomey. Thank you.

3 (Applause)

4 DR. KASARSKIS: So we are running  
5 a little bit behind here but we have the great  
6 opportunity to switch from nucleic acid to  
7 protein.

8 So Raya Zerger actually has a  
9 background in medical technology and blood  
10 banking and will be talking to us today about  
11 antigen- and antibody-based tests. She's  
12 currently with Beckman Coulter.

13 DR. ZERGER: Thank you. Well, in  
14 the interest of time I've been asked to talk  
15 about antigen- and antibody-based methods and  
16 there aren't any in multiplexing so thank you  
17 for your time and attention. Just kidding.

18 I think that we can draw some  
19 insights from the current methods that we have  
20 when we talk about what is currently out  
21 there, what the FDA has approved for use in  
22 donor screening.

1                   And what I did was I just went up  
2                   to the CBER website and I grouped by  
3                   methodology the different assays that have  
4                   been or are available, certainly have been  
5                   approved by the FDA.

6                   And you can see that certainly for  
7                   chemiluminescence there's a couple of combi  
8                   assays that are out there that I guess are the  
9                   harbingers of multiplexing. And what they  
10                  detect. Most of course detect antibody  
11                  instead of antigen, not all but many.

12                  And one of the considerations that  
13                  we need to have given the state of our medical  
14                  procedures are using cadaveric samples because  
15                  of the transplantation and use of cadaveric  
16                  samples for donor screening for organ  
17                  donations.

18                  So I just kind of took a walk down  
19                  memory lane. I feel like especially talking  
20                  to a group such as this about antigen and  
21                  antibodies is like talking about Lego's  
22                  instead of building skyscrapers but it is



1 where we came from.

2 And I think we will get to where  
3 we want to go. I have every faith in the  
4 capabilities of the scientific community to  
5 get us to the lab on the chip where we can do  
6 everything we want to do in a very  
7 multiplexed, very simple manner. However, I  
8 think we need to leverage what we have today  
9 in moving along that continuum because I  
10 suspect it will be a continuum.

11 And so just to run through these  
12 assays. EIA, I remember when that was new.  
13 I remember thinking back in the late seventies  
14 when I started in blood bank all the cool  
15 stuff had happened already. But I remember  
16 when this was new. And we can draw even from  
17 these assays. We've used them, we still use  
18 them for certain agents. And the passive  
19 agglutination which definitely seems old  
20 school is still used today quite effectively.

21 And I think that while we are on  
22 this continuum we have to look at what we

1        might be able to use from these assays. It is  
2        likely that some of these will continue to be  
3        used or maybe they won't fall into the  
4        multiplexing category in the truest sense but  
5        maybe they'll be used in parallel. Because as  
6        old school as that is it's very inexpensive  
7        and very effective.

8                        So it's hard to knock that if you  
9        can't compete on that level, especially given  
10       the economic constraints. We want it all but  
11       we can't have it for free. So I see these  
12       maybe being supplemental or getting us between  
13       where we are now and where we're going.

14                      I think that when you look at what  
15       we have available now we have to parlay that  
16       to the true multiplexing that we want to get  
17       to. So I just wanted to do a quick review of  
18       what's out there and what's available to  
19       remind everybody where we are.

20                      And also I did find two  
21       multiplexing tests that are out there right  
22       now. Or excuse me, three. And these are just

1 the methodologies. But as you can see they  
2 are not antigen/antibody-based. They are in  
3 the direction that we're heading.

4 So in the interest of time I'm  
5 going to stop there. Thank you for your  
6 attention.

7 (Applause)

8 DR. KASARSKIS: So our final  
9 speaker for this session is Jeffrey Linnen.  
10 He is with Gen-Probe, now of course Hologic  
11 Gen-Probe.

12 And he's a biochemist by training  
13 with 15 years experience developing nucleic  
14 acid tests, many in the context of blood  
15 actually. So looking forward to hearing what  
16 he has to say.

17 DR. LINNEN: I want to thank the  
18 organizers of the meeting first for the  
19 opportunity to give this talk.

20 So what I'm going to talk about is  
21 really what's happening now with some  
22 projections of what we could do with the

1 instrumentation that exists right now to reach  
2 a higher level of multiplexing. So these are  
3 assays that are currently being used in blood  
4 screening that I'm mainly going to talk about.

5           Hopefully this is not my most  
6 interesting slide but because I'm going to be  
7 talking about a lot of assays that are in  
8 different regulatory stages, some are FDA-  
9 licensed, some are just CE marked, some are  
10 under development and some are maybe just a  
11 figment of my imagination.

12           Okay. So what I'm going to cover.  
13 I'm going to give an overview of the  
14 technology and also an overview of the  
15 automation and how that's progressed through  
16 time. And then I want to talk about the  
17 assays that we have right now for screening  
18 whole blood in plasma donors.

19           And then I have a couple of slides  
20 that maybe would have been more relevant  
21 yesterday but I want to talk about at least  
22 from my perspective the challenges for

1 developing multiplex assays and then finish  
2 with looking at what we could do in the future  
3 with using basically this technology in  
4 automation.

5                   Okay, before I get into the  
6 technology overview I just want to put things  
7 in context. So this is the history of TMA  
8 blood screening. It really starts in 1996  
9 when we were awarded a contract from the NHLBI  
10 to develop a nucleic acid test for HIV and  
11 HCV. And it's really I think safe to say that  
12 we wouldn't be in the blood screening business  
13 if we hadn't been awarded this contract. We  
14 were a small company at the time and I think  
15 this really jump-started our work.

16                   And some other things. I'm not  
17 going to go through the entire time line but  
18 I want to point out a few things. If you look  
19 at when we won that contract and how long it  
20 took to get the first assay licensed it's  
21 approximately 6 years. So if you're  
22 interested in time lines this is what it took

1 back then. It could be different now.

2 Certain assays from the time that  
3 we introduced them under an IND to the time  
4 they were licensed the time was quite a bit  
5 shorter, for example, the in the case of West  
6 Nile virus. And then we developed multiple  
7 generations of our assays.

8 And you can see if you look at the  
9 present time we're still developing assays for  
10 the blood screening market. We've entered the  
11 plasma screening market. And later in the  
12 talk I'll give some information on our  
13 automated systems that you see there.

14 Okay. I think it's hopefully  
15 obvious to everyone here the way specimens are  
16 prepared is very important for any nucleic  
17 acid test. So I just want to spend a few  
18 minutes or maybe hopefully less than a few  
19 minutes talking about the technology that we  
20 use.

21 We use a magnetic-based target  
22 captured system as specific capture. The

1 specimen volume that we use in all of our  
2 samples is 0.5 ml and there's actually some  
3 importance to that that I'll get into later.

4           Probably the most important thing  
5 or one of the nice aspects of this method that  
6 we use is that the wash steps remove potential  
7 inhibitors. And this method works very well  
8 removing inhibitors from the reaction too.

9           This is the method that we used to  
10 amplify the nucleic acid. Transcription-  
11 mediated amplification works with RNA and DNA.  
12 It's a two-enzyme system. It uses reverse  
13 transcriptase and T7 RNA polymerase.

14           The reaction occurs at one  
15 temperature so it's an isothermal reaction.  
16 And you can achieve very high levels of  
17 amplification in a relatively short period of  
18 time.

19           And this outlines the method just  
20 very simply. There's a reverse transcription  
21 either creating a -- in the end a double-  
22 stranded DNA target that incorporates a T7

1 polymerase and then that -- promoter site, T7  
2 polymerase promotor. And that promoter site  
3 drives transcription to create multiple copies  
4 of RNA that can cycle back in through this  
5 process of reverse transcription. So it's  
6 worked very well for us and we've been able to  
7 develop a lot of sensitive assays using this  
8 method.

9 Detection is by chemiluminescence  
10 for all of our assays that are on market right  
11 now. We utilize Acridinium Ester labeled  
12 probes. The structures are shown here. The  
13 reaction steps, very simply there's a  
14 hybridization. There's what we call a  
15 selection step where the unhybridized probe is  
16 hydrolyzed. The hybridized probe then gives  
17 off a chemiluminescence signal. And this can  
18 be used for both quantitative and qualitative  
19 detection. You can detect multiple analytes  
20 but there is a limitation how many you can  
21 discriminate at one time. At this point we  
22 can discriminate three using both the



1 magnitude of the light and the kinetics of the  
2 light emission and disappearance. And that's  
3 what's shown in this figure right here.

4 Because of the lack of time I can't really go  
5 into the detail of that.

6 I also want to point out that we  
7 have a number of assays at Gen-Probe that are  
8 in development that use realtime TMA  
9 technology. And so this is fluorescent  
10 detection rather than chemiluminescent  
11 detection.

12 We use some probes that are  
13 similar to molecular beacons with some key  
14 modifications. So the advantage that this  
15 gives us is the ability to multiplex to a  
16 higher degree to differentiate between  
17 multiple targets in one reaction.

18 Now, I would like to give a little  
19 bit of information about the technology  
20 starting out with the system that was  
21 introduced in 1999. We refer to this as the  
22 semi-automated system. It's actually, it's a

1       pretty manual system.

2                       It's not used very much these days  
3       anywhere in the world but this is what was  
4       used to screen blood for many years in the  
5       U.S. In fact, a large proportion of all the  
6       blood in the U.S. was used screening this  
7       system. At Gen-Probe we still use it pretty  
8       frequently because it's useful in the  
9       development of assays. You can actually see  
10      what's going on in the tube as you work on the  
11      formulations or work with unusual samples.

12                     The method here just briefly.  
13      Sample processing occurs using this system  
14      right here. It's where the magnetic capture  
15      occurs. Amplification and hybridization  
16      occurred in water baths. The reading of the  
17      signals occurred automatically in a  
18      luminometer.

19                     And this has progressed  
20      substantially. This is the Procleix TIGRIS  
21      system. So this is a fully automated system.  
22      What I mean by that is collection tube, blood

1 collection tube or a pool can be placed  
2 directly on the instrument. And then it is  
3 basically the concept of a black box. The  
4 result comes out, the first result in a little  
5 bit more than 3 and a half hours.

6 This is really a workhorse. We  
7 consider this a high-throughput instrument.  
8 With our highest-throughput assays 1,000  
9 results can be obtained in 14 hours. And so  
10 this has been in routine use for screening  
11 individual donors and for pools since about  
12 2005.

13 Now, we've continued working on  
14 automation. This is our newer system, the  
15 Panther system. So this is a smaller system  
16 than the TIGRIS instrument. It's about --  
17 takes up a little bit less than half the space  
18 of a TIGRIS instrument.

19 Now there are a lot of features  
20 that are different for the Panther compared to  
21 the TIGRIS. It's a random access instrument  
22 meaning that you can order the tests by

1 specimen. You don't necessarily have to use  
2 it as a batch analyzer. You can order  
3 multiple tests from the same sample tube, or  
4 multiple replicates of the same assay if  
5 that's something that there's interest in  
6 seeing.

7                   It's also a dual format instrument  
8 meaning that you can use the endpoint or the  
9 chemiluminescent assays. You can also use  
10 realtime assays on the same instrument. The  
11 capability of doing that is in development  
12 right now and there will be software next year  
13 that will allow those two types of assays to  
14 be run on a single instrument.

15                   And I'm not going to go into the  
16 details. The throughput is somewhat lower  
17 than the TIGRIS but actually two Panthers  
18 working together have a throughput that's  
19 superior to the TIGRIS instrument.

20                   Now here's what we've been doing  
21 with this technology over the years. I just  
22 made this slide a couple of weeks ago and I

1 thought boy, we've really been busy over the  
2 years.

3           You can see this is a highly  
4 regulated field. What's shown right here are  
5 all the different -- the regulatory approvals,  
6 either U.S. or EU and the level of automation.  
7 These are the assay names, the viruses that  
8 are detected and the number of amplicons that  
9 are detected. So one of the things that you  
10 can definitely conclude from this slide is  
11 we're currently not using highly multiplexed  
12 assays.

13           One of the other things that you  
14 can see if you look at the number of viruses  
15 detected, for example, with what we call the  
16 Ultrio Elite assay which is an assay that's  
17 not available in the U.S. but it's CE marked  
18 on the Panther system. It detects four  
19 different viruses, HIV-1, HIV-2, HCV, HBV.  
20 HIV-1 we actually have to detect two regions  
21 of the genome and I'll go into a little bit  
22 more detail about that. But that's the

1 strategy that we've been taking from the  
2 development of our very first assays.

3 You'll see that the number of  
4 amplicons detected is higher in every case to  
5 the number of viruses detected because we also  
6 in each of these assays detecting an internal  
7 control.

8 Okay, now I'd like to kind of  
9 shift and talk about at least from my  
10 perspective what the challenges are for  
11 multiplexed NAT blood screening. Some of this  
12 was discussed yesterday but maybe I might have  
13 a little bit of a different angle on some  
14 things.

15 When I made this list the first  
16 thing that really came to my mind because  
17 myself and a number of people in this room  
18 have spent years trying to determine what  
19 analytes really need to be screened for. It's  
20 very hard work and can take a long period of  
21 time. So tops on my list is determining  
22 whether NAT screening is necessary or not.

1                   Can the agent be detected in  
2           asymptomatic blood donors? Is there actually  
3           disease? And I really thought that the  
4           comment that Harvey Alter made yesterday was  
5           probably one of the best ones, that you really  
6           have to be working backwards from disease, not  
7           from the sequence trying to find the disease.  
8           And Harvey knows I had some experience with  
9           that very early on in my career.

10                   Sensitivity and specificity, these  
11           are obvious ones. But one point that I really  
12           wanted to emphasize regarding sensitivity is  
13           that there's the problem of knowing whether  
14           the target is even in the sample. So a larger  
15           sample volume offers an advantage. It  
16           increases the probability the agent is  
17           actually present in the sample.

18                   And another thing I guess I should  
19           emphasize is that in all of these cases, all  
20           of these blood screening assays that we've  
21           developed except with maybe the exception of  
22           one of our plasma screening assays, we need to

1 detect the lowest possible copy levels.  
2 Because our assumption is if the agent is  
3 present the blood product will be infectious.  
4 Now that's not necessarily true but we have to  
5 work using that assumption.

6 And probably the only one that  
7 we've developed so far where we're not trying  
8 to screen with the lowest sensitivity is for  
9 parvovirus B19.

10 Specificity. There was a lot of  
11 discussion about specificity and I'll actually  
12 show what we've been able to achieve for  
13 specificity for one of our licensed assays.

14 I raise the question here could  
15 lower specificity be tolerated with more  
16 highly multiplexed assays. Because the  
17 specificity that's needed right now is based  
18 on the current work flow. So that is maybe  
19 something that could be considered.

20 Another thing for people that are  
21 not familiar with the field of blood screening  
22 is that it's very difficult to distinguish a



1 false reactive from a low titer true positive  
2 in some cases. And what this can result, this  
3 was mentioned yesterday, is deferral of a  
4 donor with a false reactive rate and often  
5 that results in donor loss. So that's an  
6 important issue that needs to be addressed.

7 Also you can't overlook that you  
8 need to be able to detect both known and  
9 unknown genetic variants. Now, some of the  
10 technologies that have been discussed at  
11 workshop deal better with these challenges.  
12 And I'll show an example of our two-region  
13 detection and a little bit more detail about  
14 our designs, how we deal with that.

15 And you can't overlook any genetic  
16 variant. You have to detect every genetic  
17 variant that could be possibly in a blood  
18 donor specimen.

19 Another point, different targets  
20 may require different sample preparation. And  
21 the example that comes to my mind, all of our  
22 assays so far are for viruses that are found

1 in plasma or serum. There are other important  
2 agents that probably should be screened for,  
3 Babesia and possibly malaria in some cases  
4 that will require possibly a different type of  
5 sample processing. So it may -- this is  
6 another challenge for multiplexing from the  
7 same specimen preparation.

8 And then last but not least is the  
9 validation, verification and then the  
10 regulatory approvals. Now, multiplex assays,  
11 from my own experience I know that they're not  
12 necessarily easy to get licensed because you  
13 have to prove that when you add an analyte  
14 that you have not affected the performance for  
15 the analytes that were present in the previous  
16 version of the assay. And it's always  
17 difficult to predict how regulations might  
18 change either here in the U.S. or in Europe or  
19 country-specific regulatory requirements.

20 And as it stands right now there  
21 are different regulatory requirements for  
22 different potential agents that could be

1 screened for blood screening. Actually, some  
2 require a submission with a review, some are  
3 just self-certifying CE marks. And so we have  
4 to be aware that those requirements could  
5 possibly change.

6 Now, just to go into some data to  
7 give you a more specific idea of the  
8 sensitivity that's required for blood  
9 screening. This is analytical sensitivity  
10 using WHO standards.

11 This is really important. I have  
12 to admit in looking at a lot of these  
13 presentations I can't compare the sensitivity  
14 of one assay to another because standards were  
15 not used. And the terminology used to talk  
16 about analytical sensitivity was not always  
17 consistent. So we always talk about  
18 international units in 95 percent detection  
19 levels determined by Probit analysis. It's a  
20 type of regression analysis where we do an  
21 endpoint dilution to where we're no longer  
22 detecting the analyte.

1                   So because most of you aren't  
2                   familiar with international units I've  
3                   converted the numbers to copies here using  
4                   estimates that have been published. And so  
5                   you can see that the sensitivity for the  
6                   different targets range from 10 to 20 copies.  
7                   That's really what we can expect with the TMA  
8                   technology. And I think on one would be  
9                   interested in going backwards in terms of  
10                  sensitivity.

11                 And the other thing that needs to  
12                 be mentioned regarding sensitivity is the  
13                 tests are not perfect. Even with this level  
14                 of sensitivity not every virus is detected.  
15                 There are low levels that are too low for  
16                 current technology to detect. So sensitivity  
17                 is critical. I don't think anyone's going to  
18                 compromise on sensitivity.

19                 You heard about specificity. I  
20                 just wanted to show you the type of data that  
21                 can go into establishing specificity. This is  
22                 a study that was done at the American Red

1 Cross. The study itself is published by Susan  
2 Stramer in the New England Journal of  
3 Medicine. In this study over 570,000  
4 individual donations were screened. This was  
5 just part of the study. There was also a  
6 pooled testing part of the study that I'm not  
7 showing.

8 The specifically that we achieved  
9 in this particular study was 99.93 percent.  
10 So that's really I think representative of the  
11 specificity that's required in blood  
12 screening. I think that's probably about what  
13 the American Red Cross is seeing on a routine  
14 basis. Maybe actually a little bit higher  
15 than that.

16 Pooled testing has some advantages  
17 where confirmation is easier because you go to  
18 the individual donation. And so it's a little  
19 bit easier to determine the true status of the  
20 sample.

21 Okay, now regarding genetic  
22 variants. Every time we design an assay we

1 look at very conserved regions of the assay.  
2 In this case this is HIV. We're targeting two  
3 regions. Both of these are conserved and in  
4 fact even within this region of the genome we  
5 have a redundant system to account for both  
6 known and unknown genetic variants. So that  
7 definitely needs to be addressed in any assay  
8 design.

9 Now just what can we do with the  
10 current automation? Well, with the Panther  
11 system because of its flexibility multiple  
12 tests can be performed from a single donation.  
13 Four different assay kits can be loaded onto  
14 the instrument. So in theory, depending what  
15 these assays are you can achieve a certain  
16 level of multiplexing just by sampling the  
17 same sample repeatedly.

18 In this case I'm showing the  
19 Ultrio elite assay 4 analyte, West Nile virus  
20 assay, HEV assay which is in development and  
21 parvo B19 HAV duplex assay which is on the  
22 TIGRIS system but we're in the middle of

1 feasibility for the Panther system. So in  
2 this case you could achieve with very little  
3 changes to what we're doing right now eight  
4 viruses from four TMA assays.

5 For the future if this is needed  
6 the same thing, four TMA assays could be  
7 added. This could be expanded with realtime  
8 detection. Four fluorescent dyes can  
9 currently be detected. This can be expandable  
10 to six. So in theory there could be 4 6-plex  
11 assays to detect 24 agents potentially which  
12 I'm just showing here as genetic assays. So  
13 up to 24 viruses could be detected by 4 TMA  
14 assays from the same sample.

15 Of course the amount of sample  
16 volume needs to be addressed. The amount of  
17 dead volume that would be used for each  
18 specimen is less in this case since you're  
19 sampling from the same tube.

20 Just to sum up. Hopefully you see  
21 that NAT blood screening has evolved  
22 significantly from its introduction in the

1 late nineties. And as you can see we're not  
2 doing highly multiplex screening and that may  
3 be due to the lack of need but there are a  
4 number of challenges towards that.

5 Current automation could allow  
6 what I define as a moderate level of  
7 multiplexing. But if needed the current  
8 automation could be adapted for more highly  
9 multiplexed testing. So maybe as many as 24  
10 viruses, possibly more. But I think the need  
11 really needs to be standard. So thank you  
12 very much for your attention.

13 (Applause)

14 DR. KASARSKIS: So Sanjai says  
15 that we should give ourselves a 10-minute  
16 break here. So I guess that would put us back  
17 here at 10:20. Thanks so much. That  
18 concludes the session obviously.

19 (Whereupon, the foregoing matter  
20 went off the record at 10:09 a.m. and went  
21 back on the record at 10:27 a.m.)

22 DR. SLEZAK: Okay, let's get



1 started. We've got a full schedule and I  
2 imagine we'll probably have the same long  
3 lunch lines awaiting us when we're finally  
4 ready to go to lunch.

5 So my name is Tom Slezak. I'm a  
6 bioinformatics leader at Lawrence Livermore  
7 Lab and I'll be running this session.

8 Our first speaker today is Matthew  
9 Meyerson. He's a professor of pathology at  
10 the Dana Farber Cancer Institute in Harvard  
11 Medical School and a senior associate member  
12 of the Broad Institute. He'll be talking to  
13 us about tools for pathogen discovery and  
14 identification using next-generation  
15 sequencing data analysis.

16 DR. MEYERSON: Tom, thank you very  
17 much for the introduction and thanks to Dr.  
18 Sanjai Kumar for the invitation to speak here.

19 So I'm going to talk about, as a  
20 lot of the speakers, about next-generation  
21 sequencing data analysis for pathogens. I  
22 just want to start by mentioning a couple of

1 relevant conflicts of interest.

2 First, I'm the founding advisor of  
3 and consultant to and an equity holder in  
4 Foundation Medicine which is a company that  
5 offers a next-generation sequencing test for  
6 cancer mutation diagnosis. I'm not going to  
7 actually speak to this test but I think it  
8 informs some of the comments that I'm going to  
9 make.

10 And I'm also an inventor on a  
11 patent on computational subtraction for  
12 pathogen discovery which is not currently  
13 licensed.

14 Just the outline of the talk, I'm  
15 going to have a sort of introduction to next-  
16 generation sequencing for blood safety. Then  
17 I'm going to talk about computational methods  
18 for pathogen discovery, three examples of  
19 pathogen detection, the discovery of  
20 *Fusobacterium* association with colon cancer  
21 which is published. And then two pieces of  
22 unpublished work, a discovery of

1     Bradyrhizobium enterica in cord colitis  
2     syndrome and the identification of novel  
3     viruses in stool from a diabetes cohort.

4             And finally I'm going to give an  
5     example of hybrid capture discovery in the  
6     cancer genome identification of NAB2-STAT6  
7     fusions in sarcoma recently published. And  
8     I'm going to close with just a brief summary  
9     and some opinions.

10            So just sort of for my own  
11     education as I was preparing this, what's the  
12     current state of infectious agent testing.  
13     Going to be obvious to you required by the FDA  
14     are hepatitis viruses, HIV, HTLV and Treponema  
15     pallidum and recommended as I understand it  
16     are the West Nile virus and Trypanosoma cruzi.

17            And these recommendations may have  
18     changed since I was able to find them. But to  
19     my knowledge all other infectious agents are  
20     currently not formally tested. And although  
21     we've been hearing a lot of methods for  
22     testing of other agents, influenza, malaria,

1 others.

2 Will next-generation sequencing  
3 enable the screening for all infectious agents  
4 both known and unknown? Some considerations  
5 include obviously, and we've heard from other  
6 speakers these same ideas, sensitivity,  
7 accuracy, cost, turnaround time.

8 And what do you do with agents of  
9 unknown significance? I think Dr. Kasarskis  
10 commented on this earlier today. Dr. Chiu  
11 commented on this issue yesterday.

12 As Dr. Kasarskis showed the  
13 increasing power of DNA sequencing is enabling  
14 pathogen discovery. And this cost is shown  
15 here by genome sequencing going from \$100  
16 million per genome in 2001 to -- this is a  
17 little bit older slide -- to on the order of  
18 about \$5,000 at the cusp of 2012 to 2013. And  
19 these costs are continuing to fall.

20 And so the penny is just shown  
21 here for scale. This is a flow cell from one  
22 of the technologies, the Illumina technology.

1     The penny's just shown for scale.  It's not  
2     the cost of, for example, a whole genome  
3     sequencing yet, but if you just follow that  
4     line maybe it will be.  And that's kind of I  
5     have to say a lot of -- what a lot of us think  
6     about next-generation sequencing is based on  
7     the assumption that costs will continue to  
8     decrease and that assumption of course is not  
9     necessarily true.  That assumption requires  
10    continued technology innovation in the field.

11                 Just a sort of overview of some  
12    types of approaches to blood safety  
13    sequencing.  One is unbiased DNA sequencing  
14    which would be the complete sequence of the  
15    entire genome plus all of DNA-containing  
16    infectious agents.  Another possibility is  
17    unbiased RNA sequencing, the sequencing of all  
18    expressed RNAs and all infectious agents with  
19    nucleic acid expression including RNA viruses.  
20    So I think this is an important point for RNA  
21    virus detection, the requirement for using RNA  
22    as well as DNA as a template.

1                   And finally, targeted sequencing  
2           is the sequencing of selected genes and/or  
3           genomes from either DNA and/or RNA. And  
4           methods include PCR-based sequencing and  
5           hybrid capture-based sequencing.

6                   And then on the next slide I just  
7           talk a little bit about hybrid capture  
8           sequencing. The method, this is something  
9           that we've used very extensively at the Broad  
10          Institute. And in fact we've done sequences  
11          of over 60,000 human exomes including about  
12          10,000 cancer/normal paired exomes. And this  
13          method was developed by Andy Gnirke and  
14          colleagues and they reported it originally in  
15          Nature Biotechnology back in 2009.

16                   So the idea is that you use a  
17          bait, typically an oligonucleotide it says  
18          here for each exon but really it can represent  
19          any nucleic acid segment whether it's an exon,  
20          a transcript fragment, or fragments of a  
21          bacterial or fungal or viral genome, or a non-  
22          exonic part of a human genome.

1                   So you've got a bait which is an  
2                   oligonucleotide for each targeted sequence and  
3                   you generate those baits on microarrays. You  
4                   cleave them off and you biotinylate them, and  
5                   then you -- or you can synthesize them by a  
6                   number of different means. And then you  
7                   hybridize to so-called, the pond. And we use  
8                   typically tumor and normal DNA, but it could  
9                   be DNA or cDNA isolated from blood and so on.  
10                  You hybridize and you capture them onto beads.

11                  And then for Illumina sequencing,  
12                  and again for other sequencing platforms this  
13                  would be different. The libraries are  
14                  generated using universal Illumina adapters  
15                  following hybrid capture. And so because this  
16                  is relatively linear the hybrid capture should  
17                  prevent linear quantitation as well as  
18                  detection.

19                  And the on-target percentages for  
20                  exome sequencing which is on the order of 30  
21                  million bases that are baited is over 90  
22                  percent. That on-target percentage drops

1 somewhat when you go to a smaller set of  
2 baited sequences. But even, you know, for  
3 example for the million base range it's well  
4 over 75 percent.

5 So I think one of the  
6 considerations for next-generation sequencing  
7 for blood safety is whether it should be  
8 unbiased sequencing based on whole blood or  
9 plasma DNA or RNA versus focused sequencing  
10 for example by hybrid capture basis. And I  
11 think the advantages of unbiased sequencing is  
12 the possibility to discover all known or  
13 unknown pathogens. And it's really the only  
14 method that can identify all emerging  
15 infectious agents. You know, the advantages  
16 of hybrid capture will be lower cost, simpler  
17 informatic analysis focused on known agents  
18 where the meaning of the discovery or  
19 detection of an agent is relatively better  
20 understood. And the possibility because you  
21 have lower sequencing costs to use higher  
22 coverage to have deeper identification of



1 polymorphisms.

2                   And I think then the other  
3 question is screening versus surveillance with  
4 the advantage of using the most in-depth  
5 method for screening being that, again, the  
6 discovery of known or candidate pathogens can  
7 be achieved in all cases and you can get the  
8 correlation between microbial sequence and  
9 subsequent disease in a discovery method where  
10 if you've got very rare or unexpected  
11 populations who've come up with transfusion-  
12 associated disease you immediately have the  
13 nucleic acid data to associate with them.

14                   The advantage of surveillance are  
15 that it's lower cost because you're looking  
16 only at a subset of units of blood. And then  
17 new microbes in the blood supply can be  
18 identified as candidates by unbiased  
19 sequencing and then can be added later to a  
20 focused test if there's evidence that supports  
21 doing so.

22                   So now I'd like to turn into the

1 data part of the discussion and start by  
2 talking about our approach to unbiased  
3 pathogen detection known as computational  
4 subtraction. And we first reported this in a  
5 paper back in 2002, work led by Griffin Weber  
6 and Jay Shendure at that time both M.D./Ph.D.  
7 students.

8                   And we call it sequence-based  
9 computational subtraction for pathogen  
10 discovery. And the principle is that the  
11 human genome sequence is nearly complete and  
12 infected tissues contain human and microbial  
13 RNA and DNA. So you can generate and sequence  
14 libraries from human tissue containing both  
15 human sequences shown in white and non-human  
16 sequences shown in red.

17                   The normal human sequences can be  
18 subtracted computationally and the remainder  
19 of the sequences are of non-human origin. And  
20 then disease-specific sequences can be  
21 validated experimentally.

22                   So Alex Kostic together with -- he

1 was a graduate student in my group together  
2 with Gad Getz and Chandra Pedamallu developed  
3 an approach that we call PathSeq for  
4 computational subtraction of next-generation  
5 sequencing data.

6 And basically in PathSeq what we  
7 do is we take the complete read set. Today we  
8 do some quality filtering. Maybe eventually  
9 that won't be necessary. We use a variety of  
10 liners. We've actually been trying -- we're  
11 working lately with the SNAP aligner that  
12 Charles Chiu was describing in his talk  
13 yesterday, but this slide is from our  
14 manuscript -- to align to human reads.

15 We do further refinement with  
16 BLAST against additional databases which we  
17 hope to eliminate over time. And we get to a  
18 final unmapped read set that we either use, do  
19 metagenomic analysis on known organisms or  
20 assembly analysis both of a nucleotide and  
21 translation level for sequences that have no  
22 match to known organisms. And this was

1 published in Nature Biotechnology in 2011 and  
2 the software is freely available.

3           So on DNA sequencing we have  
4 purification that is greater than --  
5 efficiency that's better than 1 part in 2  
6 million because the DNA sequencing databases  
7 are quite complete. And so this is an example  
8 from an ovarian cancer genome. In RNA  
9 sequencing our purification is not as complete  
10 because not all transcripts are really --  
11 spliced transcripts are really representative  
12 effectively in databases.

13           And we've implemented this  
14 pipeline using cloud computing making it  
15 universally accessible. And we're also using  
16 it on a load sharing farm. This cost is  
17 obsolete. The cost of cloud computing has  
18 dropped and probably today still the  
19 computational costs are on the order of \$50 or  
20 \$60 but I'm expecting those again to continue  
21 to drop dramatically over time especially as  
22 we incorporate these newer and faster

1 aligners.

2                   Okay, so Alex using this tool went  
3 on to identify an association of *Fusobacterium*  
4 *nucleatum* with colon cancer. And he started  
5 with a data set of nine colorectal cancer  
6 whole genome sequences and matched normal  
7 sequences that we had described in a paper by  
8 Adam Bass and colleagues in *Nature Genetics* in  
9 2011 where we had identified a *VTI1A-TCF7L2*  
10 fusion.

11                   And he took 1.5 billion reads per  
12 sample, ran them through the PathSeq algorithm  
13 and got 100,000 reads per sample afterward.

14                   So these are colon cancer tissue  
15 and normal colon tissue from surgery. They're  
16 matched from patients. We did not have normal  
17 colon tissue from patients without cancer in  
18 this original screen but we've looked later at  
19 patients from other diseases where we do see  
20 less *Fusobacterium*.

21                   So he used a method called LEfSe  
22 by Segata and colleagues in Curtis

1 Huttenhower's lab to identify what are the  
2 most tumor-enriched organisms. And he found  
3 *Fusobacterium*, in particular *Fusobacterium*  
4 *nucleatum* as the most enriched.

5 He went on then to -- this is just  
6 specific data. The tumor data are in purple,  
7 the normal data are in green. And you can see  
8 here in every sample there's enrichment of  
9 *Fusobacterium nucleatum* in the tumor.

10 I should mention that this  
11 clustering analysis says that other than --  
12 you can see in 5N/5T, 4N/4T, the tumors and  
13 normal microbiome are clustering together in  
14 general with the exception of the difference  
15 in *Fusobacterium* abundance.

16 We confirmed the enrichment using  
17 16S ribosomal DNA sequencing analysis of a  
18 larger data set. And we've also confirmed  
19 this more recently using analysis of large  
20 cohorts in data from the Cancer Genome Atlas.

21 And I should mention there was an  
22 independent paper by Castellarin, et al., from

1 Rob Holt's lab that was published back to back  
2 with our paper.

3 Finally, and I think you can see  
4 this. If we use whole bacterial probes or if  
5 we use specific probes for *Fusobacterium* we  
6 can detect *Fusobacterium* within the Lamina  
7 propria and mucus of the colon.

8 And so we see this enrichment of  
9 *Fusobacterium* species, mostly *F. nucleatum*,  
10 but also *F. mortiferum* which means "death-  
11 bearer" in Latin and *F. necrophorum* which  
12 means "death-bearer" in Greek. So you  
13 probably don't want to have either of these.

14 So we see enrichment in colorectal  
15 cancers but we're trying to ask whether  
16 *Fusobacterium* species have a role in the  
17 development of colorectal cancer. And Alex  
18 has been doing experiments in mouse models.  
19 And those of you who are frequently publishing  
20 papers will appreciate that it's going through  
21 what I call the manuscript rejection process  
22 right now.

1                   So I just want to turn to another  
2                   new and completely unpublished area of  
3                   discovery of *Bradyrhizobium enterica* in cord  
4                   colitis syndrome. This is work of Ami Bhatt  
5                   who's a medical oncologist working in my  
6                   group. She's newer in the group than Alex.  
7                   I don't have a photograph of her for which I  
8                   apologize.

9                   So what Ami -- Ami's been looking  
10                  at a disease called cord colitis syndrome  
11                  which is an idiopathic antibiotic-responsive  
12                  diarrheal syndrome found in patients being  
13                  treated for leukemia who have received  
14                  umbilical cord blood transplantation. All of  
15                  them had been discharged home before  
16                  developing colitis and even though it was  
17                  antibiotic-responsive all microbiology studies  
18                  for existing bacteria were negative.

19                 So there are two things that  
20                 suggest an infectious etiology. One is the  
21                 response to antibiotics and the other thing is  
22                 that you see granulomas at the base of the



1 intestinal crypts which is a common marker of  
2 infection.

3           So what Ami did is she took the  
4 biopsies from cases. These are two  
5 independent biopsies here from two different  
6 cases. And she did deep next-generation DNA  
7 sequencing and she found large numbers. So  
8 for example, 110 million reads. She removed  
9 low-quality reads, lots of human reads. There  
10 were known bacterial reads but in fact the  
11 unmapped reads in each of these actually  
12 exceeded the known bacterial reads. And so we  
13 could imagine that either there was some  
14 classification error or that the genome was  
15 missing in the database.

16           And so in fact she went on to do  
17 assembly and she found that almost all of  
18 those unmapped reads mapped to a new organism  
19 that classifies closely with *Bradyrhizobium*  
20 *japonicum*. And she's named this organism  
21 *Bradyrhizobium enterica* because it's found in  
22 the intestine.

1                   Many of the *Bradyrhizobia* are soil  
2                   organisms. They're associated with the roots  
3                   of plants. And we've actually got nearly  
4                   complete genome coverage of this bacterial  
5                   sequence. It's 64 percent GC enriched, very  
6                   similar to *B. japonicum* but there are a lot of  
7                   genes, all these blue genes, dark blue genes  
8                   are genes that are absent in *Bradyrhizobium*  
9                   *japonicum*. So it's the closest relative but  
10                  it is quite significantly different. And  
11                  again we've been using phylogenetic tools  
12                  developed by colleague at the Harvard School  
13                  of Public Health, Curtis Huttenhower, led by  
14                  Neal Segata.

15                 And then when we actually go back  
16                 and we use it now as a reference genome, now  
17                 we see that many of the known bacterial reads  
18                 that were mapping to other bacteria because  
19                 they had homology are actually most homology  
20                 to *Bradyrhizobium enterica*. And this is  
21                 overwhelmingly the most predominant bacterium  
22                 in the cord colitis syndrome biopsies.

1                   Just one more thing about  
2       Bradyrhizobium enterica. She was kind of  
3       wondering why is it there and was finding out  
4       where had other Bradyrhizobia been found.  
5       They had been cultured from places like  
6       charcoal filters and the clean room of the  
7       Kennedy Space Center. So one possibility is  
8       this is a bacterium that can grow very well in  
9       a clean environment where other bacteria are  
10      not present. And transplant patients  
11      obviously are being treated in a very clean  
12      manner and are in a very clean environment.  
13      So that may be why they're getting infected  
14      with an organism that others aren't.

15                  We don't know that this organism  
16      causes the disease. We only know that we've  
17      seen it enriched in a number of cases.

18                  Okay, just want to turn to now  
19      discovery of novel viruses by our approach,  
20      work led by Chandra Pedamallu, Joonil Jung and  
21      Fujiko Duke. Here we've been working with a  
22      study called the TEDDY study, The

1 Environmental Determinants of Diabetes in the  
2 Young, where we did shotgun sequencing of  
3 longitudinal samples of stool from patients  
4 who are at risk for diabetes.

5 And we performed shotgun  
6 sequencing here from 175 RNA samples and 7 DNA  
7 samples. And we found two novel viruses. One  
8 was a novel picornavirus with very high trans  
9 -- no homology at the nucleotide level to a  
10 hypothetical protein, but homology at both  
11 nucleotide and protein level to the RNA-  
12 dependent RNA polymerase. So if I said  
13 picornavirus I truncated the name. I meant  
14 it's a picobirnavirus. I apologize for that.

15 We also found a novel polyomavirus  
16 in two of the DNA sequencing samples with  
17 multiple contigs matching multiple regions  
18 including T antigens. We're continuing to  
19 study this with a colleague who's expert in  
20 polyomaviruses to try to see if these have  
21 transforming or cancer-causing potential.

22 We've actually made a complete

1 assembly of the virus from the stool  
2 specimens. This virus was also discovered by  
3 a group at Washington University who published  
4 it before we did and it's called MW  
5 polyomavirus. But we're also trying to see  
6 whether there's association with the  
7 development of diabetes.

8 So finally for data I'd like to  
9 talk about the power of hybrid capture. And  
10 I'm going to talk about work of Juliann  
11 Chmielecki in my lab -- again I apologize for  
12 not having a photo -- who discovered a NAB2-  
13 STAT6 fusion in solitary fibrous tumors using  
14 hybrid capture analysis.

15 So in cancer, I probably should  
16 have done a little introduction, there are  
17 sort of four major types of events that can  
18 cause cancer: mutations, copy number changes  
19 which are DNA quantity changes, rearrangements  
20 in genome structure, and infections.

21 And we can detect all four of  
22 these with next-generation sequencing and the

1 first three with hybrid capture of human  
2 sequence. So we can find mutations, copy  
3 number changes and rearrangements.

4 And this was published in Nature  
5 Genetics earlier this year. The fusion was  
6 also discovered in the laboratory of Arul  
7 Chinnaiyan who published back to back with us.

8 Solitary fibrous tumors are rare.  
9 This is an image of one here. You can see  
10 it's gigantic there and it's occupying  
11 normally. This is in the CT image. Normally  
12 the lung would be black as open space. This  
13 is the heart, the aorta. And this huge tumor  
14 is basically almost occupying an entire lobe  
15 of the lung.

16 They're benign, slow-growing  
17 tumors, but then they can become malignant.  
18 There's about 3,000 cases per year, and most  
19 of the malignant cases will recur.

20 So Juliann did whole exome  
21 sequencing. She found relatively few somatic  
22 mutations and really no statistically

1 significant recurrently mutated genes with --  
2 except for potentially one candidate.

3 She was able to do copy number  
4 analysis. So here red represents copy number  
5 increase, blue represents copy number  
6 decrease. And the major recurrent event was  
7 loss of chromosome 13 shown here with the blue  
8 and gain of chromosome 8 shown here in red.  
9 But many of the tumors had no significant copy  
10 number changes. So just demonstrating that  
11 you can see copy number changes with this.  
12 Again, it's very useful for quantitation.

13 And she identified rearrangements.  
14 And here purple lines represent translocations  
15 between chromosomes. Green lines represent  
16 translocations within chromosomes. And you  
17 can see seven cases here where we have the  
18 same green line with a red dot on the top to  
19 make it easier to see inside of chromosome 12.

20 And that is this fusion where the  
21 NAB2 and STAT6 genes are inverted and you get  
22 a fusion of the two genes. And we found this

1 fusion over half of cases that we believe to  
2 be an underestimate.

3 So just a summary of the results  
4 that we have using unbiased sequencing. We  
5 found the association of a known organism,  
6 *Fusobacterium nucleatum* with colorectal  
7 carcinoma compared to normal colon. Again, we  
8 have no knowledge that it's causative.

9 We discovered a novel organism,  
10 *Bradyrhizobium enterica*, in cord colitis  
11 syndrome. Again we don't know whether it's  
12 causative or not.

13 And we discovered a novel  
14 picobirnavirus and a novel polyomavirus later  
15 reported as this MW polyomavirus in stool from  
16 a diabetes cohort. And then I showed you an  
17 example using hybrid capture-based sequencing  
18 where we were able to discover a NAB2-STAT6  
19 fusion gene in solitary fibrous tumors.

20 And so I just wanted to close with  
21 what I kind of will call some uninformed  
22 personal opinions on sequencing analysis for



1 blood safety because this is not a subject  
2 that I know a great deal about. And so just  
3 my opinions from sort of thinking about where  
4 the data are and what are possible is that I  
5 would recommend development of a comprehensive  
6 hybrid capture test for application to blood  
7 screening because such a test could, one,  
8 detect transfusion-related human sequences  
9 including variants in blood group antigens and  
10 the major histocompatibility complex and so  
11 forth.

12 It could detect and quantify known  
13 pathogens and related organisms. And with  
14 decreasing sequencing and library construction  
15 costs which again is an assumption based on  
16 what's happened in the last 10 or 12 years  
17 rather than something that we know is going to  
18 happen it should be cost-feasible to do a  
19 hybrid capture test for blood screening within  
20 the time frame of test development and test  
21 validation, recognizing that that development  
22 takes a little while.

1                   And I also would recommend the  
2                   exploratory use of unbiased sequencing in a  
3                   surveillance mode because that could permit  
4                   the analysis of emerging infectious agents and  
5                   the correlation with outbreaks of disease as  
6                   they happen. And while the costs I think of  
7                   unbiased sequencing are prohibitive today for  
8                   screening further cost decreases once we get  
9                   down to that penny a human genome, for  
10                  example, could really make this approach  
11                  feasible.

12                 And so just the other sort of  
13                 related piece for surveillance is if a subset  
14                 of blood banks might save blood or save  
15                 nucleic acid to screen for association with  
16                 infectious outbreaks that could also be pretty  
17                 powerful.

18                 And finally, I just want to thank  
19                 a number of people who did the work that I've  
20                 shown, in particular Alex Kostic who led the  
21                 project on *Fusobacterium*, Ami Bhatt who led  
22                 the project on *Bradyrhizobium enterica* in cord

1 colitis, Joonil Jung who led the  
 2 identification of the picobirnavirus and  
 3 polyomavirus in the diabetes cohort, and  
 4 Juliann Chmielecki who led the fusion  
 5 discovery in the sarcoma DNA sequences.

6 And so I'm all done. And Tom will  
 7 let you know whether we take questions now or  
 8 at the end in a panel format.

9 (Applause)

10 DR. SLEZAK: Thanks, Matt. We'll  
 11 do the questions at the end. While the next  
 12 speaker is getting wired up I'll introduce  
 13 him.

14 Kevin McLoughlin is a member of  
 15 the team that I work with at Livermore. It's  
 16 a nice opportunity for me to get to allow  
 17 somebody to speak who's actually done most of  
 18 the brilliant work that I end up getting too  
 19 much credit for.

20 So I met Kevin in 1998 when I was  
 21 teaching the first bioinformatics class ever  
 22 taught in the San Francisco Bay Area. It was

1 a wonderful teaching experience and I was able  
2 to snag him a few years later when Gene  
3 Logic's research group collapsed that he was  
4 leading, the software group there.

5 So, Kevin? He'll be talking to us  
6 about bioinformatics for pathogen microarray  
7 data analysis.

8 MR. MCLOUGHLIN: Thanks, Tom, for  
9 the nice introduction.

10 Okay, so I'm going to start out by  
11 talking about where microarrays fit into the  
12 spectrum of platforms for pathogen detection  
13 based on nucleic acids. So I'll have a few  
14 slides about microarrays in general and the  
15 particular types of arrays that have been  
16 developed for this purpose.

17 And Sanjai asked us not to engage  
18 in too much sales pitch for our own particular  
19 platform so I'm going to give equal time to  
20 some of the other players out there. But my  
21 focus of the talk is going to be on data  
22 analysis and bioinformatics and some of the

1 key requirements for analysis systems.

2 So, and then I'll talk briefly  
3 about the infrastructure requirements and  
4 what's going to be needed to get theses  
5 technologies into the blood screening process.

6 Okay, so this is a variation of a  
7 slide that you've seen a couple of times  
8 already in this workshop showing the three  
9 main nucleic acid-based technologies for  
10 pathogen detection and where they fit in terms  
11 of cost, time from sample acquisition to  
12 results, and the amount of information you can  
13 get out of them as well as the types of  
14 pathogens that you can detect with them.

15 So we've heard a lot of  
16 presentations on PCR-based assays and similar  
17 assays that can deal with moderate amounts of  
18 multiplexing that can address dozens to even  
19 a few hundred analytes at the same time. And  
20 typically those produce results within a few  
21 hours, from acquisition to actually getting  
22 the results in hand.

1                   At the other end of the spectrum  
2     you have high-throughput sequencing which  
3     tells you everything that's in your sample  
4     including all the human DNA and will give you  
5     information about unknown pathogens that  
6     aren't in any of the reference sequence  
7     databases. And if you're very lucky you can  
8     find enough homology between the reads for  
9     those pathogens and something else that is  
10    characterized so that you can get an idea of  
11    whether what you're seeing is something to  
12    worry about.

13                  And of course the cost of  
14    sequencing is higher than microarrays. It is  
15    coming down at least in terms of the labor and  
16    reagent cost. What's not coming down as  
17    quickly is the bioinformatics cost of doing  
18    high-throughput sequencing since computing  
19    power and data storage is only -- the cost of  
20    that is only decreasing with Moore's law and  
21    the cost per gigabase of sequencing data is  
22    falling faster than that. It's still an

1 expensive platform to deal with for any kind  
2 of routine screening.

3           So we think that microarrays live  
4 in the happy medium space in between in terms  
5 of both the cost, the time for processing.  
6 You can get results overnight or quicker  
7 versus several days for high-throughput  
8 sequencing. And you can detect all the known  
9 pathogens, everything that's ever been  
10 sequenced, as well as some emerging pathogens.

11           We saw in Charles's talk yesterday  
12 about how SARS and various other novel viruses  
13 were detected using the ViroChip microarray by  
14 their similarity to viruses that were known.  
15 So we think microarrays are very useful for  
16 that reason.

17           Okay, so as I said there have been  
18 several platforms developed on microarrays.  
19 Charles talked about the ViroChip yesterday.  
20 That was first developed in 2001 or 2002 and  
21 has expanded so that they now cover every  
22 virus that was sequenced up through December

1 of 2010. And they currently have 60,000 long  
2 oligoprobes using the Agilent technology. And  
3 typically I think they have anywhere from  
4 three to a few probes per virus.

5 Dr. Briese talked about the  
6 GreeneChip yesterday that exists in multiple  
7 versions covering different sets of organisms.  
8 There's a pan viral chip, a pan microbial chip  
9 which covers both bacteria and viruses and  
10 some fungi and protozoa, but only covers the  
11 latter organisms through their 16S or 18S  
12 genes. So it doesn't have quite the  
13 resolution that the other two platforms do.

14 And then last but not least  
15 there's the microarray that we developed at  
16 Lawrence Livermore, the LLMDA, which covers  
17 about 6,000 species total, about 67,000 target  
18 sequences if you count a target sequence as a  
19 chromosome or a whole genome or a virus genome  
20 segment.

21 And there are different variations  
22 on our assay design but the basic design has



1 360,000 unique probes on it. Also in that  
2 range of 50-65-mers. And we target a minimum  
3 of 15 to 50 probes matching each target  
4 sequence but in practice we average more than  
5 that because we use some probes that are  
6 conserved across families. So on average each  
7 sequence is matched by about 130 probes.

8 And the key point to take away  
9 from all this is that with all these platforms  
10 there is a different data analysis algorithm  
11 and a software package that comes along with  
12 it. And that's something that you have to  
13 deal with when you're analyzing the data from  
14 these assays.

15 The microarrays can be multiplexed  
16 so that instead of having 360,000 probes for  
17 all organisms you can focus on a more specific  
18 set such as all vertebrate-infecting  
19 pathogens, or blood-borne pathogens, or  
20 whatever. And we originally developed the  
21 Lawrence Livermore microbial assay using the  
22 NimbleGen platform which is a high-density

1     oligo platform similar to Affymetrix's. But  
2     unlike Affymetrix it is much cheaper to design  
3     because it doesn't use fixed photolithographic  
4     masks for the synthesis process.

5             So we were able to go through  
6     several iterations of our design using that  
7     platform. And our current version is version  
8     5 which exists in both 3 by 720k format  
9     meaning we have 3 copies of the same set of  
10    720,000 probes, or a 12 by 135k format where  
11    we just focus on the vertebrate-infecting  
12    pathogens.

13            Unfortunately Roche decided to  
14    drop the microarray business so NimbleGen is  
15    now going into sequence capture as their  
16    primary business focus. And we, like  
17    everything else, are being forced to move to  
18    the Agilent platform which does have the  
19    advantage of having very high-quality control  
20    in their assay production process but doesn't  
21    support quite the level of density of probes  
22    that you can get with NimbleGen or Affymetrix.

1 But for blood screening purposes where you're  
2 focused on a relatively small set of pathogens  
3 there are multiplex formats on Agilent that do  
4 almost as well.

5 Okay, so here's where I get into a  
6 little bit of sales pitch for the Livermore  
7 assay. And this is just an example of where  
8 we applied it to testing blood samples. We've  
9 actually tested over 1,200 different samples  
10 on the Livermore microarray.

11 So this came out of a blind test  
12 that was sponsored by a Canadian organization  
13 called Global Health Security action Group.  
14 And they sent blinded samples of bovine blood,  
15 human blood and what was supposed to be bovine  
16 lung tissue to us, to CDC, to USAMRIID and a  
17 bunch of other national public health agencies  
18 from other countries and asked them to analyze  
19 this sample or this set of samples with their  
20 favorite technologies.

21 So I think we were the only lab to  
22 use microarrays on that set of samples. The

1 other labs used PCR assays, high-throughput  
2 sequencing, some did electron microscopy to  
3 try and figure out what was in these samples.

4 And we were probably -- well, we  
5 were definitely the fastest to come up with  
6 results and the fastest to come up with  
7 correct results on this set of samples. We  
8 actually took 3 days to produce the results  
9 because we wanted to be extra careful and we  
10 did higher stringency on our hybridizations  
11 and did extra data analysis to make sure that  
12 we were getting everything. But in a more  
13 routine case it would typically take 24 hours  
14 or less to process the assay from sample  
15 acquisition to data delivery.

16 Okay, so it turned out these were  
17 samples that were spiked with Rift Valley  
18 fever virus. And when we analyzed the human  
19 and cow blood samples we were able to  
20 successfully detect the virus. RVF has a  
21 segmented genome so we actually picked up two  
22 out of the three segments in the cow blood

1 sample and all three in human blood.

2 And the plots here you're seeing  
3 on the right are just graphs of probe  
4 intensities on the assay plotted against their  
5 expected position, their alignment with the  
6 RVF genome segments, along with plots of the  
7 expected hybridization signals for if that  
8 virus was present.

9 One of the interesting things  
10 about this test was that when we analyzed the  
11 lung sample we didn't find RVF but we did find  
12 this sheep retrovirus, Jaagsiekte sheep  
13 retrovirus, which was not expected either by  
14 the test organizers or anyone else. And we  
15 know it was there because CDC actually  
16 sequenced the sample and confirmed our  
17 identification.

18 What turned out had happened was  
19 that the Canadian lab that prepared the  
20 samples ran out of bovine lung tissue and  
21 decided to spike sheep lung instead. And we  
22 didn't detect RVF because they did the spiking

1 essentially by injecting the virus with a  
2 needle at various points in the lung. And we  
3 just didn't happen to process the segment of  
4 lung that was infected.

5 So the moral of the story is it's  
6 good to have an unbiased assay because you  
7 will find things that you're not looking for.  
8 And all the people who did PCR completely  
9 missed this because it wasn't on their panel.

10 Okay, so I'm going to switch into  
11 talking about the analysis algorithms. And as  
12 I said, each of the three main pathogen  
13 microarray platforms has its own algorithm,  
14 its own software for processing their assays.  
15 So our software is called CliMax. It stands  
16 for Composite Likelihood Maximization.

17 Yesterday Charles told you about  
18 E-Predict. There's also a group at Washington  
19 U who developed an algorithm called VIPR which  
20 is also directed at the UCSF ViroChip. And  
21 the folks at Columbia have their own algorithm  
22 called GreeneLAMP which is designed for the

1       GreeneChip.

2               So despite these different  
3       algorithms they all are doing pretty much the  
4       same thing. They're all taking data from  
5       multiple probes that match the target genome  
6       and each of these probes is capable of binding  
7       to multiple targets because many of the probes  
8       are getting conserved sequences that are --  
9       they're common within species of a family.

10              So all these algorithms have to  
11       account for cross-hybridization. That's a  
12       fact of life because we're using these long  
13       oligo probes and you can have as many as 10  
14       mismatches in a 60-mer probe and still get  
15       good hybridization.

16              Okay, so a key element of the  
17       analysis process is having a good reference  
18       sequence database. So to figure out what's on  
19       the chip we first have to take the probes and  
20       BLAST them or use some other sequence-matching  
21       algorithm to align the probes to microbial  
22       sequences in a reference database. And then

1 take the BLAST similarity scores or free  
2 energies or some other information that  
3 represents the similarity between the probe  
4 and the target sequence and turn that into  
5 some measure of an expected signal for each  
6 probe if a certain target is present.

7 So what that means is that in  
8 order for the analysis process to be accurate  
9 you have to have a good target sequence  
10 database that you can trust. And this is  
11 something that I know the FDA is working on,  
12 a different branch of FDA that we're actually  
13 collaborating with.

14 And it's important. It's  
15 absolutely essential if we're going to put  
16 this into a public health or a blood screening  
17 setting.

18 An important requirement for these  
19 reference sequence databases is that they have  
20 to be kept up to date. Because as we know the  
21 size of GenBank is doubling or maybe tripling  
22 every year. I've kind of lost track of it.



1 And so the power of microarrays to detect and  
2 identify different species and strains of  
3 microbes actually grows from year to year  
4 because you can use the same probes and align  
5 them against the new reference sequences that  
6 come out. And of course you can also update  
7 the microarray probes.

8 Okay, so the software that we  
9 developed, CliMax, and E-Predict which is from  
10 UCSF are very similar in many ways. As I said  
11 we started out by BLAST-ing the probes against  
12 the reference sequence database. And then  
13 using the similarity score, the GC content,  
14 or the predicted free energy of hybridization  
15 to come up with some measure of the expected  
16 binding of probes to targets.

17 And then in CliMax we compute a  
18 likelihood score for each probe to exceed some  
19 threshold intensity which is calibrated  
20 individually for each assay. And we basically  
21 go through a reading maximization process  
22 where we go through each potential target in

1       our database, find the one that gives the best  
2       explanation of the signals from the most  
3       probes and take that as being in the sample,  
4       and then iterate that process multiple times,  
5       adding targets until you've explained as much  
6       of the probe signals as you possibly can.

7               E-Predict is similar. They do  
8       sort of a correlation analysis between their  
9       theoretical hybridization energy profiles and  
10      the probe intensity signals. And they also go  
11      through an iterative process to try and find  
12      as many targets in the sample as possible.

13              So I'm going to talk about some of  
14      the dirty laundry that exists in the  
15      microarray analysis business because we'd like  
16      for assays to be really, really sensitive and  
17      specific. And they are very sensitive but  
18      there are some issues with sensitivity because  
19      it's a hybridization-based technology. So I'm  
20      going to talk about sticky probes, the issues  
21      with false positives and some of the issues  
22      with the different analysis algorithms and

1 interpretation.

2                   So certain probe sequences are  
3 promiscuous. They bind to many sequences that  
4 are common to many samples. And this is  
5 something that's not well understood at a  
6 detailed level except empirically we've  
7 discovered that probe sequences with low  
8 complexity that have direct repeats or tandem  
9 repeats tend to be sticky. If you compute an  
10 entropy figure for the sequence complexity  
11 there's a certain threshold below which if a  
12 probe has that little complexity, if it has  
13 that many repeats in it it's almost guaranteed  
14 to bind to something in your sample no matter  
15 what's in it.

16                   A variation on that theme is  
17 probes with G homopolymers. Basically  
18 depending on the probe length if your probe  
19 sequence contains a string of G's of length 4  
20 or greater, for us it's 5 or greater, again  
21 there's a very high likelihood that the probe  
22 is going to bind to stuff in your sample.

1                   And then there are more sequence-  
2                   specific artifacts that you have to watch out  
3                   for like in some early versions of our assays  
4                   we had probes that matched 23S and other  
5                   ribosomal RNAs. And those are sufficiently  
6                   conserved that again if you have any bacteria  
7                   in your sample you are going to get non-  
8                   specific binding.

9                   Some of the sticky probe signals  
10                  that we see are actually specific to  
11                  particular sample types. So the probes are  
12                  binding specifically to something in the  
13                  sample but the specific something is something  
14                  that's really common. And so human samples,  
15                  obviously anything that has enough similarity  
16                  to human DNA is going to bind.

17                 Another issue is probes that bind  
18                 to reagents or contaminants in reagents that  
19                 are used in the amplification and labeling  
20                 process. And we only know that because we  
21                 have observed that some of the probes that  
22                 light up all the time or a lot of the time

1     only light up when we use particular protocols  
2     or use particular kinds of reagents.  So we  
3     think that's due to probes binding to phage  
4     sequences and other -- vector sequences and  
5     other things that are common contaminants in  
6     reagents.

7                     So for this reason we have to be  
8     fairly aggressive about screening out false  
9     positive hits when we look at the output from  
10    our assay analysis.  So one example of that is  
11    we very often get hits to hepatitis D virus.  
12    And I only figured out the reason for this a  
13    few weeks ago which is that the delta virus  
14    genomes in general are riddled with G  
15    homopolymers.  And it's practically impossible  
16    to design probes against those viruses without  
17    including some of those.  So since G  
18    homopolymers stick to everything and those  
19    probes are assigned to the delta viruses we  
20    get those as very common hits.

21                    Another issue we have to watch out  
22    for, and this is an issue with the reference

1 databases actually, is vector sequences that  
2 are contaminating the human genome and  
3 microbial genomes. So if your sample actually  
4 has bacteria phages or E. coli or other  
5 organisms that are commonly used in vectors  
6 and you have a target virus or bacterium where  
7 the published sequence is contaminated with  
8 vector sequence then we sometimes get hits for  
9 those.

10                   There are also the kinds of  
11 contaminants that you get from sample  
12 handling. We often see hits from  
13 *Propionibacterium acnes* which is a skin  
14 bacterium. We always get hits to human  
15 endogenous retroviruses whenever the sample  
16 contains any human cells simply because those  
17 are endogenous in the human genome. And  
18 there's some retrotransposons that are also in  
19 our target sequence database that also show up  
20 as common hits whenever there's human DNA.

21                   The same thing is true for samples  
22 grown in cell lines. There are retroviruses

1 and endogenous sequences that are common to  
2 those that can practically tell you what kind  
3 of cell culture or cell line a virus was grown  
4 in.

5 Okay, so one of the tools that we  
6 use commonly for identifying these false  
7 positive hits is -- I think it was something  
8 that was actually suggested to me by Ian  
9 Lipkin which is simply plotting the probe  
10 intensities against the location of the probe  
11 in the bacterial or viral genome.

12 And so each of these plots has two  
13 parts to it. The upper plot is the intensity  
14 versus the genome location. And the points on  
15 the plot are color-coded according to whether  
16 they fall above our detection threshold or  
17 not.

18 The lower plot is the expected  
19 hybridization signal. So it's essentially a  
20 probability that -- or an expected probability  
21 that the probe is going to hybridize to that  
22 particular sequence.

1                   So what we like to see is  
2           something like in the upper plot where you get  
3           strong hybridization at the locations going  
4           all the way across the genome. And one almost  
5           sure sign that something is a false positive  
6           is a set of probes that only hybridize at one  
7           end or another, or just a very limited set of  
8           locations within the genome.

9                   So this is the reason it's very  
10          important to have lots of probes against each  
11          target sequence. It's not enough to have just  
12          five or six, you really need dozens in order  
13          to cover the whole span of that genome and to  
14          be able to screen these out.

15                  And we are working on an algorithm  
16          to automate this process that I just described  
17          where you look at the genome alignment and  
18          visually judge whether the probe hits are  
19          sufficiently spread across the genome or not.

20                  Okay, so as I said there are these  
21          many different analysis algorithms. There's  
22          at least one algorithm for each of the assay



1 platforms that I mentioned. And essentially  
2 all these were developed as grad student  
3 research projects, CLiMax included since I'm  
4 actually finishing my Ph.D. as we speak.

5               So basically the software needs to  
6 be highly refined and validated in order to be  
7 usable in a blood screening setting or in the  
8 clinic. As the methods exist now they require  
9 a lot of interpretation, a lot of intuition  
10 based on your experience of what the common  
11 false positive hits are, what you expect to  
12 see given the sample matrix, things like that.  
13 So there's a lot of prior knowledge that goes  
14 into the analysis. And we need to develop  
15 some Bayesian analysis methods that take that  
16 prior knowledge into account and give you a  
17 reliable prediction based on what you already  
18 know.

19              And again, to be useful in a blood  
20 screening or diagnostic setting these methods  
21 have to be standardized and validated along  
22 with the assay platform itself. The whole

1     thing has to be validated as a package and  
2     obviously there have to be clear criteria for  
3     positive, negative and equivocal results.

4             So I'm going to close by  
5     contrasting microarrays with both PCR and  
6     high-throughput sequencing in terms of their  
7     applicability for a blood safety context. So  
8     obviously PCR is much quicker and cheaper than  
9     either microarrays or sequencing but it has  
10    limited multiplexing capability. And I think  
11    that's going to become more important  
12    especially in terms of the cost of applying  
13    this technology in the blood banks.

14            The advantage of going to a highly  
15    multiplex assay such as a microarray or  
16    sequencing is that once you have that  
17    technology in place the incremental costs for  
18    testing additional pathogens is not very great  
19    compared to implementing a series of separate  
20    PCR assays. So I think that would address a  
21    lot of the concerns that were brought up  
22    yesterday by the folks from the Red Cross.

1                   Again, PCR assays are more  
2                   specific which is good in some contexts if  
3                   you're interested in detecting a very specific  
4                   strain of virus or bacterium that's  
5                   contaminating your sample. That specificity  
6                   can also be a drawback, however, unless you're  
7                   using degenerate primers or you're absolutely  
8                   sure that the primers are hitting highly  
9                   conserved regions of the target sequence. So  
10                  if you have an organism with lots of diversity  
11                  like malaria or influenza virus or something  
12                  like that you can have primers that fail  
13                  because of the diversity of the organism.

14                 Finally, microarrays and PCR tests  
15                 complement each other very well. You can use  
16                 arrays in a surveillance capacity where you're  
17                 testing pools of samples. And if you find a  
18                 contaminant in the pool you can go back with  
19                 more targeted PCR assays and test individual  
20                 samples at relatively small additional cost.

21                 Another complementarity between  
22                 assays and PCR is that when we've detected

1 organisms that seem divergent from anything  
2 that was in a reference database we could  
3 actually take the probes from the array and  
4 use those provided they align to points  
5 sufficiently close together on the genome. We  
6 could apply those probes as primers for PCR  
7 assays. So that's worked out for us several  
8 times with some of our collaborators.

9 And then comparing microarrays  
10 versus next-generation sequencing. As I said  
11 even though the cost of sequencing per  
12 gigabase is dropping faster than Moore's law  
13 the same is not true of the cost of the  
14 bioinformatics infrastructure, data storage  
15 and data analysis, and certainly not the cost  
16 of statisticians and bioinformaticists who  
17 analyze that data.

18 So we're very quickly hitting a  
19 point if we haven't hit it already where the  
20 cost of the bioinformatics infrastructure is  
21 the majority of the cost of next-generation  
22 sequencing.

1                   As we saw in Matthew's talk  
2           earlier if you're doing unbiased DNA  
3           sequencing a large part of your sequencing  
4           goes to sequencing human DNA unless you've got  
5           a very good protocol for depleting the human  
6           DNA background. So a lot of your data  
7           analysis and storage resource is wasted on  
8           those human reads that you're throwing away  
9           during the analysis. Of course the  
10          microarrays it's not an issue because it's a  
11          hybridization-based technology. You don't  
12          pick up the human sequences except the ones  
13          that look like viruses or bacteria such as the  
14          endogenous retroviruses.

15                   And on the other hand the  
16          advantage of sequencing is that it does  
17          provide sensitive detection for novel agents  
18          that are nothing like or almost nothing like  
19          anything that's in any of your reference  
20          databases. But again the sensitivity depends  
21          on being able to deplete the human DNA or  
22          other background signal.

1                   So I think in one of the talks  
2       yesterday someone said that using sequencing  
3       for routine screening is like cutting a daisy  
4       with a chainsaw and I totally agree with that.  
5       But in a surveillance capacity I think  
6       sequencing could be a good complement to  
7       microarrays.

8                   So since I'm running out of time  
9       I'm going to skip my summary since you've  
10      heard it all already. And I'd like to thank  
11      Tom and our collaborators in the microarray  
12      group at Lawrence Livermore James Thissen,  
13      Crystal Jang and Shea Gardner. Shea designed  
14      the Livermore detection assays. Crystal and  
15      Jimmy did all the experiments and Tom of  
16      course got us the money. So thank you all for  
17      your attention.

18                   (Applause)

19                  DR. SLEZAK: So now we're going to  
20      switch gears a little bit. Dr. Sukanta  
21      Banerjee is the senior director of R&D at  
22      BioArray Solutions. He's going to talk to us

1     about data analysis for red cell and HLA  
2     genotyping.

3                   DR. BANERJEE: All right.  
4     Hopefully everybody can hear me. I've started  
5     losing my voice a little bit. So if I tend to  
6     fade out please point it out and I'll speak  
7     into the mic.

8                   First of all, I would like to  
9     thank the organizers for this opportunity. So  
10    the topic of my talk today is data analysis  
11    for red cell and HLA genotyping.

12                   And the way I have organized my  
13    talk is I have tried to keep the talk fairly  
14    agnostic and not married to any particular  
15    platform per se. But I must point out that in  
16    doing so of course the content of this talk is  
17    not going to be relevant to sequencing best  
18    assays. It's mainly for analysis of these  
19    antigens using genotyping, using microarrays  
20    or SNP-based analysis.

21                   Okay, so as far as contents go the  
22    talk will cover firstly the fundamental steps

1 that are involved in data analysis followed by  
2 a slightly deeper look into probe signal  
3 intensity extractions, determination of probe  
4 status followed by genotype determination and  
5 once genotype information is there how allele  
6 assignments and prediction of phenotypes are  
7 made from it. And followed by some  
8 conclusions.

9 Okay, so the fundamental steps of  
10 data analysis. And if we look at it there are  
11 really three fundamental steps of data  
12 analysis. The first being the collection of  
13 the signal data from each probe using signal  
14 extraction algorithm.

15 And this block, particular block  
16 is platform-dependent depending on whether one  
17 is using a microarray platform, whether one is  
18 using a suspension assay, whether they are  
19 collecting homogenous fluorescence these  
20 algorithms will vary. And of course I won't -  
21 - given the length of this talk I won't go  
22 into details for this particular block



1 anymore.

2                   However, the next two blocks, the  
3 second being the processing of this raw signal  
4 data for each probe to determine whether the  
5 probe was actually positive or negative. And  
6 subsequently the conversion of these  
7 positivity or negativity data for a collection  
8 of probes into a series of genotypes and from  
9 those genotypes how allele assignments and  
10 phenotype predictions are made.

11                   These two processes or these two  
12 blocks are fairly generic. And they apply to  
13 all kinds of assays that are out there  
14 currently in the market.

15                   Okay, so I just had one slide on  
16 the extraction of probe signal intensities.  
17 And it just goes through a rough pictorial  
18 representation of what does it mean  
19 essentially.

20                   Typically what happens either in a  
21 microarray format or in a flow cytometry  
22 format as a result of the assay process you

1 are looking at generation of signal  
2 intensities, fluorescent signal intensities,  
3 on specific solid phases carrying the probe of  
4 interest.

5 So what this part of the algorithm  
6 really is doing is collecting those signal  
7 intensities for the specific probes and  
8 keeping a roster of that.

9 And the result of this process as  
10 an output, what we get are sort of average  
11 intensity bar graphs or intensity graphs. And  
12 on the X axis these are the particular markers  
13 of interest.

14 This is just an example where  
15 basically each one of the markers is a  
16 mutation of interest and there could be two  
17 signals depending on the two probes associated  
18 with that mutation, one being the normal and  
19 the other being the variant associated with  
20 that particular mutation.

21 So after the extraction of probe  
22 intensities has taken place and we have been

1     able to generate such a bar graph, what is  
2     required? Intuitively you could see what is  
3     required is from these intensities can we now  
4     say which probe or which allele was present  
5     and which was not present. So that requires  
6     some kind of thresholding.

7                 So let's look at how these  
8     thresholdings are typically done. So if we  
9     look at for probes which are looking at  
10    isolated SNPs or in other words where one  
11    unique allele is expected to bind to a  
12    particular probe. So there's a one-to-one  
13    correspondence.

14                A really popular method of doing  
15    that is using cluster plots. And for this  
16    basically in order to generate the data what  
17    needs to be done is one needs to run a  
18    training set of samples in order to generate  
19    the cluster plot.

20                So what is -- essentially what  
21    does a cluster plot have? It is basically a  
22    2D plot where the intensities of the probes

1 related with the samples are plotted in this  
2 2D plot with one of the probes being on the X  
3 axis and the other one being on the Y axis.

4 And usually the clustering process  
5 can be done on these kind of raw intensity  
6 plot itself. But what is really popular is  
7 this is followed by normalization schemes  
8 which allows further robustness to the data.

9 So typically what is done is from  
10 such a plot, it is converted into a contrast  
11 versus strength plot. So the contrast  
12 measures how well these clusters are separated  
13 and the strength is how the intensity was or  
14 how strong the intensity was on the plot.

15 So, once those cluster plots or  
16 those converted cluster plots are available  
17 the thresholds are set by noticing that  
18 typically three sets of clusters evolve  
19 depending for a particular SNP depending on  
20 the samples used for that particular training  
21 set. So one being -- and for illustrative  
22 purposes just saying A allele and B allele for

1       that particular probe.

2               So this would be the AA, this is  
3       the AB, and this is the BB. So for  
4       thresholding there are discrimination cutoffs.  
5       So these two gray bars here are the  
6       discrimination zones between these three  
7       different populations.

8               And there is also typically a  
9       strength cutoff which is saying that below a  
10      certain intensity or below a certain strength  
11      measure I am not going to take into account or  
12      I would consider that this call was not  
13      reliable enough.

14              Okay, so there are several ways  
15      these things or these zones or these gray  
16      zones can be calculated or positioned. And I  
17      won't go into the details of that. But just  
18      pictorially gives you an idea how these  
19      thresholds are set.

20              Now, once these thresholds are set  
21      though not routinely done one could also look  
22      at what is the reliability of a particular

1 genotype call given those thresholds. And  
2 that can be done by taking into account that  
3 the three clusters we talked about in the  
4 earlier slide, associated with each one of  
5 those clusters is a distribution along the  
6 contrast axis.

7                   So these distributions -- and this  
8 is a highly exaggerated plot to illustrate  
9 that these distributions can overlap. So  
10 basically given a particular contrast ratio we  
11 can then determine what is the probability  
12 that -- or how likely it was that the genotype  
13 that was assigned was actually from that  
14 particular class.

15                   Okay, so switching gears now. And  
16 basically if we look at, this is the technique  
17 that I talked about is good for looking at  
18 isolated SNPs. So for situations where there  
19 are multiple different alleles for pathogens  
20 and then for situations like HLA where there  
21 are a vast number of alleles going and binding  
22 to each probe. Then we cannot really look at

1       these kind of dot plots. And unfortunately  
2       you have to do sort of a single probe  
3       assignment.

4               So what is done is basically  
5       running a set of samples which are positive  
6       for the known samples which are positive for  
7       that probe, and a set of samples which are  
8       negative for that particular probe. And two  
9       such examples are given.

10              Sometimes this discrimination is  
11       very, very crisp and the positive state easily  
12       discriminates from the negative one. In other  
13       cases, yes, discrimination is not so  
14       straightforward. And then again of course  
15       determining where exactly to place this cutoff  
16       is a challenge, determining -- depending on  
17       the sample set and the particular probe's  
18       performance in contrast in the assay.

19              Okay. So, once these kind of  
20       thresholdings have been done and these  
21       particular clusters have been identified, et  
22       cetera, we are in a position to do a genotype

1 assignment. How is genotype assignment done?

2 Pretty simple.

3 It's shown here in this particular  
4 flow chart that you have these from the  
5 training exercise which give you the cutoff  
6 parameters. And then for assay the same  
7 operation is done for the signals collected.  
8 The ratios are computed and then compared to  
9 the cutoff parameters.

10 And once this comparison is done  
11 depending on the ratio you generate basically  
12 the genotype call. And once the genotype  
13 assignment is done we will see now finally how  
14 the allele assignment is made. So this part  
15 is pretty straightforward.

16 So, the next couple of slides I  
17 have a few examples how allele assignments and  
18 phenotype assignments are made once the  
19 genotype is known after the exercise I  
20 described in the previous slide.

21 So this is a simple example of the  
22 Duffy plot group where on the top panel here



1 are the examples of the four known alleles  
2 which are based on three different SNPs being  
3 monitored in the particular assay. Now, the  
4 phenotype associated with these particular  
5 alleles are also listed here.

6 So, however, what is done or as a  
7 conversion engine within the software what one  
8 needs to do is to do the biallelic  
9 combinations. So, this is an example of a  
10 genotype to phenotype combination chart.

11 So these biallelic combinations  
12 are made and basically based on this known  
13 information the phenotypes from these  
14 biallelic combinations are predicted. And  
15 that's shown in this example.

16 So this is pretty generic for all  
17 genotype-based assays when one goes from  
18 either an allele assignment or a predicted  
19 phenotype from a genotype call, isolated  
20 genotype calls. This is essentially the  
21 exercise that is going on in the background.

22 As an example it is shown here

1       that from the assay if for these three  
2       particular markers the genotypes were AB, AA,  
3       AB then you go to this phenotype assignment  
4       chart. The phenotype will come back FYA  
5       positive, FYB weak.

6               All right, so not always the  
7       allele assignment is so simple or looking at  
8       a small set of markers. If we move over to  
9       the RH marker then there are lots more  
10      mutations or lots more markers that are of  
11      relevance and one needs to look at in order to  
12      make the call.

13             However, the process or the table,  
14      the table gets a lot longer and more  
15      complicated but the operation behind it  
16      remains the same.

17             So the next example I have is from  
18      RHD where there is a yet more or yet another  
19      level of complication. For example, there  
20      could be cases where lots of the probes have  
21      no signals because there are partial deletions  
22      or full deletions of a sample. So this

1 creates some kind of an issue because when  
2 such an allele is mixed with a wild type  
3 allele or an allele where the deletion is not  
4 there then the processes of the microarray  
5 which processes I'm talking about cannot  
6 distinguish between these zygosities. So it  
7 cannot distinguish or detect this partially  
8 deleted allele.

9 So just as an example. And for  
10 the HLA I just don't want to spend much time  
11 because this has already been looked at at  
12 some detail in the earlier talks. But  
13 essentially the process is the same, that you  
14 have the alleles and then you have to create  
15 a biallelic hit table.

16 And this was already discussed  
17 yesterday, how phase ambiguities or  
18 ambiguities arise and how that in microarray-  
19 based techniques are not really well suited  
20 for taking care of these.

21 So looking forward the current  
22 approaches are all project- or training-based

1 basically. You needed pre-training of the  
2 samples before moving on.

3 And requires SNP by SNP cutoff  
4 determination. There is no universal cutoff  
5 for all SNPs. Also, it cannot accommodate  
6 large SNPs in cluster positions.

7 And so there is a need for next-  
8 generation methods which can do better in  
9 these kind of -- and provides additional  
10 flexibility.

11 So looking forward, however,  
12 development of these kind of unique and  
13 proprietary algorithms has the potential to  
14 lengthen and complicate the regulatory  
15 approval processes. And hence it is important  
16 to come up with strategies and cost-effective  
17 methods for complying with the regulations.

18 And while clearly the development  
19 of robust assays are needed defining the level  
20 of adequacy and acceptability of the multiplex  
21 data, the final data set that is coming out of  
22 the assay, is also pretty important. Whether

1       that string is to be considered in its  
2       entirety or if even partial calls can be used.

3               And finally, development of a  
4       flexible data analysis framework that easily  
5       allows -- and this was mentioned before in  
6       this talk also -- incorporation of new  
7       alleles, incorporation of new probes is  
8       clearly critical. But however, linked to that  
9       is how will such software updates be handled  
10      from a regulatory point of view.

11             And that's all I have. Thank you  
12      for your attention.

13             (Applause)

14             DR. SLEZAK: I think that last  
15      point is a really important one. We'll come  
16      back to that later on.

17             So we've heard about sequencing  
18      assays and red blood cell and HLA genotyping.  
19      We're now going to try to bring this back to  
20      the focus of this workshop which is to  
21      understand some of the realities from the  
22      blood center point of view.

1                   So the final speaker in this  
2 session is Ed Notari from the American Red  
3 Cross. Talking with Ed before the session I  
4 found out, he said yes, some people from  
5 Lawrence Livermore have been renting space in  
6 one of our facilities for a number of years.

7                   And it's interesting because what  
8 it was was the local Biowatch lab that has  
9 been protecting the whole National Capitol  
10 Region actually daily since some of us brought  
11 it up on October 6, 2001 after the first  
12 anthrax letter death.

13                  Our operational security was very  
14 good. Ed had no idea what those people were  
15 doing in his lab for all those years. They've  
16 gone somewhere else now so now I can finally  
17 say yes, that was actually the Biowatch lab.  
18 They're still in the area so don't worry.

19                  MR. NOTARI: Hi. I'd like to  
20 start out the talk with a general slide about  
21 the mission of a blood center, to provide  
22 safe, reliable, cost-effective blood products.

1 And that's really where I want to gear the  
2 talk.

3 So the goals would be review the  
4 role of bioinformatics and data analysis in a  
5 blood center right now, look at some functions  
6 and examples. And what does multiplex  
7 technology offer a blood center or new, next-  
8 generation multiplex? What kinds of data will  
9 these technologies produce and how much? And  
10 finally, is there a role for genomic  
11 sequencing data in a blood center? Why and  
12 why not? I think I'll probably level you with  
13 more questions than answers for this talk but  
14 I think it's a good way to start the dialogue.

15 So currently bioinformatics at a  
16 blood center would involve utilization of data  
17 generated on the FDA-approved testing  
18 platforms to determine the disposition of  
19 collected units and donor suitability. Can  
20 the unit be released? Does a donor have a  
21 deferrable risk? And is it safe for the donor  
22 to donate?

1                   One example as we saw Dr. Stramer  
2                   say yesterday was this slide. And I'm not  
3                   going to go through it again. She did a great  
4                   job of it yesterday. But what I really wanted  
5                   to highlight here is the number of screening  
6                   tests, the platforms and the supplemental  
7                   testing platforms.

8                   There's a lot. Blood centers are  
9                   asked to do a lot of screening and  
10                  supplemental testing on a lot of different  
11                  platforms. And of interest is the zeroes. So  
12                  blood centers still need to do screening for  
13                  some agents only in nucleic acid testing. As  
14                  well for others they need to screening only in  
15                  a serological fashion. And that has more to  
16                  do with the agents themselves than the  
17                  technologies.

18                  For data analysis at a blood  
19                  center we use -- and obviously I'm gearing  
20                  this towards infectious diseases. That's my  
21                  prejudice for what I do. Infectious disease  
22                  testing can identify changes in prevalence and



1 incidence in donor populations. It can also  
2 be used to ensure process quality by looking  
3 at the number of false positives and other  
4 metrics to ensure that assays are performing  
5 correctly. Donor deferrals as well due to  
6 health history response can detect changes in  
7 the overall risk profiles in the donor  
8 population.

9 One of the examples of data  
10 analysis was presented at this year's or I  
11 guess last year's AABB presentation on HTLV  
12 prevalence looking at several years of testing  
13 data, identifying all the positives, breaking  
14 them down into male and female, and then  
15 comparing those two rates.

16 Similarly the same presentation  
17 looking at the incidence of donors as well by  
18 male and female but now being able to use the  
19 data collected on donors to look at them in a  
20 geographic distribution.

21 The challenges of testing  
22 algorithms is complex to say the least. We're

1 using multiple screening tests, serology and  
2 NAT, supplemental testing as we saw in the  
3 slide for more than one agent at a time using  
4 more than one testing strategy. And the  
5 problem is also there are issues with  
6 interpretation of unexpected results. And  
7 algorithms sometimes need to change. Recently  
8 with the availability of HCV RIBA, algorithms  
9 for determining final HTV status had to  
10 change.

11 All right, I don't expect  
12 everybody to read all the little bits. This  
13 is the example of current HBV testing  
14 algorithm at a blood center. And at this  
15 point we're using three different screening  
16 tests performed in parallel just when the  
17 donation comes in. It starts off with  
18 antigen, core as well as NAT. And there are  
19 29 possible outcomes of which only 1 allows  
20 unit release. Luckily most of our donors fall  
21 into that category and that's good.

22 Now also in this slide once all

1 the screening is done, the nucleic acid, the  
2 hepatitis B core and the surface antigen,  
3 that's the point where if those donors are  
4 non-reactive for all three of those tests the  
5 decision can be made as to whether or not the  
6 unit gets disposed of and has further testing  
7 or goes onto further manufacture and release.

8 So it's important to understand  
9 where all these testing algorithms start.  
10 They start with that core. What happens next?  
11 And this is what a blood center needs. But is  
12 it?

13 What would a blood center need  
14 from the next-generation multiplex testing  
15 format? Well, I think there are four  
16 principles that need to guide this:  
17 simplicity, economy, efficacy and safety.

18 But what they really want is a big  
19 black box. They want an FDA-approved all-in-  
20 one platform, one sample in, the final results  
21 come out, there's serology, there's NAT,  
22 there's confirmatory and there's a happy

1       little gnome. And it'll do all your tests.  
2       As well it'll be capable of adding in further  
3       testing as needed.

4               Next I wanted to look at a very  
5       simplified diagram of testing, processing and  
6       data flow to blood center. We receive the  
7       donation sample, health history comes in,  
8       screening, resolution of reactive pools and  
9       discrimination, everything getting reported  
10      back into the database, repeat reactives going  
11      onto further testing, confirmatory,  
12      supplemental, non-reactives heading out for  
13      manufacture. And finally, and importantly,  
14      donor notification and counseling.

15              Now, not to think that this is too  
16      simplistic. Remember all of our algorithms,  
17      HBV, HCV, HIV, HTLV, all these algorithms fit  
18      into this. It may look deceptively simple but  
19      all this stuff, it's a lot of information and  
20      it's a lot of work to keep going.

21              Well, will the next generation  
22      help? All of this will still need to happen.

1 We'll still need to find out if a donation is  
2 deferred or used. We'll still need to collect  
3 the health history. But will the results from  
4 the next-generation system help us to reduce  
5 that burden of complexity with all the  
6 algorithms that we're using?

7 So, for processing analysis we're  
8 already using two multiplex systems with  
9 multiplex NAT and one would argue PRISM as  
10 well as a multiplex-type system.

11 The analysis of large amounts of  
12 data generated from host systems might require  
13 substantial investments. IT systems would  
14 need to be redesigned to enable more control  
15 point automated process decisions. The  
16 hardware platforms would need to be redesigned  
17 to accommodate excess storage as well as the  
18 processing of these data.

19 Also, as more tests run at the  
20 same time with all the results channeled into  
21 the system the surge data and that processing  
22 capability would need to be redesigned as

1 well.

2 Blood centers would need to decide  
3 if these new data meet their core mission.

4 And will every donation get additional  
5 testing. If not every donation how many  
6 donations per year? In general 0.07 percent  
7 of all donations confirm for infectious  
8 diseases. Do we, you know, 0.05 percent are  
9 repeat reactive or reactive for donations.  
10 Are these the only donations we really care  
11 about getting further sequencing or deep  
12 sequencing on? How will the results be  
13 managed, analyzed and reported? And to whom?

14 Bottom line, what is the benefit?  
15 You know, the donors' gifts of time, money and  
16 blood are precious and we need to be good  
17 stewards of these resources.

18 Blood centers need systems that  
19 are easy to operate and maintain. They need  
20 systems that reduce the burden of operation,  
21 the cost for QC training, space, reagents,  
22 staffing. They need to be robust and

1 resilient. And the safety profile of any  
2 systems that we may be thinking about putting  
3 in place would need to be at least as safe if  
4 not safer than the systems we currently have.

5 In summary, does the added cost of  
6 testing and further study for disease agents  
7 provide additional value to the blood centers,  
8 to the donors and to the recipients? If it's  
9 not going to work at a blood center, if it's  
10 not going to help a recipient the expenditure  
11 to get it done may not be at the core mission.

12 Management of these additional  
13 data should also be considered. If you're  
14 going to get extended testing on a donor  
15 sample who do you report it to? Do you just  
16 hold it? And if you are going to report it to  
17 a donor how do you explain it? And should it  
18 be available to a donor's healthcare provider  
19 or is it just another donor notification of  
20 you're positive?

21 For a blood center to implement  
22 these additional testing there would need to

1 be licensed and required or under IND or they  
2 most likely won't be done. Additional testing  
3 may be limited to blood-borne transmissible  
4 agents, not discovery efforts in the human  
5 genome. And the principles of simplicity,  
6 economy, efficacy and safety should drive  
7 development and implementation of new  
8 technologies at a blood center.

9 And a point so good I had to make  
10 it twice, donors' gifts of time, money and  
11 blood are precious and we need to be good  
12 stewards of these resources.

13 And finally a little pie in the  
14 sky proposition. Perhaps sentinel blood  
15 centers would be the way to go. Could  
16 research level grant-funded testing be  
17 employed at a diverse sample of blood centers  
18 to monitor several suspect agents from a  
19 sample of donations?

20 And as we've heard before SARS and  
21 some other infectious agents are examples of  
22 what would have been and may still be



1 candidates for extended testing in the  
2 sentinel site. Thank you.

3 (Applause)

4 DR. SLEZAK: So I'll try to do my  
5 best to balance hearing from the panelists and  
6 also questions from the audience. Okay, if we  
7 can have the questions for this review? While  
8 we're waiting for that to get put up there was  
9 a number of questions that were sent out for  
10 these two sessions.

11 The first one was what are the  
12 anticipated advantages and disadvantages of  
13 highly multiplex technologies in terms of  
14 sensitivity, specificity and adaptability to  
15 blood donor screening? Are there other likely  
16 added values, e.g., speed, flexibility, cost  
17 saving, et cetera?

18 What I don't want to do in this  
19 session is run over what we've heard very well  
20 from almost all of you, the analyses of pros  
21 and cons of the different techniques. Let's  
22 cast this again in terms of moving this to the

1 blood donors.

2 If I could summarize what I  
3 thought I heard we definitely know that PCR is  
4 apparent winner today anyway on cost. So we  
5 heard some cost figures. If I recall Pejman  
6 mentioned about \$12 for certain kinds of  
7 multiplex PCR for about 25 assays.

8 We heard from some speakers about  
9 microarrays and in general for a large-format  
10 single sample would be around \$400 to \$500,  
11 the low quantity price for the 12 samples per  
12 slide of highly multiplexed assays that can  
13 drop as low as \$100.

14 I wanted to ask a couple of  
15 speakers, and Elena, we didn't hear a ballpark  
16 quantity one-sample price for the OpenArray.  
17 Is there something you can say about that?

18 DR. GRIGORENKO: Yes, definitely.  
19 I think depending on how many targets per  
20 subarray you can spot on. It could be in the  
21 range from \$10 to \$12 per sample.

22 DR. SLEZAK: Thank you. We heard

1 several people say about the cost of DNA  
2 sequencing. And the realistic costs I think  
3 we heard coming down to around about \$5,000  
4 for a human genome size scale. Expected to  
5 drop probably to \$1,000 or so in the next year  
6 or two. Not quite sure when sequencing is  
7 going to become infinitely fast and free.

8 So again let's focus this first  
9 question really on what's the likelihood of  
10 these technologies moving in to really help  
11 out the blood centers. And just turn on your  
12 little mic if you have a comment. There's too  
13 many people here for us to run through  
14 everybody on every question.

15 MR. NOTARI: That's kind of what I  
16 was talking about. But yes, I think it has to  
17 have a direct benefit either to the donor and  
18 the donor base or to the recipient.

19 The goal of it all I think from my  
20 perspective is the recipients. We need to  
21 keep the blood as safe as we can for them.  
22 And at the same time we need to make sure that

1       our donor base, we have sufficient screening  
2       to defer those who have risk even though the  
3       units may not have infectious agents in them,  
4       but prior experience shows they had risk.

5                   DR. MEYERSON: I'd just like to  
6       comment that I think that really the first  
7       step in this will be research projects. And  
8       actually research projects where blood banks  
9       will do next-generation sequencing panels and  
10      will see if there are any safety consequences.

11                   So I actually think that either  
12      the FDA and/or the FDA working with the NIH  
13      should start thinking about supporting some  
14      research programs to support development and  
15      application of next-generation sequencing  
16      tests in blood banks and evaluating what they  
17      actually learn clinically both in terms of  
18      transfusion reactions and in terms of  
19      pathogens.

20                   DR. SLEZAK: So I actually have a  
21      question for maybe some of the blood center  
22      folks in general. You've been looking at this

1 as these are added burdens and added costs.  
2 What about the flip side? Opportunity to  
3 make money. I can see for both the donors,  
4 hey, donate blood and we'll update you on the  
5 latest knowledge of various biomarkers that  
6 you have or health status. And recipients  
7 maybe charging people a little more to know  
8 that their blood was really thoroughly  
9 screened. Any comments on that as an  
10 approach?

11 DR. TIBBETTS: First I'd like to  
12 thank Edward for a very pragmatic view of the  
13 end users that really count here. And a very  
14 open mind to what some of these technologies  
15 can offer. And I think there's a role to play  
16 that would be win-win.

17 It's an unfair burden to put on  
18 the blood centers to do the screening and  
19 surveillance for emerging diseases but it's a  
20 critical need they have to be able to  
21 recognize natural variants.

22 And perhaps there would be a

1 pathway of supplying rejected samples or  
2 outdated samples that, you know, it's hard to  
3 imagine that blood, so precious, wouldn't be  
4 used but I'm sure you have samples that don't  
5 get distributed. But if there could be a  
6 pathway to put those usefully into a funded  
7 screening program that's dedicated to  
8 identifying emerging variants that would  
9 provide information back to you and hopefully  
10 a platform of multiplexing that could readily  
11 integrate the new results.

12 And I'd just like to add a couple  
13 of real quick things. I want to thank Moussa  
14 Kourout, an ORISE Fellow at FDA who did most  
15 of the work in my presentation. I had the  
16 wrong slide slipped into my slide deck and I  
17 really should never have missed that  
18 opportunity to acknowledge his help. And he's  
19 here in the audience today. Thank you.

20 DR. SLEZAK: Let's take the  
21 question from the floor next.

22 DR. DODD: Yes, I'm Roger Dodd

1 from the Red Cross. And I think I'd like to  
2 comment a little bit on the trend of this  
3 discussion because I think that the last  
4 comment is absolutely right. It's a big  
5 burden to put on us to look for potential  
6 problems when we're not seeing them.

7 The pattern to date has been that  
8 we've reacted to diseases. And I think that  
9 that's going to continue to occur for the  
10 foreseeable future.

11 And the only situation, perhaps  
12 two situations that I can recollect with 40  
13 years in this business where we've reacted  
14 really before the impact of the disease has  
15 been apparent in one case was initiating  
16 testing for HTLV. We knew that was a disease-  
17 causing agent but we hadn't seen any evidence  
18 of transfusion transmission.

19 And a reaction which I think was  
20 justifiable in terms of the severity of the  
21 disease to the potential risk which was  
22 unknown at the time of transmission of variant

1 CJD by blood. We now know that this can  
2 occur. And we had in place a carefully judged  
3 deferral policy.

4 So I think that the concept that  
5 we're going to look for things that might turn  
6 out to be a problem is just not the way it  
7 works. I think the important thing is  
8 readiness and the availability of platforms  
9 that can be adapted.

10 And the best example of this was  
11 West Nile virus and the fact that in fact  
12 within less than a year of recognition of the  
13 transmissibility of this agent by transfusion  
14 which was somewhat unexpected because it was  
15 an acute infection and that wasn't the mental  
16 paradigm we had we were doing uniform testing  
17 across the U.S. using a nucleic acid  
18 amplification approach.

19 The only reason we could do that  
20 was that the platform was there and that  
21 everybody had a mysterious agreement that it  
22 was something that really needed to be done.



1       So I think we need to rethink the paradigm.

2               These technologies clearly are  
3 going to be of value but it's how we can use  
4 them when the need arises, not how we can use  
5 them to invent the need for them.

6               MR. MCLOUGHLIN:  So I'd just like  
7 to make -- or to reiterate one of the points  
8 I made earlier which is that with these new  
9 multiplex technologies like microarrays and  
10 the high-throughput sequencing the whole idea  
11 of this is to screen comprehensively for  
12 hundreds or thousands of agents at once so  
13 that the incremental cost of testing for  
14 additional agents is relatively low.

15               Basically when you decide that a  
16 particular pathogen is a problem you choose to  
17 look at the results for that particular agent  
18 in the multiplex assay.  And if it turns out  
19 not to be a problem then you don't look at it.  
20 So I'm not sure that the extra burden would be  
21 that much in this case.  But what I liked was  
22 Ed's idea of setting up sentinel blood centers

1       where you can do this kind of surveillance  
2       work.

3                       And I think to address the first  
4       question, I think this is probably the kind of  
5       situation where you're first going to see  
6       these technologies applied in blood safety not  
7       for individual blood centers but in a  
8       surveillance scenario. And as those  
9       technologies become validated through their  
10      use in a surveillance capacity some of that  
11      can migrate down to the level of individual  
12      blood centers. But I think we have to take  
13      this incrementally and not, you know, not make  
14      the blood centers choke all this new  
15      technology down in one big bolus.

16                    DR. SLEZAK: That flows into the  
17      second question, really looking at some of the  
18      parameters like speed and total turnaround  
19      time and throughput. These are things that  
20      appear to be readily available for the  
21      multiplex PCR but not so much for the assays  
22      or the sequencing.

1                   So maybe some of the people  
2           involved with assays and sequencing can give  
3           their ideas of what sort of speed increases we  
4           might see, what sort of breakthroughs are  
5           needed to get the speed increases and what  
6           kind of multiplexing we might expect down the  
7           road.

8                   DR. TIBBETTS: Speaking from the  
9           middle of multiplex PCR and next-gen  
10          sequencing part of our strategy has been to  
11          develop high-multiplicity assays that would  
12          leverage sequencing-based information.

13                   And in a high-throughput situation  
14          that we're beginning to get familiar with in  
15          products of other domains we're seeing now a  
16          turnaround time that's in practical terms 24  
17          hours from sample-in, data-out. And for the  
18          quantity of sequence information that's still  
19          a substantial advantage over the several days  
20          to longer that it can take to prepare a sample  
21          ensemble for what now is pretty rapid data  
22          acquisition.

1                   And then the analysis is virtually  
2                   realtime from the scale of 50 to 100,000 bases  
3                   of sequence from the microarrays. So a 24-  
4                   hour turnaround is realistic. Implementing  
5                   that on a 24/7 basis is a logistics challenge.

6                   And frankly there's not a  
7                   significant difference between running 100 PCR  
8                   tests or 20 PCR tests in 4 to 8 hours and  
9                   running several hundred samples in a  
10                  microarray in 24 hours. Your action  
11                  opportunity window is almost the same.

12                  And in terms of cost the new form  
13                  factor that I described that we're working on  
14                  for food safety and that is in anticipated use  
15                  in Beijing at the CDC is a lower-cost assay.  
16                  And the whole analysis of up to 65,000 base  
17                  pairs partitioned among as many targets as you  
18                  want is less than \$100. So it's come down  
19                  substantially. And that's a low-volume  
20                  estimate.

21                  DR. SLEZAK: So Andrew, I'd be  
22                  curious about your opinions on where

1 sequencing might be going.

2 DR. KASARSKIS: Just, I mean on  
3 the speed thing there's a group out at Mercy  
4 Children's in Kansas City I believe that  
5 demonstrated they can go in approximately 72  
6 hours from sample patient blood to a diagnosis  
7 of a previously unknown genetic condition with  
8 sequencing on the Illumina 2500 machine which  
9 is what we are now running as well.

10 And certainly with gene panels the  
11 sample prep is going to be a little bit longer  
12 perhaps. But still the sequencing on the  
13 Illumina MiSeq, a Pacific Biosciences machine,  
14 an Ion Proton or an Ion Torrent, these are all  
15 things which would give the possibility of  
16 getting sequence and data analysis well within  
17 a 24-hour period even coupled with sample  
18 prep.

19 So I think a standard next-  
20 generation sequencing platform, you know,  
21 everyone's trained to think about that as a 2-  
22 week procedure followed by some substantial

1 data analysis. We've seen a lot of progress  
2 in speeding the analysis and we've also seen  
3 a lot of progress on shrinking the sequencing  
4 time.

5 Where there needs to be a lot more  
6 progress actually is on effective and rapid  
7 reliable sample preparation. But even so 24  
8 hours is I think a reasonable benchmark for  
9 almost any panel that someone would want to  
10 implement. But you're talking about a year in  
11 the future. I don't know if you would agree  
12 with it.

13 DR. MEYERSON: Yes, I agree  
14 completely with what Andrew just said. I have  
15 nothing to add to it.

16 DR. SLEZAK: All right. So let's  
17 look at the next. The next question is what's  
18 a realistic time frame in which some or all of  
19 these technologies might be implemented for  
20 routine donor screening.

21 I think we've pretty much come to  
22 a conclusion that the first step is going to

1 be more of the surveillance. And there's  
2 probably no reason why that couldn't start  
3 immediately.

4 But in terms of the routine one  
5 how many years? You know, we've got enough  
6 people here for Delphi, Oracle. How many  
7 years before we might see 24-hour turnarounds  
8 realistically for both the assays and the  
9 sequencing?

10 DR. LINNEN: Well, I think what I  
11 presented in the time line you can at least  
12 get the historical sense of what it has taken  
13 in the past. You know, it's hard to predict  
14 how things will go. It may depend on the  
15 technology. It could be faster. But it's a  
16 multi-year process even with -- in our fastest  
17 experience with West Nile it was less than a  
18 year, it was 9 months to get the kit out. But  
19 it was another 2 years to get the product  
20 licensed.

21 DR. SLEZAK: And even that's  
22 pretty fast, 2 years.

1 DR. LINNEN: Yes, that's -- well,  
2 that's actually our fastest approval for a  
3 licensed blood screening test.

4 DR. SLEZAK: I guess that argues  
5 for starting first in the research mode.  
6 Clark?

7 DR. TIBBETTS: I appreciated your  
8 experience that you shared. And there were  
9 other kits that took longer.

10 And one of the things we have to  
11 think about with cost is that the regulatory  
12 burden that has to be met is going to  
13 dramatically increase the final cost of the  
14 assay. There's no way around it.

15 The R&D leading to the state of  
16 art that we've heard about today probably is  
17 5 to 10 percent of the cost of getting  
18 products to a market fully licensed and ready  
19 to use, not including any of the marketing  
20 materials. So that's going to be a problem.

21 And it raises a question that I've  
22 been wondering about for some long time.



1       There's been a decade at least that the FDA  
2       has been struggling with how to translate its  
3       reliance on single-plex diagnostic PCR tests.  
4       And I emphasize diagnostic.

5               And using that technology for  
6       screening. Using the Department of Defense,  
7       using diagnostic PCR tests for biodefense  
8       technology.

9               The purpose for which these  
10       diagnostic tests were developed and reviewed  
11       and validated and regulated is well met for  
12       acute medical diagnostics. But it's not  
13       serving a good purpose. In fact, it's a huge  
14       barrier to getting these technologies in place  
15       for screening and applications that we're  
16       talking about here today.

17              So I wonder if with DNA having  
18       demonstrably less problems of interference  
19       from one analyte to the next to the next and  
20       a whole genome approach which every single  
21       assay that's ever been done is looking at all  
22       the possible multiplex combinations of

1 interfering analytes maybe it's time for the  
2 FDA to seriously review the idea that  
3 sequencing-based tests need a different  
4 pathway than tests that have been developed by  
5 indirect biomarkers like small-signature PCR  
6 primers and probes. And that that might  
7 reduce the regulatory costs and delays to  
8 getting some of these technologies in place  
9 that could contribute to better public safety  
10 without compromising better quality  
11 healthcare.

12 DR. SLEZAK: I'd like to jump on  
13 that soapbox with you but let me just say that  
14 the first speaker after lunch, Peyton Hobson,  
15 is from the relevant part of the FDA. He and  
16 I are working together with some DoD funding  
17 to try to break that logjam. So the good news  
18 is it is being addressed and maybe we'll hear  
19 his comments on the time line.

20 Let's go to some questions from  
21 the floor. We've got two people who have been  
22 standing there for awhile. Let's have both of

1       those questions.

2                   DR. NAKHASI:  Hi, my name is Hira  
3       Nakhasi.  I'm from FDA.

4                   So I think -- I had a comment and  
5       then a question to the panel.  The comment is  
6       basically we heard from yesterday and this is  
7       a prevailing question that we don't want to  
8       fall into this category of Chagas testing.  
9       You know, we did the testing and then the  
10      manufacturer did not, you know, the issue was  
11      then can we be screening all of the time or  
12      only once a time.  So the manufacturers get  
13      disinterested.

14                  But then the question I have here  
15      is can that be a lesson learned from that  
16      experience having these surveillance type of  
17      assays which then usually research type of  
18      assays.  Do those kind of studies to figure  
19      out whether there is that pathogen in the  
20      blood, whether it causes the disease and then  
21      use that -- if there is that research type  
22      tool then it can be developed into a screening

1        assay.

2                        So what I'm trying to say is that  
3        we need to have this both approaches. And  
4        that's the question here I have. And million  
5        dollar question. How can we combine the  
6        research-based assays or surveillance-based  
7        assays. And you heard that you don't need  
8        regulatory requirement for that approvals. To  
9        then have this kind of a surveillance and then  
10       go and do the select testing for a particular  
11       pathogen. I think that's the key question.

12                      And then how do we take advantages  
13        of these multiplex technologies where we, you  
14        know, just -- cannot go just one at a time but  
15        look at several pathogens at the same time.  
16        Will it reduce the cost of the testing during  
17        the research development.

18                      And if there is that potential  
19        there then further you can be used in inter-  
20        donor screening. Obviously there are  
21        challenges in the donor screening area as you  
22        heard, that you need to pass muster through

1 regulatory hoops.

2                   So, but I think the question  
3 really is how can we use these multiplex  
4 technologies and what are the barriers. We  
5 need to hear from everybody what are those  
6 barriers which will not -- which does not  
7 allow it to go to the -- in a screening assay.

8                   And the important thing is we need  
9 to also be thinking how can we use these  
10 research type technologies or new gene  
11 sequences or microarrays to really get that  
12 initial screening and initial analysis done  
13 whether that particular pathogen is important  
14 for donor screening or it impacts the blood  
15 safety. Thank you.

16                  DR. SLEZAK: Anybody want to try  
17 to tackle any of the 15 questions that were in  
18 there?

19                  DR. KASARSKIS: So just regarding  
20 the overall question of how you would be able  
21 to apply the larger sort of multiplex  
22 technologies. I mean I think that the

1       proposal of sentinel blood centers actually is  
2       probably will take you a long way there.

3               Because every single one of these  
4       technologies before you can start to make  
5       inferences about whether or not this would be  
6       routine -- would be useful for routine donor  
7       screening you need some information on  
8       baseline frequency of what it detects in a  
9       sample of individuals.

10              That data does not exist right  
11       now. We'll be able to infer some of it from  
12       incidental findings from the 1,000 Genomes  
13       Project, from exome sequencing projects, from  
14       various sorts of medical genome sequencing  
15       that's being done around, all the cancer  
16       genome sequences that are being done at most  
17       major cancer centers now.

18              But none of that is explicitly  
19       looking at blood from healthy, normal, happy,  
20       human individuals. And to do that you  
21       probably would do well to actually put  
22       together a well thought out sampling paradigm.

1 I would recommend probably more than one  
2 technology in every thousandth or ten-  
3 thousandth or whatever it turns out to be  
4 sample add a couple of sentinel blood centers  
5 from different places, perhaps places where  
6 you would expect to see different pathogens or  
7 great ethnic diversity. Because of course  
8 we've not touched in this discussion at all on  
9 the question of immune compatibility between  
10 donor and recipient which I think is an  
11 important one. So something along those  
12 lines.

13 And then look at the data after 2  
14 years. And in an ongoing way if you gather it  
15 you'll learn a lot about what can be used.

16 DR. GRIGORENKO: And I'd just like  
17 to add from a manufacturer point of view from  
18 the company who is making tools for research  
19 such as Life Technologies I think for us it's  
20 important to have some guidelines from  
21 regulatory agencies such as FDA, CDC and  
22 others on what are emerging pathogens in the

1 field and what could be -- potentially what  
2 kind of tools can we develop for potential  
3 screening for those assays.

4 So I a little bit touched on in my  
5 presentation that in the assessment of  
6 OpenArray technology we include some assays  
7 for Leishmania, T. cruzi and others. And we  
8 made it based on the project we've been doing  
9 together with Dr. Duncan at FDA.

10 Working at the company making  
11 tools we have very limited knowledge on what  
12 is really needed in the field. And I think  
13 information from regulatory agency would be  
14 very useful for us.

15 DR. SLEZAK: So we're sitting here  
16 at the NIH at an FDA meeting. There's people  
17 from CDC present. We have people from  
18 industry and research. I think we have the  
19 critical mass here to think about what the  
20 next steps would be, to pull together a group  
21 that would be focused on improving blood  
22 safety and trying to work together in a



1 partnership.

2 Let's go -- okay, one comment  
3 here.

4 DR. LINNEN: I just wanted to make  
5 a quick comment. There has been a good effort  
6 to establish emerging pathogens. What's  
7 really difficult is determining whether it  
8 needs to be screened for. It's a long, hard  
9 road.

10 I mean the guy at the microphone  
11 knows with dengue virus we've been working on  
12 that for years and we still don't really have  
13 a super clear idea of where you need to screen  
14 and what the impact of screening for dengue  
15 virus will be.

16 So it's the same way. Everyone  
17 knows the XMRV story. We're getting ready to  
18 do hepatitis E virus studies in the U.S. to  
19 look at prevalence because there's a lot of --  
20 there's growing interest in that virus  
21 worldwide.

22 And the first step is very

1       difficult, to screen a large number of  
2       unlinked donations. But that doesn't even  
3       really get to the real question of is disease  
4       being caused by transfusion transmission of  
5       HEV.

6                   DR. SLEZAK: Thanks. Let's go to  
7       the next question.

8                   DR. BUSCH: Mike Busch. I think  
9       both Susan and I will kind of discuss those  
10      issues this afternoon.

11                   I think this is a good discussion  
12      and it's useful for us because we do kind of  
13      have a network, both the larger blood  
14      organizations like Red Cross and Blood  
15      Systems. And then fortunately NHLBI has  
16      funded the REDS Program which now not only in  
17      the U.S. but internationally, in Brazil, South  
18      Africa and China has large funded initiatives  
19      focused on blood safety. And these can be  
20      expanded and there's even more opportunity to  
21      reach out to sentinel organizations, blood  
22      organizations.

1                   A couple of points. One is we do  
2                   a pretty good job. I think the Red Cross  
3                   again has kind of led the way of freezing away  
4                   samples from positive donors. So those can be  
5                   made available. In general we just save  
6                   plasma. But a lot of the discussion about the  
7                   ability of these technologies to probe into  
8                   whole blood, it's fairly straightforward for  
9                   us to capture and freeze whole blood off the  
10                  donation samples or again get the filters. So  
11                  understanding what kind of sample types would  
12                  be useful to you folks.

13                 And also providing those large  
14                 cross-sectional positives so that you can  
15                 evaluate the sensitivities of your test. As  
16                 Jeff showed, I mean these tests that we're  
17                 using are extraordinarily sensitive. They're  
18                 optimized. And the question of whether the  
19                 newer technologies can really achieve those  
20                 sensitivities I think needs to be validated  
21                 and in order to do that you need the samples.  
22                 You can bulk dilute virus but you also really

1       need clinical samples. So helping us to  
2       understand what kind of samples from positives  
3       need to be -- would be useful.

4               And again the positives we get are  
5       the positives we detect. So if you're looking  
6       for variants that we're missing we're not  
7       getting them. So we do this a lot. We do  
8       these NIH-funded molecular surveillance  
9       studies but always with the limitation that  
10      the only infections we pick up are the ones  
11      that the tests we're employing now can detect.  
12      So this is why you have to reach beyond just  
13      the units we're picking up and do some  
14      sentinel new infection finding.

15             And just the last point on your  
16      question about can we make money off  
17      sequencing. We've actually done studies,  
18      surveys that show that a lot of donors would  
19      be very interested in getting a GWAS or an  
20      informative health genetic test. They'd even  
21      be willing to pay for it.

22             But then you get the push back.

1       You get the push back from the organizations  
2       saying that's not our business and these  
3       people are coming in to give blood. Now are  
4       we going to charge them to do this.

5               And then FDA also has rejected the  
6       allowance of genetic testing in informed  
7       consents of donors. So figuring out if this  
8       is a business opportunity, if so how to pursue  
9       it is a challenge.

10              DR. SLEZAK: Thanks. We have 15  
11       minutes left so I want to run through.  
12       There's three people standing. We'll take  
13       their three questions and comments. Then we  
14       have three questions here. So I don't have  
15       Sanjai yelling at me too much. Then we'll see  
16       if it's time for lunch after that. Next  
17       question.

18              DR. KLEINMAN: Yes, I'm Steve  
19       Kleinman. I'm senior medical advisor at AABB.  
20       And I've been involved in a lot of infectious  
21       disease research over the years in blood.

22              And I'm a proponent of

1 surveillance but I think there's some  
2 sloppiness in the thinking here. And that is  
3 we're equating emerging pathogens with  
4 surveillance of normal people. And I think  
5 there's a big disconnect there.

6 We should look for emerging  
7 pathogens in groups of people where emerging  
8 pathogens are likely to be present. So we  
9 should do studies in injection drug users,  
10 maybe other sentinel populations.

11 If we do surveillance in blood  
12 donors, what are we really looking for? I  
13 think we're -- in a sense we're looking for  
14 the normal virome. We know we all have viral  
15 sequences and that's what we're going to find.

16 And I don't find that to be the  
17 right population to go to at this point. I  
18 think if what you want is 1,000, sure, blood  
19 centers can provide you with 1,000 samples  
20 from the so-called normal population. And  
21 then I think that can be screened. But  
22 massive screening for unknown agents just

1       seems to me, as has been said by a few other  
2       speakers, to be kind of putting the cart  
3       before the horse. And I think these assays  
4       need to be used more in other situations  
5       before we start setting up sentinel  
6       surveillance systems.

7                   MR. MCLOUGHLIN: I'd like to  
8       respectfully disagree with part of that  
9       comment. Having samples from so-called normal  
10      patients or normal donors is absolutely  
11      essential to us to be able to do any kind of  
12      statistics to know what the normal virome and  
13      the normal bacteriome in blood is.

14                   It's our expectation that we're  
15      going to find a lot of things that people can  
16      carry without having symptoms or people with  
17      subclinical -- people who are ill but are  
18      subclinical and have never been to the doctor  
19      for whatever infection they have. We need to  
20      know what that baseline infection rate is and  
21      how that associates with disease symptoms.

22                   So I agree with the point that we

1 do need to focus on sampling the populations  
2 that are at risk for exposure to these --

3 DR. KLEINMAN: Well, you need a  
4 normal control group. And blood centers can  
5 be a place to get that. But that's different  
6 from doing sentinel surveillance which implies  
7 an ongoing sampling scheme and a massive  
8 thousands and thousands of donors that would  
9 be sampled with their -- presumably with their  
10 consent which I don't think we have right now  
11 for this kind of screening.

12 I mean you can get anonymized  
13 blood donor samples but start small and I  
14 think show us the data on the virome before we  
15 then go and say we need to do this on 10,000  
16 people a year throughout the U.S. to look for  
17 changing patterns.

18 MR. MCLOUGHLIN: I agree. I think  
19 we need to have both.

20 DR. NARAGHI-ARANI: So one  
21 potential way that we could get around this  
22 would be that, you know, right now -- where



1 are we right now is single tests for detection  
2 of various agents and possibly a couple of  
3 multiplex tests, yes? And then there is also,  
4 you know, then the other end of the spectrum  
5 is next-generation sequencing, microarrays and  
6 some of the more deeper multiplex PCR assays.

7 Why not do an initial study where  
8 we can do a multiplex PCR looking for the  
9 specific agents that everyone is concerned  
10 about, right? And in the same samples use  
11 next-generation sequencing and microarrays to  
12 be able to understand the baseline and the  
13 load that is in the samples, right?

14 So multiplex PCR will not be able  
15 to pick up the things that we don't know are  
16 causing disease. The microarrays and  
17 sequencing will be able to detect those other  
18 viruses that are part of the normal virome.  
19 And I would imagine that from a good sampling  
20 scheme you would be able to get all the  
21 information you need through that process.

22 Because you would understand

1       whether or not multiplex PCR will work for the  
2       intended use that you have. You will also  
3       understand what is the utility of the other  
4       deeper multiplexes that are available through  
5       assays and sequencing. And truly understand  
6       which of these diseases that we are concerned  
7       about are really -- which of the pathogens are  
8       really causing disease.

9                   DR. SLEZAK: Let's move on to the  
10       next question, please.

11                  DR. STRAMER: Yes. Sorry, Jerry,  
12       I cut you off.

13                  DR. HOLMBERG: Go ahead.

14                  DR. STRAMER: But I will.

15                  (Laughter)

16                  DR. STRAMER: Susan Stramer,  
17       American Red Cross. I have two comments, one  
18       from the ongoing discussion.

19                  We in blood centers, at least at  
20       the American Red Cross we have a mechanism  
21       where donors call back if they have acute flu-  
22       like syndrome to say do not use our blood.

1 And for a number of years now starting with  
2 one of the REDS projects for influenza in  
3 blood which we didn't find we continue to do  
4 that.

5 So we do have a repository of  
6 donors with quote unquote "acute viral  
7 syndrome." And we continue to accrue those in  
8 a repository. Those donors do not have --  
9 those are untested so we really don't know if  
10 they have routine screening markers. Well, in  
11 some cases they may have been tested depending  
12 on when they call in with their post donation  
13 information. So that's another source of  
14 samples to continue for the future.

15 And then I would like to make my  
16 second comment to Dr. Grigorenko. When you  
17 said what do we need. Well, the AABB  
18 Transfusion-Transmitted Diseases Group put out  
19 a supplement that I referenced yesterday in  
20 2009. It lists 68 agents in paper volume.  
21 But if you go onto the AABB website -- you  
22 probably need to be an AABB member which would

1 be good. I'm conflicted there too as  
2 president. But anyway to say we're updating  
3 the fact sheets, we're updating all the  
4 information on infectious diseases today that  
5 we think are current threats to blood safety.

6 And we put that supplement  
7 together not to talk to us but to talk to you  
8 as industry to say this is what we need. And  
9 if you go through those fact sheets it tells  
10 you everything that's known about the agent,  
11 is it transfusion transmitted, where the  
12 reservoirs are, what human diseases are  
13 caused, what technologies are available for  
14 testing, would it be a candidate for pathogen  
15 reduction. So really that information is  
16 there.

17 So I encourage you to look at that  
18 to apply it to your technologies. What are  
19 the agents that really concern us as an  
20 industry the most. Thank you.

21 DR. HOLMBERG: Yes. Before I give  
22 my comments I want to correct something that

1       you said and it's to everybody on the panel.  
2       And that is that the information about the  
3       disease fact sheets is on the public side of  
4       AABB. So it's accessible to everyone that  
5       wants to tap into it and it's very valuable.

6                 Jerry Holmberg from Novartis. I  
7       want to comment on the sampling. And I think  
8       that the idea of -- I think the details, the  
9       devil's in the details. I think the FDA hears  
10      some of the comments in that, you know,  
11      clearly if we get into the donor base we  
12      really need to have the releases, the  
13      disclosures to the donors. But also it has to  
14      be de-linked from the donor name.

15                And I think that there's plenty of  
16      repositories out there. We heard about the  
17      donor recipient repositories, various  
18      repositories that even CDC has with the  
19      hemophilia population and then also the  
20      thalassemic, some of the chronic users. So  
21      there's a great population to tap into and to  
22      look at.

1                   I want to go back to Hira's  
2       comment though. And I think there's a lot of  
3       frustration because you're hearing pushback  
4       from the blood banks. And they're saying we  
5       can't do this. And industry around the table  
6       is saying we'd like to have access to this.  
7       And yet there's expense that is involved.

8                   And really, Hira, what we're not  
9       addressing is who has the role and the  
10      responsibility. And that's a big issue that  
11      needs to be tackled.

12                  The only way that you're going to  
13      get people to step up to the plate is through  
14      funding. I mean we saw perfect examples with  
15      GenProbe and the advances that took place  
16      there. So you really, you know, how can you  
17      make this so that it would be feasible is that  
18      someone has to take responsibility. And it  
19      has to be funding and I think that the  
20      government has had a track record in the past.

21                  My other comment was, it goes back  
22      to Clark Tibbetts' comment. And I don't want

1       that to be lost. And that is how is the FDA  
2       going to go through the approval process.  
3       What's the validation process? We saw the  
4       complexity from PCR to microarray to  
5       sequencing. So what -- how is FDA going to  
6       get there? And what is the validation process  
7       for that? So I think that that's a whole  
8       realm of discussion that needs to happen.

9               DR. SLEZAK: And perhaps that will  
10       be in the final wrap-up session for those of  
11       you who will hopefully stick around for that.

12              The last three questions I just  
13       want to make sure we at least get them touched  
14       on. They relate to sample prep, the  
15       possibility of dealing with sort of a  
16       systematic laboratory contamination and  
17       database quality. And I'll just let the panel  
18       here address any of those that they would like  
19       to tackle. First light on wins.

20              DR. NARAGHI-ARANI: So in my mind  
21       I think that we really have the extraction  
22       processes pretty well worked out for

1 everything other than anthrax in blood. So  
2 total nucleic acid extraction from whole blood  
3 would work quite nicely combined with some of  
4 these extraction technologies that we've  
5 talked about would really answer in my mind  
6 pretty much the sampling problem.

7 MR. NOTARI: But what would the  
8 turnaround be? I mean the time. I mean some  
9 of the products that we're talking about in a  
10 blood center need to start manufacturing  
11 process within a very short time line, less  
12 than 24 hours.

13 Well, we collect platelets.  
14 Platelets are labile. They only are good for  
15 5 days, 7 maybe someday, but right now 5 days.  
16 So some of these aren't on the shelf for more  
17 than a day or two. The testing has to get  
18 completed. How fast can that testing be  
19 accomplished.

20 DR. NARAGHI-ARANI: Well, I mean  
21 if we're talking about total nucleic acid  
22 extraction it's quite rapid. No, you just put



1 the material into TRIzol or other favorite  
2 thing that strips things apart and you get to  
3 the nucleic acid.

4 The hard part then becomes which  
5 technology do you use for the application that  
6 you want, right? Because as we heard some of  
7 the technologies have issues with the host  
8 nucleic acid. Some have fewer issues, but  
9 that definitely is an issue to address. And  
10 that is the question is how long will that  
11 additional purification take. And I'm sure  
12 that people who have worked in blood centers  
13 know much better than I what it takes to do  
14 that.

15 DR. SLEZAK: Somebody else with a  
16 comment on any of these last questions?

17 DR. LINNEN: Just wanted to  
18 comment that yes, this sample preparation has  
19 been figured out. There are a lot of  
20 different methods that have been shown to be  
21 automatable. So I have a lot of confidence  
22 that can be worked out. But yes, there are a

1 lot of details.

2                   Regarding the false reactive  
3 potential problem. Really the key is  
4 automation. You get human hands off of the  
5 samples and I think that the problem can  
6 really be solved. Because that's a large part  
7 of how we achieve high specificity because we  
8 still cannot control before the sample gets on  
9 the instrument the potential for cross  
10 contamination.

11                 DR. TIBBETTS: Our experience  
12 resonates with what you just said. Human  
13 error in sample-handling in prototype assays  
14 that are still manual and not fully automated  
15 accounts for the vast majority of what we  
16 would otherwise ascribe to be template  
17 failures in assays.

18                  But I would say that it would be  
19 very helpful if blood banks and other  
20 resources are going to share archived  
21 materials that there be some research done to  
22 assure that the templates that would be looked

1       for are stable under the archival conditions  
2       that are being used.

3                       And particularly some of the RNA  
4       viruses that we've tried to work with with  
5       graciously provided samples are so small that  
6       perhaps they might work for a 30-base pair  
7       amplicon in a PCR assay but it won't deliver  
8       any useful sequence at all. So some research  
9       on template stability of the different classes  
10      of pathogens that are of interest would be  
11      really helpful so that time's not wasted on  
12      graciously provided materials that give poor  
13      assay results.

14                     DR. SLEZAK: So we have time for  
15      one last comment. I'd like to ask Kevin to  
16      talk about the last question.

17                     We heard several people talk about  
18      using everything that was in NT for their  
19      design of their signatures. And I think maybe  
20      there's others who have had issues with the  
21      quality of the database. Any comments you  
22      might have?

1 MR. MCLOUGHLIN: Well, the idea of  
2 taking sequence reads and BLAST-ing them  
3 against NT and using that even in a  
4 surveillance context gives me chills.

5 I think having some kind of  
6 curated reference database along the lines of  
7 what we've been working with with another  
8 branch of the FDA, I think that's going to be  
9 essential to be able to put these assays into  
10 any kind of practice.

11 And as far as the methods go the  
12 methods themselves have to go through some  
13 sort of quality validation. And the  
14 methodology for doing that is pretty well  
15 established but it needs to be done. It  
16 hasn't been done yet because these are all for  
17 research only kinds of tools and that applies  
18 to the software and methods even more so than  
19 the technology itself.

20 DR. SIMONYAN: I think two  
21 comments. One of them, there is at the  
22 Genomic Working Group organized at FDA and

1       their efforts in December to come up with  
2       definite standards of accepting the  
3       applications for certification of the  
4       procedures. So it's long work and we are  
5       working with NCBI teams to come up with data  
6       standards, submission standards, computational  
7       validation standards and protocols.

8               So FDA knows about the situation  
9       and it is clear that the existing  
10       infrastructure is not able even to take the  
11       data. The FASTQ formats are not accepted or  
12       analytics is not verifiable. So these efforts  
13       are being -- are taking place.

14              And another comment about  
15       surveillance at blood centers is that it is so  
16       much cheaper to generate the data but so much  
17       more expensive, I mean time-wise expensive to  
18       compute on the data. The optimism behind the  
19       scientific optimism which we all have, there  
20       is an industrial realism that if you generate  
21       this data, you buy a sequencing machine, put  
22       in a blood center and you start screening

1 everybody. And then what do you do with the  
2 data? I mean you end up with 600 gigabase in  
3 one run and then you need a computer cluster  
4 to even come up with some conclusion. And  
5 what conclusion? It will take time and  
6 effort.

7 I think there is a gap between  
8 getting the data and trying to understand the  
9 data. I think that might be one factor which  
10 will be holding the usage of this technology  
11 in every blood center.

12 DR. SLEZAK: So let's hold onto  
13 that optimistic thought and head to our long  
14 lunch line. So I was told that there's also  
15 another cafeteria in Building 38 nearby. So  
16 some of you might want to try that as well.  
17 See you after lunch. How about a hand for  
18 everybody on the panels.

19 (Applause)

20 (Whereupon, the foregoing matter  
21 went off the record at 12:45 p.m. and went  
22 back on the record at 1:49 p.m.)

1 DR. HOBSON: I'd like to thank the  
2 CDRH. The Division of Microbiology Devices  
3 actually hosted a public workshop very similar  
4 to this to see where could we actually make  
5 advances in the regulatory science for  
6 multiplex devices.

7 We got basically all the experts  
8 together in the field much like is here,  
9 discussed the issues. We put out a guidance  
10 document in draft form.

11 And I'm going to touch on the  
12 salient points from that guidance document in  
13 my talk, then go over some of the lessons that  
14 we've learned and kind of where we stumbled  
15 and what do we see kind of on the horizon.

16 So, really the driving force  
17 behind our reevaluation of how we evaluated  
18 multiplex devices really came from two parts.  
19 Internally reviewers started asking questions  
20 of why do we need this level of information  
21 for a multiplex device. And then are the  
22 sponsors who are really causing not so much a

1 disturbance but asking a lot of questions why  
2 do you need so much information, is this all  
3 scientifically valid caused us to really  
4 reevaluate what was really the minimum amount  
5 of data that we needed to show safety and  
6 effectiveness of devices.

7                   So if we started and just kind of  
8 break it out into the challenges that we  
9 observed as the FDA, if you break it out and  
10 look at the clinical challenges, first and  
11 foremost the biggest one was the availability  
12 of positive specimens. And this is true for  
13 many, many even individual measurements,  
14 especially for an emerging disease. Simply  
15 the positive specimens are not there.

16                   There's also the availability of  
17 sufficient sample volume. All of our tests  
18 have to be evaluated for clinical truth to  
19 establish the specificity of the assay. And  
20 you can run out of all of your precious  
21 samples to show the validation of your device  
22 simply by doing all the reference tests,



1 especially as the multiplexes increase in the  
2 number of analytes that are represented.

3 Another big problem we saw were  
4 kind of inappropriately designed multiplexes  
5 for patients with signs and symptoms of a  
6 certain type of disease. It didn't make sense  
7 for certain bugs to be even tested for in a  
8 certain specimen and yet sponsors were coming  
9 in with things like that.

10 So we were looking at really how  
11 do we make the multiplexes have an appropriate  
12 design and make sure that the targets that  
13 were included were appropriate not only for  
14 the intended use of the device which is the  
15 most critical but also for the relevant  
16 specimen type.

17 There were also a number of  
18 analytical challenges. And as a multiplex  
19 increases in number it almost gets to the  
20 point where the simple in-house analytical  
21 validation studies performed by all developers  
22 become too burdensome.

1                   Things simply like the variability  
2                   in current approaches to accurately quantify  
3                   the input in materials was going to be almost  
4                   cost prohibitive as these multiplexes expanded  
5                   into 20, 30, 50 targets per panel. So we  
6                   proposed various ways around that, doing  
7                   molecular calibration, et cetera. I'll talk  
8                   a little bit about that later.

9                   But some of the more kind of  
10                  mundane ways to validate or mundane tasks that  
11                  you have to go through to validate an  
12                  individual measurement such as cross-  
13                  reactivity within device competition,  
14                  interference, et cetera, all increase  
15                  significantly every time you add a target. So  
16                  when you approach even a 20-plex the level of  
17                  in-house validation really becomes a  
18                  significant burden on the developer.

19                 So what we did as a group, we  
20                 pulled together a small working team within  
21                 the Division of Microbiology Devices and  
22                 really thought about what is it that we need

1 to see for a 510(k). And if you look here at  
2 the list nothing really changes.

3 These are still what we asked for  
4 for something for an individual measurement  
5 type of assay for a single analyte or even a  
6 duplex. We still want to see multi-site  
7 clinical evaluation of reproducibility,  
8 clinical performance to establish PPA and NPA.

9 The in-house studies, nothing  
10 changes there. Things like LOD, cross-  
11 reactivity, inclusivity and exclusivity. We  
12 wouldn't -- there was no validation study that  
13 we could just dismiss wholesale. So what we  
14 had to do is come up with kind of solutions to  
15 make them a little bit easier for developers  
16 to perform.

17 We want these assays out on the  
18 market. We realize that there's a need for  
19 them so we have to essentially think about  
20 what is it that we need to see to make sure  
21 the device performs safely and effectively so  
22 that it can get out there and it can be used

1 to protect public health.

2 For the evaluation of multiplex,  
3 this is just kind of comparing and  
4 contrasting. Originally we would look at  
5 multiplexes on a per-analyte basis. This is  
6 for every analyte on your test panel  
7 everything gets evaluated.

8 The analytical evaluation is  
9 usually used to establish performance  
10 parameters and that's done in-house. And that  
11 is things like LOD, cross-reactivity, et  
12 cetera.

13 In our historical approaches the  
14 magnitude of the clinical validation was  
15 really driven by a prevalence-driven study  
16 whereby all of the prospective all-comers had  
17 to -- you had to actually achieve a certain  
18 number of positives to establish a point  
19 estimate and an agreed-upon lower level of the  
20 95 percent confidence interval for each of the  
21 analytes in the multiplex test device.

22 And that's kind of hard to do for

1 things that are either seasonal or newly  
2 emerging. You're really not going to get a  
3 lot of those positives no matter how big of a  
4 study you do unless you start reaching the  
5 tens of thousands and that's really -- you're  
6 not going to get too many devices that come  
7 through the FDA in terms of a diagnostic  
8 device with that.

9 And this, in the historical  
10 approach most of the emphasis was on the  
11 clinical validation, the comparative analysis  
12 to establish the device performance in the end  
13 user environment. And that should kind of  
14 really be in the middle. We haven't gone away  
15 from that. We still want to see device  
16 performance in the end user environment.  
17 That's critical because that's who's going to  
18 be doing the testing.

19 But in our current multiplex  
20 concept for evaluation we're actually shifting  
21 a lot of the emphasis into the analytical  
22 validation using alternative approaches to

1 really reduce the testing load. Things like  
2 pooling, making test panels ahead of time that  
3 you can actually use that are well  
4 characterized and calibrated.

5 We've kind of been involved with  
6 some efforts to actually put together high-  
7 quality test panels and those are kind of  
8 growing and ongoing now. Nothing has really  
9 come out of it yet but that's something that  
10 would be a tremendous benefit is really high-  
11 quality well pedigreed panels for things like  
12 inclusivity and exclusivity that can be made  
13 available to the developers. We also allow  
14 some in silico testing mainly to guide the wet  
15 testing.

16 Our clinical validation is done  
17 through a modified clinical study. I'm going  
18 to touch on this a little bit later. But we  
19 have actually opened up to allow the use of  
20 more than just prospectively collected  
21 positive specimens. And that's a real shift  
22 for us in the diagnostic side.

1           The other thing to make evaluation  
2 easier and to make everything make more sense  
3 is we've proposed the use of syndromic panels.  
4 We spoke with our network of experts. They  
5 very much agreed with us, things like GI  
6 panels, upper respiratory panels, lower  
7 respiratory panels, sexually transmitted  
8 infection panels.

9           This is something that we also  
10 encourage, not only us but the sponsors to  
11 engage with their medical officers on their  
12 boards to come up with appropriately designed  
13 test panels.

14           So just really quickly our  
15 proposed concept for multiplex validation  
16 actually if you kind of crunch the numbers  
17 leads to greater than an 80 percent reduction  
18 in the overall test load on a sponsor. Now in  
19 some cases that's a huge, huge benefit. In  
20 other cases when we see multiplexing systems  
21 that are approaching 1,000, 2,000, 5,000 such  
22 as what we saw at Livermore and stuff like

1       that, those types of things may actually  
2       require us to even consider even more  
3       innovative approaches. But for right now  
4       looking at kind of the 20-plex as our  
5       benchmark we've been able to get down to an 80  
6       percent reduction in the overall test load.

7               And sponsors are pretty happy with  
8       this. It has actually caused a lot of devices  
9       to come into us now for regulatory review and  
10      clearance.

11             So the multiplex clinical  
12      evaluation. Device evaluation is done in the  
13      intended use environment and with the intended  
14      use population, these syndromic patients.  
15      These are not healthy patients at all.

16             Sensitivity and specificity is  
17      established through a predetermined number of  
18      positive and negative samples. That's usually  
19      done through interactions with the FDA. And  
20      this is our historical approaches now I'm  
21      speaking about.

22             But this format did not work well



1 for low-prevalence targets or bioterror  
2 targets which was another kind of driving  
3 force behind our multiplex meeting. And it's  
4 really not feasible at all for multiplexes  
5 because of things like sample volume and the  
6 large number of comparator tests that are  
7 required to be run.

8 For each -- a comparator test is  
9 used to establish a clinical truth. And you  
10 can obviously see as the number of targets  
11 increase the number of assays to establish a  
12 clinical truth in that specimen also  
13 dramatically increases. And you'd run into  
14 scenarios where you actually run out of sample  
15 volume.

16 So to establish sensitivity we  
17 propose really alternative positive specimens.  
18 This is to establish the PPA of an assay.

19 We've opened up to use obviously  
20 prospective. There's still a prospective arm  
21 to this so prospective, any of the positives  
22 you get in your prospective study we'll

1 evaluate.

2 Archived samples, especially those  
3 that have a pedigree and you can actually get  
4 multiple ones that span the clinical range.

5 Retrospective specimens are kind  
6 of the next tier where you actually know what  
7 sponsors have. These are very, very well  
8 characterized specimens that are in  
9 researchers' freezers.

10 And finally we also have even  
11 moved to in certain cases allowing mock  
12 specimens to be used made in negative clinical  
13 matrix.

14 There's a whole list of things  
15 here that I have and these are all in the  
16 guidance document so I'm not going to go  
17 through them. But there's really a lot of  
18 interactions that we go through with the  
19 sponsors before they even send a submission  
20 in.

21 And this is a critical point. We  
22 have an agreement up front on how they're

1 going to confirm things, what their testing  
2 scheme is going to be, and the numbers. We  
3 have an agreed-upon level of performance and  
4 also the number of positives that they're  
5 going to be testing or going to be using.

6 If they have to use mock clinical  
7 specimens all of that information has been  
8 provided to us ahead of time and it's been  
9 agreed upon through pre-submission  
10 interactions.

11 And another thing here at the  
12 bottom is the use of processed nucleic acid  
13 remnants. Another thing that we do is we  
14 encourage all of our developers to hold onto  
15 the processed nucleic acids in case they have  
16 to down the road make some modification to  
17 their device. They already have starting  
18 material to go back from which they know  
19 really what's in that tube.

20 So specificity. This is really  
21 done through a prospective armless study.  
22 It's around 1,500 prospectively collected

1 specimens from patients with signs and  
2 symptoms. These are, whether it's a GI panel,  
3 a URI, an STI panel, they're all prospectively  
4 enrolled and tested.

5 The comparator measurements that  
6 are made on this is done by a randomized  
7 method that's agreed upon with us and our  
8 statisticians prior to undertaking the study.  
9 And the specimen volume in many of these is  
10 actually going to drive the comparator test to  
11 some of our cleared multiplex devices anyway  
12 so they can get more comparator information on  
13 a per-sample basis.

14 This is a really critical slide  
15 and that's why -- the only slide that has red  
16 ink in it. This is for a modification of a  
17 cleared multiplex device. We've already had  
18 cases where we've cleared a multiplex device  
19 and we didn't keep up with nature or nature  
20 kind of outpaced the device of a mutation in  
21 flu or another kind of organism that is prone  
22 to mutation.

1                   So developers, we have these  
2                   devices out there that are cleared at a  
3                   certain level of performance and we want them  
4                   to maintain that. So we're very interactive  
5                   with the developer. When they come to us and  
6                   say hey, my assay is not picking up this  
7                   strain. Can we add this probe, can we move  
8                   these primers around. These are for targeted  
9                   molecular assays.

10                   And this has worked well for us.  
11                   I mean companies are very transparent. We're  
12                   having a problem. Help us fix this.

13                   The validation unfortunately for  
14                   these is really dependent on the nature of the  
15                   change though. It has to be done on a case-  
16                   by-case basis because it's really not a one  
17                   size fits all thing.

18                   But there are some kind of  
19                   existing examples that we've taken from lower  
20                   order multiplexes or duplex measurements or  
21                   individual measurements that we could modify  
22                   to use in these multiplex cases. And some of

1       these things are -- the way that we can allow  
2       people to add new targets if they did not have  
3       all the data in their clinical study, you  
4       know, it wasn't powered sufficiently for some  
5       reason, ways they can mask analytes, then un-  
6       mask them later. So we actually have a lot of  
7       ways to move forward in making changes to a  
8       device or opening up new analytes on a device.

9               So just really quickly I'm going  
10       to summarize these last two slides. We have  
11       really successfully launched our diagnostic  
12       validation multiplex concepts. They came out  
13       of the 2011 workshops. A number of the people  
14       who were participating today were also there.  
15       And I'm hearing a lot of the same things. So  
16       a lot of the same problems are found in the  
17       blood screening community also. So it's kind  
18       of neat to see everything together again.

19               We've been promoting our concepts  
20       through the pre-submission process with  
21       numerous sponsors earlier on. And I cannot  
22       stress how important it is to engage with

1 sponsors and talk with them. I mean a lot of  
2 times they don't know. Unless they're one of  
3 the big Roches or Abbotts a lot of these  
4 companies are small companies with barely one  
5 foot sometimes out of the academic lab and  
6 they really need the FDA's guidance to be  
7 successful. So I think that's what we're here  
8 for is to really reach out to them.

9 So to date we've actually cleared  
10 a number -- after the publication of our  
11 guidelines we've cleared a number of devices  
12 for things like blood culture ID, upper  
13 respiratory infection and then gastroenteritis  
14 devices.

15 So some of these are on the order  
16 of 20 to 25 analytes. So they're not terribly  
17 huge but they are rather complex. And some of  
18 them actually contain resistance markers and  
19 markers of pathogenicity, et cetera.

20 So really in summary our multiplex  
21 diagnostic concept. It has reduced the burden  
22 and sponsors came in. We put these concepts

1 out and put them into play and the folks came  
2 in for regulatory clearance.

3 We continue outreach at the early  
4 stages of development. A number of the  
5 federal funding agencies at this point who are  
6 -- put it in their BAAs when they are putting  
7 money out there for the development of a  
8 diagnostic device that says hey, one of your  
9 milestones is now to go meet with the FDA and  
10 tell them about your technology. Make them  
11 aware of what you're doing so that they know,  
12 so something doesn't come to us out of the  
13 blue.

14 And this was really an  
15 interdisciplinary approach. I mean it took  
16 medical officers, lead reviewers, software,  
17 hardware reviewers, statisticians. It was a  
18 very large effort on our part to pull this  
19 together.

20 Like I said there's several  
21 already on the market and there's many, many,  
22 many more on the horizon. Things from simple



1 paper-based densely multiplexed devices all  
2 the way up to these highly dense assays and  
3 mass spec types of devices. And everything in  
4 between from PCRs to next-generation  
5 sequencing.

6           Some of the problems that we've  
7 seen, and I'm going to close on these last two  
8 points, is reporting results from a multiplex.  
9 Sometimes the physicians say it's kind of  
10 information overload. What does all this  
11 information mean? Especially when there's a  
12 co-infection or multiple co-infections. But  
13 what this does is it gives a tool to actually  
14 highlight previously unknown co-infections.

15           Then also things like colonization  
16 versus infection. When is something  
17 colonizing versus when is something actually  
18 infectious.

19           And finally, I'm not going to  
20 touch on this but a big, big issue with  
21 multiplexes is obviously reimbursement. If  
22 you guys ever have a chance to see Christine

1       Ginocchio speak she is very much an expert in  
2       this and she gives a really good talk about  
3       it. But this is very much a big black box  
4       right now from what I understand. But CMS and  
5       the end users I believe are actually working  
6       through this now.

7                       So that's basically all I've got  
8       and I'd like to thank the organizers again for  
9       having us here. Thanks.

10                      (Applause)

11                      DR. BUSCH: Excellent. Thank you  
12       very much. So the next presentation is mine.

13                      So I was asked to -- and I think  
14       my talk will complement Sue Stramer's coming  
15       from the Red Cross. So to talk about kind of  
16       the perspective of blood organizations.

17                      And specifically for me I work for  
18       a company called Blood Systems. And I'll just  
19       give you an overview of that. It has a large  
20       testing comparison called CTS. I'll describe  
21       that. And then I oversee the research  
22       institute. So we kind of are doing everything

1 we can to address the residual risk and the  
2 emerging agents. So through the talk I'll  
3 kind of give some examples of what we've dealt  
4 with and how we've tried to address the  
5 specific test needs.

6 So again my company has -- it's a  
7 non-profit like Red Cross and it has a large  
8 testing component -- I'm sorry, collection  
9 component, a pharmaceutical component, and  
10 then a research division.

11 But then we also have a testing  
12 laboratory that was about 3 years ago spun off  
13 to create a new cooperative testing program  
14 called Creative Testing Solutions which now  
15 has four and a fifth lab is joining. So it  
16 tests about 5 million donations a year.

17 And I think this plus what you'll  
18 hear from Sue in the Red Cross is probably 90  
19 percent of the U.S. blood collections are now  
20 tested in less than 10 centralized  
21 laboratories. So we've seen massive  
22 consolidation of testing in the U.S.

1                   And again, we test for large  
2           numbers of not only the participating blood  
3           centers that kind of house these laboratories  
4           or own the labs but also many other blood  
5           collection organizations and hospitals.

6                   And one of the things that we've  
7           recently done is to kind of meet some of the  
8           comments from the earlier discussion is to  
9           create an integrated what we're calling  
10          research consortium where the six largest  
11          blood providers, the organizations, are  
12          collaborating to create a data warehouse, a  
13          central data warehouse similar to what Ed  
14          Notari runs for the Red Cross called ArcNet  
15          and build research initiatives with an  
16          oversight committee and building repositories.

17                   So capturing the positive samples  
18          on a concerted basis, defining which units  
19          qualify for repositing those samples  
20          centrally, but also building the capacity to  
21          respond quickly. So having each of the  
22          centers, each of the laboratories have the

1 SOPs and the procedures and the donors being  
2 consented so that if an outbreak does occur we  
3 have the systems, the freezers in place to  
4 respond to outbreaks. So this really I think  
5 is relevant to some of the comments earlier  
6 about establishing kind of the centers for  
7 excellence or the consolidated systems to  
8 maintain surveillance and respond.

9 This is a slide that actually, I  
10 forget if Brian McDonough or Tony Hardiman  
11 from Ortho first developed. But it just  
12 serves to emphasize the barriers and the  
13 impact over the last decade on the providers.  
14 We now really have only two NAT and two  
15 serology providers in the U.S.

16 And these companies are not  
17 bringing tests as you saw from Sue's talk  
18 yesterday to the U.S. at the pace that they're  
19 available outside the U.S. And a lot of that  
20 has to do with the burden of cost of taking  
21 the test through the licensure process in the  
22 U.S. is about five times as high as ex U.S.

1           The volume of donations that need  
2       to be tested per year in order to justify that  
3       kind of investment they've estimated at about  
4       8 million. So they need essentially at least  
5       half the blood supply tested, every donation,  
6       every time in order to justify this kind of  
7       investment to bring forward a new assay.

8           Also, historically at least there  
9       was a substantial delay in these companies  
10      being able to get their platforms and tests  
11      approved. So the PRISM and the Vitros for  
12      example were available outside the U.S. some  
13      8 to 10 years before in the U.S.

14           So what we've seen as a  
15      consequence of all this is very limited  
16      interest, willingness to step up as new  
17      emerging considerations, concerns arise. So  
18      we see very few of the enhancements that tend  
19      to be observed outside the U.S., improvements,  
20      modifications to tests brought to the U.S.  
21      market.

22           Supplemental testing is really a

1 problem where we're still dealing with tests  
2 that were first either licensed or still  
3 unlicensed 20-30 years ago. And most recently  
4 the hep C RIBA has gone off market and we have  
5 no confirmatory hepatitis C assay other than  
6 doing an alternate EIA.

7 For emerging agents we heard a  
8 little bit about the so-called "Chagas effect"  
9 where we initially said we want this test, we  
10 implemented it universally, but then we  
11 realized that there were no seroconversions so  
12 why test the 80 percent of repeat donations  
13 that repeatedly are negative. So we moved to  
14 a one-time donor testing and the companies  
15 said you can't do that but they got their  
16 money anyway. They raised the price.

17 But as a result of that we hear  
18 this every time we say we need a test for  
19 dengue or Babesia. The companies say well,  
20 how do we know you're not going to decide to  
21 just test a small proportion of donors. And  
22 they look at the market and they say well,

1 Babesia you may only test in the summer and in  
2 part of the country so is it worth investing.

3 And more and more we're trying to  
4 rationally selectively design testing  
5 strategies. But the companies view that as a  
6 problem in terms of their decision to move  
7 forward.

8 The other reality in the blood  
9 industry is whereas blood banking for decades  
10 continued to grow in terms of blood  
11 utilization, both red cells and particularly  
12 platelets, over the last 5 years or so there's  
13 been a progressive and more recently a rather  
14 precipitous drop in the use of blood.

15 And a lot of this is appropriate.  
16 We had too high a transfusion trigger. The  
17 U.S. uses substantially more blood per capita  
18 than other countries.

19 But bottom line is the decline in  
20 the utilization of blood has reduced the  
21 revenues in the blood organizations and has  
22 reduced the number of tests that are needed by



1 the laboratories. So the more you multiplex  
2 the fewer tests. But if we have fewer  
3 donations to test and often these are multi-  
4 component collections, apheresis, the testing  
5 volume declines which in turn makes the cost  
6 balance difficult.

7                   Nonetheless we continue to see in  
8 a recent paper that just came out from Brian  
9 Custer at our center blood transfusion  
10 continues to strike a lot of fear in the  
11 public. So there's a continued sense of dread  
12 and severity and lack of understanding that  
13 results in blood transfusions having a  
14 substantially higher perceived risk by the  
15 public. So there's an expectation of  
16 continued surveillance and response and  
17 safety.

18                   So from our perspective stepping  
19 back and especially with the companies sort of  
20 saying we're not sure we're ready to invest  
21 and lots of dialogue. But we've really begun  
22 to think about alternative paradigm to working

1 both with the old players, we still respect  
2 and understand the major four vendors for  
3 blood tests. But we're also looking to bring  
4 in new, smaller players to the industry to try  
5 to particularly address these selective  
6 testing needs.

7 We're also, as discussed earlier,  
8 we're very interested in doing the studies  
9 ahead of time. So not getting into testing  
10 until we know the right way to test. So do  
11 the clinical trials, the epidemiologic studies  
12 so that we can have evidence-based  
13 recommendations as to how to screen, which  
14 technology, nucleic acid, serology, regional  
15 testing, et cetera.

16 And get those findings out and  
17 communicate them and share them and design the  
18 studies with FDA so that we're all on the same  
19 page as to when a test should be implemented.  
20 But this is where the work Jeff Linnen  
21 mentioned. There's a lot of work to do and  
22 I'll illustrate that as will Sue.

1                   And then in terms of the  
2           regulatory process trying to identify  
3           alternative paths to get targeted testing  
4           available. What we saw was a very creative  
5           strategy with NAT where the FDA allowed  
6           initial INDs that were allowed to continue  
7           screening under IND prior to licensure, as  
8           Jeff showed 3 or 4 years of screening under  
9           IND before the test may have been licensed for  
10          these viruses. And right now Red Cross is  
11          screening under IND for dengue virus on an  
12          ongoing, open-ended basis without a clear  
13          decision on whether a BLA will be filed and  
14          licensure sought.

15                   Other strategies of encouraging  
16          manufacturers that have tests outside the U.S.  
17          to file master files with the FDA allowing us  
18          to file clinical INDs and the reagents to be  
19          labeled "investigational use only" but  
20          employed in particularly supplemental testing,  
21          not for primary screening but as confirmatory  
22          tests to help with donor counseling.

1                   And then the other strategy of  
2                   actually working with small partners to  
3                   actually develop assays that may not move onto  
4                   a full-scale licensure. They may essentially  
5                   be in large blood center lab developed tests  
6                   that are offered to provide unique testing  
7                   services to address the safety or novel assay  
8                   needs. And if that data supports advancing  
9                   those tests towards a licensed test then  
10                  either we or the big manufacturers will step  
11                  in.

12                  So how do these things happen? A  
13                  lot of these studies are funded fortunately by  
14                  the NIH, to some extent the FDA and the CDC.  
15                  So one of the big programs that we're  
16                  fortunate to be part of and has contributed  
17                  enormously is the REDS program. And I'll  
18                  allude to that a little bit.

19                  Also specific RFPs. So as Jeff  
20                  indicated the NHLBI has put out RFPs for large  
21                  contracts to develop assays. They've got  
22                  similar initiatives for the multiplexing

1 concepts we're talking about here. So NIH has  
2 clearly in the past put a lot of money into  
3 blood safety and really contributed a lot to  
4 advancing that.

5 There are the usual investigator-  
6 initiated grants. And we've been successful  
7 as have others at getting these to address a  
8 number of these emerging agents and test  
9 development.

10 The SBIR for small businesses has  
11 been quite successfully achieved by a number  
12 of companies to build early-stage assays. And  
13 these phase I are quite small but phase II  
14 SBIRs can be \$5 million and support very large  
15 studies including full-scale clinical trials.

16 And then the traditional industry  
17 has stepped up. And even though they may not  
18 make firm decisions to take a test through  
19 licensure they're often willing and able to  
20 build prototype assays that are very high-  
21 quality and collaborate and participate in the  
22 evaluations of those.

1                   And then the blood organizations  
2 themselves. We're always -- it's our  
3 responsibility to address blood safety so our  
4 organizations do substantially fund these  
5 initiatives.

6                   We've heard all about this. I  
7 just show this again. What is necessary to  
8 warrant introduction of a new test or policy.  
9 And it really has to be an infectious agent  
10 that can be transmitted by blood and that  
11 causes serious disease that warrants testing.

12                  The recipients also have to be  
13 susceptible. So you've got places where  
14 everybody is already infected, seropositive  
15 for malaria, et cetera, where you can then do  
16 the studies and show that there's really no  
17 significant transfusion disease burden on top  
18 of background endemicity. And we'll touch on  
19 that.

20                  And of course the final decision  
21 really is dramatically influenced by the  
22 epidemiology, whether this is a new agent or

1 something that's been around for a long time.  
2 And the critical issue of the disease outcome,  
3 particularly in recipients.

4 So in terms of infectivity and  
5 these studies one critical issue is to  
6 understand is the agent transmitted by blood  
7 and if so what's the infectious dose that's  
8 able to be transmitted.

9 So what you have to do is combine  
10 studies that include often animal infectivity  
11 experiments, viability during storage, testing  
12 of repositories, and I'll go into this, that  
13 may exist that have linked donor/recipient  
14 samples to see what is the rate of infection  
15 in the donors and is it being transmitted to  
16 recipients.

17 And then we move onto larger  
18 prospective studies of donors and then  
19 potential transfusion transmission studies.  
20 And this issue was reviewed recently by Steve  
21 Kleinman and colleagues.

22 Just to mention the repositories

1       that are so valuable and important. The NHLBI  
2       has over the last now three or four decades  
3       built a series of repositories every 5 years  
4       or so containing literally now millions of  
5       samples spaced over time from donors and  
6       recipients. And these have been invaluable to  
7       both initially measure risk and more recently  
8       go back and look at many other both infectious  
9       and non-infectious questions.

10               So these repositories are  
11       available on a program called Bio-Link. You  
12       can access that and understand what's  
13       available and request these samples. And they  
14       are extremely useful in doing these kinds of  
15       prevalence and transmission studies.  
16       Limitations being though that they were  
17       defined in terms of when they were collected  
18       and where they were collected. Some of these  
19       are linked donor/recipient repositories.  
20       Others are just large-scale donor or recipient  
21       samples. And most of them are serum or  
22       plasma, but a fair number more recently do



1 have large numbers of frozen whole blood  
2 aliquots that are available as well.

3           Again, just the same point that  
4 these are extremely important to look at the  
5 transmission rate question. But they are  
6 time-specific, geographically limited to the  
7 centers that collected them and they are --  
8 although they're large repositories, depending  
9 on the prevalence of the agent in the donor  
10 samples the ability to accurately prove  
11 transmission and define the rate of  
12 transmission is dependent on the prevalence  
13 and the transmission rate and the scope of the  
14 repository. And these are very expensive and  
15 challenging to execute.

16           The NHLBI, again the program both  
17 through REDS and otherwise has done a lot of  
18 studies. I'm going to just touch on a couple  
19 of examples as illustration. But a lot of  
20 studies to address many of these agents of  
21 concern over the last 10-15 years.

22           The RADAR repository is one that's

1 particularly relevant in that it's a linked  
2 donor/recipient repository, 3,500 recipients  
3 with pre- and post-transfusion samples,  
4 received 13,000 donations. There's a large  
5 group of donor samples that were collected  
6 from consenting donors that did not go into  
7 recipients. And so these become a resource to  
8 pre-test.

9                   And this algorithm here which is  
10 in a review article, or an article about the  
11 repository again led by Steve tells us how we  
12 work through the repository to decide whether  
13 using these samples, whether testing is  
14 warranted.

15                   And as an example we did studies  
16 on parvovirus B19 where we did a phase I study  
17 that established the assay sensitivity and  
18 applied it to define the prevalence in the  
19 donations that were not transfused into the  
20 enrolled recipients, and then calculated  
21 whether we were powered in terms of the rate  
22 of infection in the donations and the

1 background seroprevalence which defined the  
2 proportion of the recipients that would be  
3 susceptible.

4 In an infection like parvovirus 80  
5 percent of all of us have antibodies and are  
6 resistant. So it's only the antibody-negative  
7 recipients that are informative to a  
8 transmission question. So you have to in this  
9 case do the calculations and say was there  
10 enough viremia, and it was about 1 percent, to  
11 warrant studying the transmission question.

12 In this case there was and a large  
13 study was done. And there were 21 susceptible  
14 recipients who were transfused with viremic  
15 donations and none of them became infected.  
16 All of those donations had antibody and most  
17 of them had fairly low levels so we were  
18 looking at non-transmission from tail end  
19 viremia, lower level which is as you heard  
20 earlier avoided by the new NAT assays.

21 But this led to a decision to not  
22 adopt universal screening of donors for parvo

1 but rather to do what's called in-process  
2 testing.

3 A subsequent study of this  
4 repository because it had whole blood actually  
5 showed that the levels of B19 virus in whole  
6 blood is a hundredfold higher than in plasma.  
7 So just illustrating again the utility of  
8 these repositories with paired whole blood and  
9 plasma to address this issue of what's the  
10 optimal sample. Is it plasma or is it whole  
11 blood.

12 Just to mention Harvey Alter is  
13 leading a study ongoing here at NIH and with  
14 D.C. Children's, an adjacent public hospital.  
15 This is enrolling heavily transfused patients,  
16 both patients at the NIH campus that are very  
17 sick, small infants, as well as just cardiac  
18 surgery patients collecting pre- and  
19 longitudinal samples post transfusion, whole  
20 blood, plasma, serum.

21 And these samples are routinely  
22 tested for NAT for not only the classic

1 viruses but for a number of viruses that we're  
2 interested in is there transmission. And  
3 indeed they documented a transfusion  
4 transmission of parvo B19 although the  
5 recipient completely asymptomatic. But  
6 clearly this is another critical resource and  
7 an ongoing collection for emerging agents.

8 Now XMRV, just one slide to just  
9 point out that when that first report came  
10 out, the Lombardi paper saying chronic fatigue  
11 syndrome may be linked to XMRV, this virus  
12 that turned out to be a recombinant mouse  
13 virus that was contaminating lots of samples,  
14 it took us about 2 years to do all the  
15 studies, to build large panels, distribute  
16 them to lots of laboratories and to come up  
17 with the conclusion that this was simply  
18 contamination. And that paper was published  
19 in Science and in parallel the Red Cross did  
20 a transfusion linkage study that showed no  
21 prevalence and no transmission.

22 So just to point out that we can't

1 wait 2 years. If we've got a real problem  
2 we've got to be much more prepared to respond  
3 early. Thinking back to Nathan's presentation  
4 on trying to catch that epidemic on the up-  
5 slope.

6 Just a couple of final examples.  
7 We've now developed a partnership to  
8 illustrate that kind of new paradigm with the  
9 small business called Immunetics based in  
10 Boston that has a long track record in  
11 building assays for sort of neglected diseases  
12 and parasitic infections to try to develop a  
13 Babesia assay.

14 And the initial work on that was  
15 actually supported by a phase I SBIR and also  
16 by our organization. And then we have a pre-  
17 IND and just literally the IND was filed today  
18 to support moving forward. And this is being  
19 funded by a phase II SBIR.

20 And then we're hopeful of getting  
21 a grant that will allow us to follow these  
22 donors and better understand the pathogenesis.

1       So this pre-IND study involved testing 15,000  
2       donations mostly in hyperendemic regions.

3               The IND study will involve over  
4       20,000 prospective donors plus lots of  
5       archived samples from known clinical cases.  
6       The donors will be enrolled and followed to at  
7       least understand the initial reactivity and  
8       then hopefully through the additional funding  
9       long-term follow-up to both define the  
10      duration of parasitemia, the evolution of  
11      antibody over time and guide setting cutoffs  
12      and policies around how to screen.     And this  
13      is just the timing.

14              These are complicated and involve  
15      studies to execute and particularly if they  
16      move into realtime screening to prevent  
17      transfusion of these units that are detected  
18      during the IND phase.   That means putting  
19      these tests into place in realtime and then  
20      triggering all of the regulated activities  
21      that kind of Ed Notari talked through.

22              Last agent to mention is dengue.

1 I think Sue will come back to us. But I think  
2 we're all aware that this is a major agent of  
3 concern. There was actually just this week a  
4 nice Nature paper that summarized the global  
5 burden of dengue.

6 And it's about 293 million  
7 asymptomatic cases and 96 million symptomatic  
8 cases that are being observed every year. So  
9 this is a huge and expanding problem globally.

10 In terms of transfusion there have  
11 been three transfusion transmission clusters  
12 that have been documented. But the studies  
13 that the Red Cross and we've done on rates of  
14 viremia are showing very high rates, half a  
15 percent, a percent of donations during  
16 epidemic periods are viremic.

17 And Lyle Peterson and Brad  
18 Biggerstaff recently modeled Puerto Rico  
19 estimating the risk of transfusion of a  
20 viremic donation over time. And these axes  
21 aren't here but this can get up to 1 percent  
22 during peak epidemics are theoretically being



1 transmitted.

2 And the AABB task force that Sue  
3 alluded to has prioritized dengue along with  
4 Babesia as one of the three high-priority  
5 agents.

6 Now the problem we faced was that  
7 at the time the only assays that were proved  
8 were serologic tests for diagnostics. There  
9 are MS-1 antigen assays that are available  
10 outside the U.S. and for a period the Red  
11 Cross evaluated those assays for donor  
12 screening. They turned out to be both non-  
13 sensitive and non-specific. So NAT tests  
14 clearly are the answer, especially after kind  
15 of what we've learned with West Nile, a  
16 similar mosquito-borne arbovirus.

17 So we had to essentially determine  
18 the rates of viremia in the donors and the  
19 transmission. A critical question is what's  
20 the transmission rate and the disease outcome  
21 burden.

22 So this is just a schematic

1 summarizing the time since the first  
2 transfusion case and then a few more  
3 transfusion cases. And then the Red Cross  
4 launched retrospective and then prospective  
5 screening, first with the antigen test and  
6 then with TMA. And then now we've launched a  
7 large -- and just completing a large study of  
8 transmission in Brazil.

9 And this, just to mention that the  
10 dengue work that Sue will summarize the  
11 details on actually was in part funded by a  
12 grant from NIH, what's called the Grand  
13 Opportunities Grant, to support both West Nile  
14 and dengue.

15 And identified and enrolled, there  
16 were actually 40 dengue viremics -- that's a  
17 typo -- that were enrolled and characterized  
18 and studied. These are all frozen down into  
19 a repository of longitudinal samples that are  
20 available to the scientific community.

21 And then a final slide. In Brazil  
22 we were able to under the REDS-III program

1 launch a study of transfusion transmission of  
2 dengue in two cities, in Recife here and in  
3 Rio. And this past year we were fortunate  
4 that they had a huge dengue 4 outbreak.

5 So we've literally identified  
6 large numbers of viremic donations that were  
7 transfused into recipients and are now just  
8 working through all the data as to the  
9 transmission rate. We have symptom findings  
10 on all these recipients at the time of  
11 accrual. We have pre-transfusion, post-  
12 transfusion samples. And we're working  
13 through the data.

14 We also did a sero survey and they  
15 had about 8 percent of the donor pool became  
16 infected during this epidemic. It was all  
17 dengue 4 that was being transmitted for the  
18 first time in these two cities in a  
19 hyperendemic region.

20 The bottom line takeaway from this  
21 study as it's evolving is that the  
22 transmission rate, we actually found 6

1     probable transmissions but that's out of about  
2     40-plus transfusions of viremic units. So the  
3     transmission rate is much lower than we  
4     thought. And the recipients did not develop  
5     clinical disease that got infected. So  
6     although the conclusion here is that  
7     transmission may be lower and in an endemic  
8     area where everybody's got antibody disease is  
9     actually pretty unusual.

10                 So this may lead to a  
11     determination that at least in endemic  
12     countries screening may not be needed. And  
13     we're working through this. But it just shows  
14     the complexity of the studies that need to be  
15     done. And the answer may end up being it's  
16     not worth it. So this is kind of what we live  
17     with in our world. Thank you.

18                 (Applause)

19                 DR. BUSCH: Okay, now we have  
20     hopefully an interesting talk. A colleague  
21     from AdvaMed which is -- he'll describe the  
22     sort of trade organization for the diagnostics

1 manufacturing.

2 Peter Scott will discuss multiplex  
3 donor testing for blood donors, looking ahead,  
4 development and system constraints.

5 MR. SCOTT: Well, good afternoon.  
6 We've had a lot of talks going on.

7 I'd like to start by saying -- so  
8 industry is committed to innovation in blood  
9 technology. We commend CBER for holding this  
10 workshop to explore opportunities.  
11 Collaboration is key to meet needs of  
12 patients, the blood community, manufacturers  
13 and regulators. We have a shared goal to spur  
14 timely development of blood technologies to  
15 market and support overall blood safety and  
16 availability.

17 We encourage considering flexible  
18 approaches to meet public needs and spur  
19 development. Overall time lines and costs of  
20 clinical studies are key barriers to  
21 development of new technologies.

22 So in the past 2 days we've heard

1 a lot about the blood concerns, blood group.  
2 We've also heard a lot about the science of  
3 different tests. What I want to go over just  
4 a little bit today was talking about the  
5 overall development and system constraints  
6 that we have as an industry.

7 So our presentation will cover  
8 general and internal considerations, user  
9 needs, product requirements, clinical and key  
10 development considerations, regulatory pathway  
11 time lines and looking ahead.

12 So what is needed and how do we  
13 get there? Technology, is it available? Does  
14 it need to be developed? Is it simple or  
15 complex? Are we looking at the entire  
16 spectrum of antigens or are we looking at a  
17 discrete portion of it?

18 Looking at development, and in  
19 this case what I mean is looking at the  
20 resources needed within the company to make  
21 the product. So are we going to make it  
22 internally or are we going to send it out for

1       being made? Do we have to hire people? Do we  
2       have to consider a clean room or a controlled  
3       environment?

4                   Clinical studies. Is this a rare  
5       antigen? How many donors are we going to  
6       need? How many sites are we going to need?  
7       What is the availability of the sample types?  
8       What will be the time line of the clinical  
9       study?

10                   We have to look at the controls  
11       that we'll utilize during this testing. Will  
12       they be a biologic or synthetic? Is a gold  
13       standard technology available for concordance  
14       or comparison?

15                   Research and development. How are  
16       we going to fund that? Who are we going to  
17       staff that with? Again, are we going to go to  
18       the outside for people? Are we going to bring  
19       consultants in? Are we going to outsource it  
20       or are we going to do it internally? And do  
21       we have to hire additional people?

22                   U.S. regulatory pathway. We heard

1 a little bit just a little while ago about  
2 510(k)'s and the amount of effort that is. We  
3 also have the PMA and the BLA routes.

4 Patents and intellectual property.  
5 How do we protect what we've created? And  
6 what is the overall time line from the very  
7 beginning to getting a product to market?

8 Concept. What is it? What will  
9 it be? Who will use it? How will it be used?  
10 When will it be used? That's all part of the  
11 considerations.

12 Life cycle. We have to look how  
13 long before the platform is outdated. Quite  
14 often a new technology can be outdated within  
15 5 years. What's the intended use? Screening  
16 of donors? Monitoring of the population? Are  
17 we looking for a discrete point in time of  
18 taking a test?

19 Design development. How long is  
20 it going to take from taking a concept to  
21 becoming a product?

22 Software verification and



1 validation. How does the software integrate?  
2 What does it do? How does it do it? It's  
3 every piece of software we have. Not just the  
4 piece of instrumentation we're talking about  
5 but everything that controls our manufacturing  
6 systems.

7 Risk analysis. What are the risks  
8 involved? How do we mitigate them? Test  
9 method validations, QC test method  
10 validations, batch records. There's a lot of  
11 paperwork that goes along with this.

12 Process validation. IQ, OQ and  
13 PQ. Installation, operational and process  
14 validations. We do that with every piece of  
15 equipment. We do it with every piece of test  
16 equipment.

17 Do we need a specialized platform  
18 that we developed or is one available out  
19 there? Is it going to be a bench test? Will  
20 it be designed for high-throughput testing  
21 with large batches? How about automation?  
22 Will it be fully or semi-automated?

1                   We heard before they're like a  
2                   black box. You put something in, get a result  
3                   out. It's a good concept. Might be hard to  
4                   do. Will we develop for routine screening or  
5                   for rare events?

6                   Laboratory training programs. We  
7                   have to look at is it going to be highly  
8                   complex or is it going to be a wave test? We  
9                   have to design the training programs for the  
10                  users involved. What types of controls will  
11                  we have? Do we need reference panels?

12                  Military use. Does it have to be  
13                  smaller, possibly portable, possibly able to  
14                  withstand combat conditions? Is there a  
15                  special or non-standard environment? High  
16                  altitude, desert conditions.

17                  Will the technology replace an  
18                  existing test or offer a unique benefit?

19                  We've heard a lot about analytical  
20                  sensitivity, analytical specificity. Of  
21                  course -- yes, I'm in regulatory affairs. I  
22                  get to deal with regulators worldwide. My job

1 is easy if I have 100 percent sensitivity and  
2 specificity. Anything less than that is we  
3 start having a conversation. So we would  
4 prefer to be having the 100 percent also.

5 The interference. What will stop  
6 the product from working?

7 Precision repeatability and  
8 reproducibility. We have to make sure it  
9 works in every lab the same way wherever it  
10 is, whichever technician is running it.

11 Stability. We're looking at end  
12 of life but you're looking at also onboard and  
13 in use.

14 And then we start talking about  
15 populations and genetic considerations. What  
16 we may make for one population, say the U.S.  
17 population, may not be sufficient to work  
18 properly in the Mediterranean or Asian  
19 populations.

20 What are the sample requirements  
21 that we're going to have to use? Is the  
22 sample blood, urine, tissue, saliva, DNA, a

1 combination of those? Can we use bank  
2 samples? Will we need informed consent?

3 What will be sample storage  
4 conditions? We want them ambient,  
5 refrigerated, frozen? Where should samples be  
6 obtained? Should they be gotten at remote  
7 areas and then shipped to a central  
8 laboratory?

9 What are the statistics that drive  
10 the sample size? How many samples will be  
11 needed? How many sites will be needed?  
12 What's the rarity of the sample size and the  
13 sample size required?

14 What sites can be used? We have  
15 to have geographically diverse. But then we  
16 look at the site capabilities. Is the site  
17 capable of doing this test? And if they're  
18 capable are they available? And if they're  
19 available do they have the patient population  
20 we need? The sites we use also have to  
21 represent the intended user group.

22 How long will this take to become

1 a product? What's the cost of clinical  
2 studies? It's a very significant  
3 consideration. At one startup company I was  
4 with we spent over \$2 and a half million on a  
5 clinical trial following people from inception  
6 of disease till death.

7 When we're looking at  
8 reimbursement it's not always predictable nor  
9 reflective of the value to the healthcare  
10 system. Funding is also a consideration for  
11 startup and established corporations. That  
12 same company I was talking about a few moments  
13 ago, we spent \$25 million before we got our  
14 first product to market. That is a lot of  
15 money for a startup and it's sometimes very  
16 hard to get.

17 Where will this product be sold?  
18 U.S., Canada, Europe, China, Japan, Brazil?  
19 Each one has their own regulatory  
20 requirements. In the U.S. it's the 510(k),  
21 PMA or BLA. But around the world we can look  
22 at licensure or approvals and each country is

1       wanting a different requirement.

2                   Are there opportunities to better  
3       incentivize product development for unmet  
4       clinical needs? Well, we hope so.

5                   Could early advisory meetings with  
6       FDA facilitate the process? If you have a  
7       novel product or a new technology, absolutely,  
8       and I would encourage that. I've found it  
9       very useful and extraordinarily helpful.

10                  What guidance documents might be  
11       available? Well, there's a lot of guidance  
12       documents and some of them are old, some of  
13       them are brand new. So when we look at the  
14       guidance documents we're not only looking at  
15       what's current, we're looking at some of the  
16       old ones and to see what is pertinent to our  
17       product. The guidance document for a  
18       particular product might be 10 years old. But  
19       if you compare the old one to a new one you're  
20       getting current FDA thought. So you really  
21       want to kind of do both.

22                  Developing a new product and

1 preparing for submission can be 3 to 6 years.  
2 It's not fast. We heard a company earlier  
3 saying it was 6 years.

4 Clinical studies can also be very  
5 lengthy. As I mentioned we had one that was  
6 over 2 years long.

7 Then you look at the regulatory  
8 review times. It varies with the type of  
9 submission and the country you're going to.  
10 It's not uncommon -- some of the easier  
11 submissions, the 510(k)'s can take 45 days.  
12 They're looked at very quickly, very smoothly,  
13 and they go through. Others aren't that easy.  
14 When we look at say China, that could be a 2-  
15 year process.

16 And then we add on top of that  
17 reimbursement. If we need a new code now we  
18 have a significantly longer time. So this  
19 isn't quick.

20 So, looking ahead. There's  
21 definitely different opinions on what's really  
22 needed. What is the unmet need? It's always

1       an issue. Quite often it's unsure what that  
2       is and we try to address that.

3               What technology today is there and  
4       where is it going? We will clearly have  
5       additional regulatory constraints in the  
6       future and reimbursement is probably not going  
7       to get easier. Funding will also continue to  
8       be an issue.

9               Medical devices are continually  
10       getting smaller and faster with more  
11       versatility. Science is continuing to add new  
12       possibilities. Thank you.

13               (Applause)

14               DR. BUSCH: Thanks very much. The  
15       final presentation is Dr. Susan Stramer again  
16       from the Red Cross. And Susan is going to  
17       talk about the implications for donor and  
18       blood product management.

19               DR. STRAMER: Thanks, Mike. Good  
20       afternoon. It's nearly the end of the  
21       sessions. I'm the last formal presentation.

22               So as Mike said my topic is



1       implications for donor and product management.  
2       So what I'd like to call this in short is a  
3       reality check.

4               So my goal as outlined in the  
5       materials for this meeting are to address some  
6       of the considerations and challenges for the  
7       implementation of next-generation nucleic acid  
8       and protein-based testing technologies applied  
9       on multiplex platforms for the application to  
10      ID screening.

11              So what I'd like to really focus  
12      on as I said in my goals is implementation.  
13      So some of this will be similar to the  
14      presentation that you just heard where we're  
15      listing all of the things that we must  
16      overcome. But you know, these are the things  
17      that need to be discussed so again we're able  
18      to move forward.

19              So just for some clarifications,  
20      you know, we frequently equate donor with  
21      donation screening and they're very different.  
22      Donor screening is donor suitability testing

1 or health history to make sure we're  
2 collecting from appropriate donors. And then  
3 donation screening is actually testing which  
4 is what we're talking about.

5 So my presentation, as I call it  
6 the review, considers the implementation of  
7 one marker on one platform. And that's a very  
8 important concept because what we do, even if  
9 it's multiplexed we still have to deal with  
10 one agent at one time.

11 So multiplexing will save effort  
12 but all steps related to each unique agent are  
13 still required. We don't notify a donor that  
14 you have a multiplex reactive result. We have  
15 to notify them of specifically what they have  
16 and what it means.

17 So multiplexing will save use of  
18 one versus multiple systems but what my  
19 concern is that we'll be consumed in some part  
20 by the effort required to sort and verify  
21 reactivity or the integrity of each individual  
22 test that's required to carry on further

1 steps.

2 Now even though we may have  
3 multiplex systems that give us a final answer  
4 we probably still will do additional testing  
5 to verify that final result prior to giving a  
6 result to a donor.

7 So going through processes which  
8 we really haven't touched on here, we started  
9 donor collections. And something that I  
10 didn't even think of and I gleaned over from  
11 my next slides is I assumed collections would  
12 not change. And maybe that's an error that I  
13 made in assuming for this presentation.

14 And in all of the processes we  
15 can't make any errors of assumptions, assuming  
16 things won't change. Because one of the  
17 themes of my talk here is everything is up for  
18 grabs. And when we make changes we implement  
19 the entire system. So they're not testing  
20 changes, they're really process changes.

21 So when Dr. Linnen went through  
22 his presentation about multiplex test and

1       talked about the different number of tubes,  
2       each tube may contain up to six tests. Four  
3       tubes with six tests or six tubes with four  
4       tests, each of those tubes requires a half a  
5       ml input. So that really changes then the way  
6       we do donor collections. We just don't put  
7       one tube on an analyzer.

8               So we start with collections, go  
9       through product labeling including recipient  
10      investigations of if we have transfusion  
11      transmissions whether it's triggered by a  
12      seroconversion in a donor or whether it's  
13      triggered by a hospital notifying us of a  
14      clinical case in a recipient. But everything  
15      that I mention from the beginning to the end,  
16      or someone yesterday mentioned vein to vein,  
17      it all uses regulated processes and documents.

18             So changes in testing touches  
19      multiple quality systems within a blood center  
20      operation and to its consignees. Changes in  
21      the associated verifications and validations  
22      will require hundreds of procedures and

1 process changes, and also computer  
2 configuration changes and their validation.  
3 So all of this is complex to say the least.

4 Here in my process slide, again I  
5 didn't include donor collections because I  
6 assumed that that's something that wouldn't  
7 change. So all of these impact changes in the  
8 system. Donor registration, the way we take  
9 health history and the way we assess donor  
10 suitability. Jeff also mentioned malaria  
11 testing.

12 In a perfect world we'd have a  
13 great DNA test for malaria and could get rid  
14 of the donor malaria questions that we ask.  
15 That would be an unbelievable kudo.

16 We need to have consent that  
17 requires signature. We provide information  
18 sheets letting donors know what they will be  
19 tested for. And that was alluded to in  
20 questions yesterday. All of those materials  
21 that go to donors have to be produced in  
22 multiple languages. So if we're doing

1 research tests we have to let donors know at  
2 the beginning that we're doing that and that  
3 has to be available again in whatever language  
4 the donor is familiar with.

5 Testing, we can do realtime  
6 testing. We can do delayed or in-process  
7 testing as Mike referred to.

8 And let me just comment on in-  
9 process testing. When we implemented in-  
10 process testing the reason we did that is  
11 because we the blood centers told the  
12 regulatory agencies that we couldn't do  
13 anything but in-process testing in that we  
14 couldn't have results realtime.

15 Well, that's not true anymore.  
16 There are two duplex tests available for parvo  
17 and HAV. So I asked the question is in-  
18 process testing for transfusion-transmissible  
19 agents that do cause morbidity and mortality  
20 in recipients, maybe it's all relative what  
21 the numbers are, but is that model still  
22 justifiable?

1           Another type of testing we do is  
2           confirmatory and supplemental. And I again  
3           would urge that that's ripe for the pickings,  
4           ripe for us doing something smarter for the  
5           way we confirm reactive results.

6           We have to integrate the results  
7           of all of our testing algorithms into a  
8           composite interpretation for the donor. So  
9           anything changes, changes all of that.

10          We have donor deferral  
11          notification and counseling. We enroll donors  
12          in follow-up. That requires consent. There's  
13          a whole process for that.

14          And lastly, we always want to  
15          consider donor reentry. We have processes for  
16          quarantine labeling and release. These are  
17          all impacted when we make changes. Consignee  
18          notification, product quarantine retrieval,  
19          recipient tracing, also recipient  
20          complications. Our hemovigilance program,  
21          what are we going to see.

22          And then with all of this we have

1 to consider also the impact of pathogen  
2 reduction technologies and how those also will  
3 change all of these processes.

4 So we've already gone over this.  
5 I created these slides obviously before I  
6 heard 2 days of talks so I don't need to again  
7 repeat the types of testing technologies that  
8 we have.

9 But consider these testing  
10 technologies probably started in the late  
11 nineteen thirties, early nineteen forties. So  
12 how long is it going to take for us really to  
13 get to the next generation?

14 So we have a variety of serology  
15 platforms, nucleic acid platforms. Some of  
16 these platforms are single-test or multiple-  
17 test delivery systems. We have talked about  
18 black boxes. We already do have black boxes  
19 in that we put a sample in and get a result  
20 out. We have those for blood group serology,  
21 for serology, infectious disease serology and  
22 for NAT. So to some degree multiplex multi-



1       array systems are already in use today. And  
2       of course we want to encourage their further  
3       development.

4               So Ed showed this slide. I showed  
5       this slide yesterday but then only to again  
6       reinforce the fact that we have good systems  
7       for screening although we need to be vigilant  
8       about what's out there that we're not  
9       considering that could be a threat. But  
10       again, the supplemental tests to me are a  
11       really nice place to start to bring new  
12       technology for a limited scope into a blood  
13       center environment.

14              So how do we get there? We have  
15       to define a need and I think that's already  
16       been alluded to. Why are we doing this?

17              We need a concept, the type of  
18       analyte detection that's needed. We'll do  
19       pre-clinical studies, clinical trials with all  
20       the bells and whistles, linked using donor  
21       recipients as our subjects. So we will need  
22       consents and again information sheets. We'll

1       need materials for notification and  
2       counseling.

3               Again we'll go through follow-up.  
4       We'll have to validate the index test results  
5       by doing donor follow-up or retesting an  
6       independent sample. We'll have to take  
7       product actions.

8               All of this involves INDs and  
9       institutional review boards. We have to  
10      consider how we recover our cost and will all  
11      of our cost be recoverable.

12              Will we do post-marketing studies  
13      as part of further validation studies? And  
14      even if we do post-marketing studies many of  
15      the above considerations, that is IRBs, will  
16      still be part of the mix.

17              We have to consider  
18      implementation, then our assessment and  
19      assessment of the success of the  
20      implementation. And of course tweaks always  
21      occur once we implement something.

22              So I sent around emails to the

1 various departments at Red Cross to say when  
2 we implement a change, what happens. So I'm  
3 just going to go through one of the responses  
4 that I got and that's from our testing groups.

5 So this is two pages of items that  
6 have to be done when we make a change  
7 regardless of how small. So when I call and  
8 want to institute a change at the Red Cross  
9 people want to hang up on me because they  
10 really don't want to go through the nightmare  
11 it takes to get change implemented in a CGMP  
12 environment.

13 So we write user requirements and  
14 specifications, contact vendors to request for  
15 information. We select a vendor and a  
16 product. We do feasibility studies. They  
17 could be post-marketing. We write our  
18 contracts. We go through change control. We  
19 identify the stakeholders and who's going to  
20 be part of this project. We perform review of  
21 our vendor materials.

22 Then we define and redefine the

1 scope. We develop our project plan for  
2 implementation, determine who's going to do  
3 what. Frequently we have to develop a  
4 business case so that we get final approval  
5 from the business.

6 We engage our IT department with  
7 changes to electronic transfers of test  
8 results. This is highly complicated. And we  
9 identify high-level risks.

10 This continues. We write  
11 procedures. We develop communication plans.  
12 We obtain materials for PT surveys. We notify  
13 regulatory agencies. We verify changes to  
14 scope, timing and our cost, release documents  
15 for training, arrange standing orders with  
16 vendors, perform our qualification, our  
17 operational trials, implement the assay,  
18 measure the effectiveness of the project,  
19 close all of our change control documents and  
20 monitor the effectiveness of the change.

21 Now to go through -- that's for a  
22 typical license test. But Mike and I

1 yesterday have both highlighted Babesia as  
2 something we're doing that's really outside of  
3 the traditional way that we've operated in the  
4 past.

5 We've had an IND protocol with  
6 IMUGEN, another small company in the Northeast  
7 for about 1 year now. We've tested about  
8 60,000 donations both retrospectively and  
9 prospectively, have about 300 identified  
10 donors who were reactive, over 150 of those  
11 who were actively participating in follow-up.  
12 So a lot will be learned from these  
13 investigational studies.

14 One thing that we have learned is  
15 just like we think we know for all the other  
16 agents there's an early phase of infection and  
17 a late phase of infection so you really need  
18 to interdict at both ends, that is a PCR-based  
19 method and an antibody-based method.

20 So we took this through our change  
21 control as I highlighted in prior slides. We  
22 have a million steering councils that we have

1 to go through, project steering councils,  
2 executive leadership councils are required for  
3 approvals.

4 So rather than opening hundreds of  
5 system documents to implement this change we  
6 did one universal SOP which we call a BSL, not  
7 for Blood Systems Laboratories but blood  
8 systems ladders, the regulated procedures, and  
9 we coupled those with local SOPs so that we  
10 could implement testing.

11 And this was -- although this was  
12 a simple approach it still was highly complex.  
13 So currently we're doing testing in highly  
14 endemic counties in four states. We have a  
15 cost recovery model. It's not implemented yet  
16 because we have to make changes to our  
17 computer system. Currently the Red Cross is  
18 embroiled in one of the most complicated  
19 changes that the organization has ever gone  
20 through and that's changing our national  
21 computer system. So we have to, so to speak,  
22 get in the queue to make changes to implement

1 Babesia testing electronically.

2 The process involved an IRB. We  
3 have thus far had seven amendments with  
4 another amendment in continuation just  
5 submitted today. We've had IND approvals that  
6 involved 22 IND amendments. And again we have  
7 to give our senior management and change  
8 control routine updates.

9 So as far as our 1 procedure it  
10 involved 21 attachments. And I'm not going to  
11 give you a listing of all the local  
12 attachments. But listed here in bullets all  
13 of the attachments that we had to do be it  
14 from collecting samples for routing for  
15 testing to receiving test results, entering  
16 test results in the computer system, deferring  
17 donors, notifying donors, follow-up of donors,  
18 recipient notifications, et cetera. So it's  
19 quite complicated even for 1 small change let  
20 alone 20 or 30 that we may want to do for  
21 emerging infectious diseases.

22 So now I want to take us really

1 back to reality and what is the value. So we  
2 have to ask with all of these changes, I think  
3 it's apparent for Babesia, but why -- we have  
4 to ask ourselves the question why is the  
5 change being made. Will it add to recipient  
6 safety? What triggers action? Are we  
7 responding to an emerging infectious disease  
8 agent or threat? Is such action warranted to  
9 address safety?

10 The technology will exist to test  
11 for hundreds of agents. Are the agents  
12 transfusion-transmissible with clinical  
13 outcome in recipients? I think this gets back  
14 to Harvey Alter's comment is we start with the  
15 disease. What questions are to be answered to  
16 determine if safety is added? We need to be  
17 able to address transmission before and after  
18 the intervention to truly address our success.  
19 And then of course, are further changes  
20 required?

21 So again, will what we're doing  
22 add to public health? A question that we ask



1 or we get asked, are blood centers part of the  
2 public health system? I think we believe we  
3 are but we're not reimbursed as if we are.

4 Will what we do reduce cost? Will  
5 it reduce complexity for the system? This  
6 gets back to what Ed Notari covered.

7 And if cost is to increase, who  
8 will pay? And any change -- I remind us of  
9 regardless of how simple it may appear adds  
10 cost.

11 So in closing, multiplex multi-  
12 assay systems are available today. But even  
13 though they are we still encourage further  
14 development. Adding new agents and platforms  
15 need to be considered carefully. What problem  
16 are we trying to fix? Is it real? Is it  
17 quantifiable? Or do we have to model it with  
18 many assumptions that may not really, truly be  
19 reality?

20 Change is complicated and costly.  
21 And who will bear the burden of these costs?  
22 And we need to assess the availability and

1 success of alternate technologies at the same  
2 time that we'll be competing for our attention  
3 and our resources including pathogen  
4 reduction.

5 And I think that's it. So thank  
6 you. I'm sorry if I left you with more  
7 questions than answers.

8 (Applause)

9 DR. BUSCH: Thank you, Susan, very  
10 sobering. So we have about 10 minutes to  
11 break. But we will reconvene at 10 after, so  
12 about 12, 13 minutes. Then we'll have an  
13 initial small group discussion, then the large  
14 closing discussion.

15 (Whereupon, the foregoing matter  
16 went off the record at 3:00 p.m. and went back  
17 on the record at 3:25 p.m.)

18 DR. BUSCH: Paul Mied and Melissa  
19 Greenwalk from FDA, maybe you'd like to just  
20 briefly tell us your focus and then another  
21 person from the Department of Defense will  
22 introduce himself.

1 DR. MIED: Yes, I'm Paul Mied.  
2 I'm deputy director of the Division of  
3 Emerging and Transfusion-Transmitted Diseases  
4 in the Office of Blood in CBER.

5 DR. GREENWALD: I'm Melissa  
6 Greenwald and I'm in the Division of Human  
7 Tissues in the Office of Cellular Tissue and  
8 Gene Therapies. And so I'm largely interested  
9 in testing tissue and organ donors.

10 MAJ. DITUSA: Hi, I'm Major Chuck  
11 DiTusa. I'm the project manager for rapid  
12 transfusion-transmitted disease diagnostics  
13 with the United States Army Medical Materiel  
14 Development Activity. We're currently in the  
15 process of moving both a rapid amino assay and  
16 a NAT test through the approval process.

17 DR. BUSCH: Great, thank you. So  
18 we have these questions that were sort of  
19 developed by FDA with input from the  
20 organizing committee. And then we can open it  
21 up to the group as a whole.

22 So the first, how should multiplex

1        assay be validated as safe and effective for  
2        detection of each pathogen in an assay for  
3        many pathogens?

4                    DR. MIED:  Mike, I just wanted to  
5        say at the start that you said it right.  
6        These are questions that have been formulated  
7        by FDA.  And so they really I don't think are  
8        for FDA to answer at the present time.  What  
9        we're here to do is to listen to what industry  
10       has to say about how we can facilitate the  
11       introduction of these types of multiplex assay  
12       systems.

13                   We really are interested in  
14       encouraging development of multiplex test  
15       platforms by lowering the barriers that exist  
16       to the development and the approval of these  
17       multiplex technologies for donor screening is  
18       what we're addressing specifically here.  So  
19       we're interested in talking about and hearing  
20       your ideas, the ideas from the test  
21       developers, the test manufacturers as well as  
22       the blood organizations about how we can

1 streamline clinical trials, the pre-clinical  
2 studies, the analytical studies so that we can  
3 proceed in reducing the costs of all those  
4 studies to expedite the availability of these  
5 platforms for blood screening.

6 DR. BUSCH: Well, we heard from  
7 John, you know, a nice sense of how CDRH has  
8 sort of attempted to do the same thing in the  
9 diagnostic arena and negotiated, it seems  
10 like, some substantial I wouldn't call them  
11 compromises but balanced rational approaches  
12 to reduce the required sample number, the  
13 expectations in terms of numbers and the  
14 unique characteristics of many of these  
15 samples results in the inability to achieve  
16 the kind of numbers often that you used to  
17 require.

18 And of course CDRH requirements  
19 are substantially less onerous than CBER  
20 typically for blood as a biologic. So can we  
21 follow that lead? Can there be a beginning  
22 discussion with manufacturers and/or with the

1 CDRH as to would those same or some of those  
2 same compromises be reasonable for blood-  
3 related diagnostics?

4 DR. MIED: Well, I think those are  
5 -- that's a very valuable guidance. It's  
6 certainly very helpful. It is for the  
7 diagnostic setting.

8 As we talk about test platforms  
9 for use specifically in blood banks some of  
10 the same considerations will apply. But as I  
11 said before we certainly are interested in  
12 looking at ways to streamline the clinical  
13 trials, reduce their costs. And some of the  
14 things that CDRH has put into that guidance I  
15 think are very helpful to us. But we want to  
16 hear from industry about ways that we can do  
17 those things.

18 DR. STRAMER: If I may comment.  
19 Actually what CDRH presented was extremely  
20 impressive I think, an overall 80 percent  
21 reduction.

22 I think from talking to some of

1 the diagnostic manufacturers and I know with  
2 Brian you're going to make a comparable  
3 comment from manufacturers' perspective. I  
4 think harmonization between CDRH and CBER is  
5 one, it's not directly answering the question.  
6 I think we talked about it in AdvaMed meeting  
7 as well. So if you have a certain test you  
8 have to submit a separate filing to CDRH if  
9 you want a diagnostic claim and then to CBER  
10 if you want a blood donation screening claim.  
11 So that's two sets of clinical trials, two  
12 sets of positive populations that you have to  
13 resource. The trials are a little bit  
14 different in scope. I mean the way CDRH runs  
15 against a predicate device, you know, control  
16 device. So I think that's one comment that  
17 I've heard in the past, if we could harmonize  
18 between the two centers that would be a  
19 tremendous regulatory burden.

20 But to just my own personal  
21 experience from being on both sides of this in  
22 industry in my time working with blood

1 actually I don't think the CBER regulations or  
2 the requirements for blood donor screening,  
3 that is clinical trials are really that  
4 onerous. I think some of the pre-clinical  
5 validations or antigen characterizations may  
6 be a lot of what is more costly.

7 And from now a user I'm happy that  
8 we do robust clinical trials because I think  
9 one thing that we're frustrated with is  
10 sometimes the performance of the assay when  
11 you run 22,000 samples a day or half a million  
12 donations a month doesn't parallel what you  
13 see in clinical trials when they're really  
14 small with only 10,000 or so donations.

15 So I mean the clinical trial is  
16 supposed to prove safety and efficacy, but  
17 then it may not prove reality. And that's one  
18 of the concerns that I have when we actually  
19 implement the test.

20 DR. BUSCH: Thank you. Melissa?

21 DR. GREENWALD: So I have a  
22 comment that I won't say is in response to



1 Sue's comment because I just thought of it  
2 before you started speaking. And I don't want  
3 anyone to get the wrong impression.

4 But I also though wanted to sort  
5 of add onto what was being discussed right  
6 before and some of the things that were  
7 discussed yesterday about so if we're talking  
8 about looking at the approaches that CDRH is  
9 taking for some of these diagnostic assays and  
10 then some of the things people have been  
11 talking, specimen types and specimen handling  
12 and how important that is to consider, one of  
13 the things that I can see after a recent  
14 workshop we had talking about organ donor  
15 testing is that some of the clinical questions  
16 actually about whether or not these specimens  
17 are different from each other haven't been  
18 well established.

19 And also though looking at  
20 different types of specimens when we're  
21 testing organ donors we're testing people who  
22 are brain dead. And when we're testing tissue

1 donors we're testing specimens collected after  
2 someone has died. And it'll be very important  
3 to develop some panels or something. We can't  
4 take an approach like CDRH described when the  
5 tools that they're using to evaluate those  
6 assays haven't been developed for those  
7 different types of specimens which is  
8 something that I'd like to bring up for people  
9 to keep in mind.

10 DR. BUSCH: Okay. Brian  
11 McDonough, please.

12 MR. MCDONOUGH: Yes, I want to  
13 address Paul's question which was how can we  
14 help.

15 Currently there are significant  
16 hurdles for any what I would call a naive  
17 company, a new company that wants to bring in  
18 a complete testing system to the U.S. donor  
19 screening market.

20 And that was made all the more  
21 difficult by the recent decisions of both the  
22 Red Cross and CTS to go single source.

1       Because what that has done is narrowed the  
2       window of opportunity for a new company to  
3       gain either the Red Cross or the CTS business.  
4       Because if you miss that window you have to  
5       wait another 5 or 7 years to begin getting a  
6       return on your investment.

7                       So my question is that the process  
8       if you're a protein-based company is you've  
9       got a menu of at least six, probably seven  
10      assays by the time you could get to market.  
11      And the typical method for doing that  
12      historically has been to do an assay at a  
13      time. If you're looking at a multiplex system  
14      could you envision facilitating a  
15      comprehensive clinical trial process for all  
16      of the assays in the system in one process?

17                     DR. MIED: Yes, absolutely, I can  
18      see that. I can see there's certainly great  
19      value especially to a small company in doing  
20      that. So yes, we would do whatever we can to  
21      facilitate --

22                     MR. MCDONOUGH: Doing that might

1 shorten an otherwise 12-year time line down to  
2 4 or 5.

3 DR. MIED: Absolutely.

4 MR. MCDONOUGH: Which helps in a  
5 dramatic way reduce cost.

6 DR. MIED: Absolutely.

7 MR. MCDONOUGH: Thank you.

8 DR. KLEINMAN: Steve Kleinman,  
9 AABB. I have two questions and comments on  
10 two different aspects of this.

11 So the first one is we haven't  
12 talked that much yet about the information-  
13 handling regulatory issues that might come up.  
14 And I think -- and I suppose it depends on  
15 which system ultimately gets presented to FDA.

16 But many of these systems we heard  
17 about today for nucleic acid testing have  
18 complicated computer algorithms internally  
19 within the device to generate an output. And  
20 I know FDA has certain requirements for  
21 decision-making, you know, for computerized  
22 decision-making when this is put into the CGMP

1 environment of blood banks.

2 And I think, I don't know whether  
3 that is also true for CDRH when they evaluate  
4 diagnostic tests but if it isn't I think we  
5 have -- that to me seems like a significant  
6 issue. And I don't have the answer to it but  
7 I'm hoping that people may talk about how you  
8 can not only validate the reagents and the  
9 automation but what your level of requirements  
10 are for validating the internal computer  
11 software to generate the answers. So Paul, I  
12 don't know if you have some -- I know you  
13 don't want to answer the questions but I think  
14 if you could give us a general sense of how  
15 that part is currently regulated it would be  
16 helpful going forward.

17 DR. MIED: Well currently of  
18 course we do review the software for every  
19 assay that comes to us. That's part of the  
20 approval process. So we understand that as  
21 these systems, for example, next-generation  
22 sequencing entail more and more complex

1 sample-handling and data analysis hurdles then  
2 we usually have seen this becomes a real  
3 concern about how that type of barrier can be  
4 overcome. But yes, again this is something  
5 that we're certainly looking at very closely.

6 DR. HOBSON: Yes, you can actually  
7 look at the CDRH website for computer  
8 validation systems. They are rather rigorous.

9 DR. KLEINMAN: Is there a  
10 difference? So my question is is there -- and  
11 maybe for the gentleman from CDRH and for  
12 Paul. Is there a difference in the rigor that  
13 the two parts of FDA look at the computer  
14 decision-making algorithms in an automated  
15 piece of equipment?

16 DR. HOBSON: So I'm actually not  
17 familiar with CBER's approach to it. I'm  
18 going to speak only on CDRH's.

19 We look at everything in its  
20 entirety. All the automation steps are  
21 included in our review, all the software that  
22 controls that automation. And then also any

1 type of diagnostic algorithm that is used in  
2 output of the results all the way to that  
3 point we review.

4 Because we take a holistic  
5 approach. We've found that problems in the  
6 sample processing automation can have a  
7 downstream effect. So we actually do look at  
8 every step along the way and look at the  
9 validation of each of those processes and that  
10 software in its entirety.

11 There's actually been for CDRH  
12 specifically yesterday I think there was a  
13 guidance published specifically addressing  
14 some of these things.

15 DR. KLEINMAN: Yes. So I suppose  
16 I can't redesign the FDA but let me still make  
17 a comment. And that is that it might be  
18 helpful since some of these diagnostic  
19 devices, some of these systems are in front of  
20 CDRH first and you do evaluate these things  
21 and have cleared some systems, if maybe CDRH  
22 and CBER could talk.

1                   Because I think maybe CBER has in  
2 fact been -- taken a very, very, very  
3 stringent attitude towards these things in the  
4 past. And maybe if we're looking for ways to  
5 make things go faster you might have an  
6 algorithm that I'm sure is thorough but maybe  
7 is less onerous for applicants. So maybe you  
8 guys could talk.

9                   DR. HOBSON: Yes, I don't know  
10 that we don't talk. I'm sure we do.

11                   (Laughter)

12                   DR. HOBSON: But I think there's  
13 kind of some differences there. I mean we're  
14 evaluating -- the algorithms that they're  
15 going to use for the outputs on their devices  
16 are going to be different from our needs. So  
17 especially if it's some type of algorithm for  
18 the decision of what's in that sample. So  
19 they're going to have to apply their own kind  
20 of review principles to that.

21                   But in terms of streamlining the  
22 upstream kind of processing stuff I'm not sure



1       what the kind of level of communication is  
2       between us but --

3               DR. MIED:   Actually, there is a  
4       good deal of communication between our  
5       software reviewers and those in CDRH.  We're  
6       looking at the same things.  Now yes, we do  
7       have a level 3 of concern, a high level of  
8       concern for an agent such as HIV testing which  
9       you don't have very often in CDRH.  So the  
10      level of concern is different.

11             But still when it comes to hazard  
12      analysis and mitigation of risks we apply the  
13      same principles that CDRH does.  And there is  
14      a lot of back and forth between us and their  
15      reviewers.

16             DR. STRAMER:  I think the overall  
17      comment still goes back to the point I was  
18      trying to make about harmonization, whether  
19      it's in software systems, results input.  
20      Clearly there will be quantitative assays that  
21      will go through diagnostics and maybe only the  
22      qualitative claims will come through for a

1 blood donor screen. But still the general  
2 notion of how results are integrated into a  
3 final interpretation, what studies need to be  
4 done for licensure. I mean it would seem  
5 redundant to have two cycles of review and two  
6 submissions of data.

7 MAJ. DITUSA: If I can make a  
8 comment on that. The military's interest is  
9 a little bit different than the standard  
10 civilian blood bank blood donor screening  
11 test. We are in the process of developing a  
12 product that will be used in the field in  
13 situations where blood transfusions have to be  
14 made and we don't have traditionally FDA-  
15 approved blood components to use. So we need  
16 a point of care device that can serve as a  
17 blood donor screen in that urgent situation.

18 Right now we're working with both  
19 CBER and CDRH to get that approved because it  
20 also has a diagnostic claim. And HIV and  
21 hepatitis B and hepatitis C are all on the  
22 same device.

1                   And so we've found that although  
2                   there are differences in the requirements from  
3                   both centers they've been pretty flexible with  
4                   getting together and working with us and  
5                   helping to get some of those requirements to  
6                   meet both. And we're going to be able to put  
7                   in a package that will simply duplicate both  
8                   centers and have one PMA for the device from  
9                   both centers. So that can be done.

10                  DR. STRAMER: I think that's great  
11                  for the military and the military may have  
12                  more clout if you will than civilian blood  
13                  centers when we go to CBER.

14                  But you know, I've heard this from  
15                  all of the manufacturers. And I know we've  
16                  discussed it at AdvaMed, that it's not always  
17                  that simple for the routine test kit sponsors.

18                  MAJ. DITUSA: Right. The intended  
19                  use here is much narrower so I'm sure we'd be  
20                  getting some consideration for that.

21                  DR. BUSCH: Steve, did you have  
22                  one point?

1 DR. KLEINMAN: Yes, but I can  
2 wait. It's on a different topic.

3 DR. BUSCH: Okay, please.

4 MR. BINDER: Steve Binder from  
5 Bio-Rad Laboratories. Just in the interest of  
6 getting things on the table for the FDA, two  
7 other considerations.

8 One is the special collections  
9 that are required. There's been some talk  
10 already about how many samples need to be  
11 tested. But there's always special  
12 collections such as pregnant women.

13 One of the problems today is that  
14 we live in a post-HIPAA world. Some of these  
15 things that were a lot easier to do in the  
16 nineties or even 10 years ago than they are  
17 now. So the special collections requirements  
18 are often very onerous and add significant  
19 time to preparing a submission.

20 Another point I'd like to make  
21 because we do have experience with multiplex  
22 assays on the diagnostic side is that the more

1 analytes that you have in a multiplex test if  
2 it's in a protein-based test at least the more  
3 likely that you're going to need to make  
4 changes.

5 Because if you have one analyte  
6 there's one system that might need updating.  
7 If you have 10 analytes there's 10 systems  
8 that might need updating. And the process for  
9 changing on the blood bank side is  
10 significantly more onerous than on the CDRH  
11 side. And that can also be scary and might be  
12 one reason why launching kits quickly in the  
13 U.S. is not that easy to do.

14 DR. MIED: Yes, this is actually  
15 question number two. When a manufacturer  
16 makes a change either they're adding the  
17 pathogen or taking out a pathogen out of their  
18 multiplex assay of 20 or 30 or 40 pathogens.  
19 Or if they're changing the reagent, some of  
20 the critical reagents in the multiplex assay.  
21 What level of validation do they need to go  
22 through to make that type of change? This is

1 one of the questions we're asking.

2 DR. BUSCH: Right, but the problem  
3 is who's going to answer that.

4 DR. MIED: Oh, I can answer that.

5 DR. BUSCH: That's the problem,  
6 that we have not seen the changes. The reason  
7 RIBA's not here anymore is because we were  
8 getting a test that was being manufactured for  
9 20 years exactly the same but they didn't even  
10 have the historical kind of -- they didn't  
11 update it because the onerous, quote,  
12 "onerous" process that would be required to  
13 take it to a next generation or enhance it.  
14 So I don't know the barriers but clearly there  
15 are substantive costs and regulatory barriers  
16 to updating and modifying existing tests.

17 And the first issue, I mean in the  
18 U.S. once a test is licensed it is licensed  
19 and there is no ongoing systematic sort of  
20 reassessment and determination that the test  
21 still meets requirements other than through  
22 user feedback unlike in Europe where they seem

1 to go through iterative reassessments.

2 So it's really only when that --  
3 therefore the barrier to licensure here, at  
4 least for blood screening, is large because  
5 once it's on the -- available it's available  
6 forever until it's replaced by an individual  
7 manufacturer.

8 Yes, even with single analyte  
9 assays both these things are very problematic.  
10 And then as soon as you're into multi-analyte  
11 tests it just adds another level.

12 DR. LINNEN: I wanted to comment  
13 on that if I could. Because Mike is exactly  
14 right. We really hesitate to change the  
15 design of an assay after a period of time even  
16 though we see evidence that, well, the assay  
17 could be better if we made some modifications.

18 But I think we're at a point now  
19 where we could start doing that kind of thing  
20 because there are a lot of really good panels  
21 that have been developed. If we had a  
22 standardized way with clinical specimens and

1       move a lot of the testing outside of doing  
2       outside clinical studies to in-house testing  
3       at the manufacturer. If they're using  
4       standardized panels to prove the clinical  
5       sensitivity is the same.

6               The specificity doesn't  
7       necessarily have to be run at a blood center  
8       site. We're using the same instruments, the  
9       same samples. Specificity could be assessed  
10      in-house. We save a lot of money doing those  
11      kind of studies in-house. And I think the  
12      quality of the data is just as good. So I  
13      think that's one approach.

14             And then when you validate an  
15      assay initially the studies that you do make  
16      a lot of sense. But if you're just making a  
17      change to the nucleic acid component of the  
18      test you can look at the different factors  
19      that might be affected by that change and just  
20      validate those.

21             For example, we look at all kinds  
22      of problematic samples like high lipemic



1 samples and things like that. If we can  
2 convince people with our science that this  
3 change doesn't affect that kind of thing we  
4 just validate what we consider might be  
5 affected by the nucleic acid change. So I  
6 think that's the general approach to  
7 streamlining, small changes, primary changes,  
8 for example.

9 DR. MIED: Yes, Jeff, I agree with  
10 you. The main thing we look at of course when  
11 you add a pathogen to a multiplex assay is  
12 that you haven't reduced the sensitivity of  
13 detection of any of the other agents. So what  
14 you're suggesting I think can certainly be  
15 done. You don't need to do the full-scale  
16 validation again that you did initially.

17 DR. HOBSON: I'd like to add  
18 something to that. I agree with what the  
19 gentleman said. I mean and we take that  
20 approach.

21 But one of the things we've found  
22 helpful is to really kind of bin the changes.

1 I mean there's different types of changes.

2 One of the things we wanted to  
3 avoid was when somebody puts together a 15-  
4 plex and then all of a sudden 2 years later  
5 their competitors put out a 20-plex and they  
6 say oh, well I want to add these 5 and then 10  
7 more. You know, we want that stuff designed -  
8 - the homework done ahead of time.

9 Adding an emerging pathogen is  
10 something that we see as a higher priority  
11 than kind of reshaping the focus of your  
12 multiplex. And then also ways to kind of  
13 correct performance degradation, that's  
14 something that we saw as key.

15 So if you kind of put them in  
16 different bins and come up with a logical  
17 approach, you know, look at what validation  
18 experiments are necessary to repeat and which  
19 ones really are not. That's how we've  
20 actually tackled that problem too.

21 DR. BUSCH: Excellent, thank you.  
22 Please.

1 DR. SLEZAK: Tom Slezak from  
2 Livermore. At the risk of changing the focus  
3 here from bash the FDA or save money on  
4 industry testing I have a science-based  
5 question I'd like to ask.

6 One thing that didn't come out in  
7 my bioinformatics session was that there's a  
8 fundamental difference I think between next-  
9 gen sequencing and PCR and microarrays. And  
10 that's with PCR we're very comfortable with  
11 the results because we know first of all  
12 bioinformatics went to pick which regions and  
13 then you test the heck out of them so you're  
14 sure they work. Microarrays are designed  
15 similarly and can be tested reasonably  
16 similarly.

17 With the sequencing from some of  
18 the data that was shown you don't know what  
19 regions you're going to get. And so my  
20 question is more of a rhetorical one to later  
21 but I'd be happy to have any answers you might  
22 have. How much is enough?

1                   So the deep sequencing I've seen  
2           from blood samples, if you blast and look  
3           deeply enough you'll find hits to, for  
4           example, just about every category A pathogen  
5           because there's at least one read there that  
6           has significant homology at maybe 50 or more  
7           base pairs at 90 percent homology to some  
8           piece of something that you'll see showing up  
9           in BLAST as a cat A pathogen primarily because  
10          that's what we've sequenced the heck out of  
11          and populated the databases with.

12                   So I think this is something that  
13          as regulatory agencies you will have to tackle  
14          is what are the algorithms. How do you know?  
15          How many reads? What regions do they have to  
16          hit on? And how do you get around the fact  
17          that you're not going to see deeply enough  
18          those pathogens if you're doing unbiased  
19          sequencing?

20                   Come on, Peyton, you're the  
21          science-based guy. Go ahead.

22                   DR. BUSCH: One point. Are there

1       any in deep sequencing or next-gen sequencing  
2       based diagnostics cleared?

3                   DR. HOBSON:   Not at the moment.  
4       But there's -- there's a lot of reasons why  
5       too.   I mean as you saw in a lot of the talks  
6       really the back end comparator data sets may  
7       not be there yet for regulatory use.

8                   There's, you know, GenBank for  
9       what it is is great as a research tool but it  
10      may not have the level of quality and the  
11      level of certainty to make a diagnostic call  
12      or a screening call.

13                  The other problem is, you know,  
14      these tests are not quite there yet.  They're  
15      on their way but they're really not there in  
16      terms of cost yet.  So I think there's  
17      probably going to be a little bit of a lag in  
18      terms of clinical incorporation.

19                  But the biggest, kind of the  
20      fundamental hurdle is everything that Tom just  
21      summarized in his statement, question there's  
22      a lot of unknowns that we still have to work

1 through as a regulatory agency so that these  
2 things can eventually be adopted in the clinic  
3 for diagnostic use and then also I would  
4 assume for also blood screening use too.

5 DR. BUSCH: Is it reasonable to,  
6 from our perspective, say these tests should  
7 get cleared and get used in the clinical  
8 diagnostics arena? I mean NAT for blood  
9 screening was 10 years behind PCR for viral  
10 loads, et cetera, et cetera. And a lot of  
11 kinks have been worked out, et cetera. So  
12 should we be waiting to think about next-gen  
13 sequencing based blood screening until there's  
14 a few years of approved tests?

15 DR. HOBSON: I'm really not the  
16 person you want to address that question to.  
17 I mean I have my own opinions and I'll gladly  
18 share them with you. But I think we heard at  
19 this talk today, or at these presentations  
20 today that maybe next-generation sequencing  
21 maybe is not ready for prime time for stuff  
22 like this. Maybe it is, I don't know. But

1 just sitting back in the audience that's kind  
2 of a recurring theme in many of the talks. So  
3 I think that's something that the CBER folks  
4 would have to really work out and address for  
5 their needs.

6 DR. BUSCH: Okay, we'll take this,  
7 please.

8 DR. NEDJAR: Sayah Nedjar, OBRR,  
9 CBER. I just have a couple of actually  
10 comments on harmonization between CBER and  
11 CDRH or lack of. Actually from Dr. Stramer  
12 and Kleinman.

13 So I think the first comment is  
14 about software that is used in platforms.  
15 Again CBER, CDRH, I believe we use the same  
16 regulatory pathways, same requirements.  
17 Except when you look at the submission that is  
18 approved, licensed as a biologic devices  
19 versus a medical device the requirements then  
20 change. The software takes on a higher level  
21 of concerns. That's why CBER looks at it as  
22 because it takes on a regulatory pathway for

1 the BLA versus a 510(k) or a PMA. So these  
2 are maybe the differences. But I can tell you  
3 that we use same guidance document, same  
4 applicable 21 C.F.R. whether it's 600 or 800,  
5 whatever applicable there.

6 Second comment on also  
7 harmonization or I would say dual intended use  
8 for some of the devices that we approve,  
9 whether under BLA, 510(k) or PMA. Keep in  
10 mind FDA is really -- or CBER I would say  
11 guided by the 1991 Inter-Center Agreement. So  
12 you may see actually hepatitis, all the  
13 hepatitis for donor screen, they come to CBER.  
14 But CBER cannot I think at this stage -- Jay  
15 may comment on that -- grant you a diagnostic  
16 use. You have to go to CDRH. For HIV that's  
17 a different ball game.

18 DR. STRAMER: Thanks, Sayah. I  
19 understand that but that's why I asked the  
20 question. It just makes it so much more  
21 difficult to get something that should have a  
22 diagnostic claim and a screening claim both



1 because again it's two separate clinical  
2 trials, two separate sets of meetings, two  
3 separate submissions, two different review  
4 cycles, two different sets of questions to  
5 answer. It just doubles the amount of work to  
6 do. Maybe I've stirred up a sleeping dog.

7 DR. MIED: No, I think we hear you  
8 on this point. This is something we would  
9 like very much to harmonize on.

10 MS. CALLEJA: Could I make a point  
11 of clarification? I'm Khatereh Calleja with  
12 AdvaMed.

13 I just -- I think these  
14 discussions are very helpful. I only wanted  
15 to clarify, when we talk about CBER and CDRH  
16 our first objective is process coordination.  
17 So manufacturers, you said it doesn't have to  
18 go through two separate submissions.

19 The idea is that CBER and CDRH sit  
20 around the table and come up with basically  
21 try to help -- the correct term, I don't know  
22 if it's harmonize or more to really coordinate

1 the submissions so that they're working  
2 together and so we're not having to basically  
3 on the up front be able to meet both the needs  
4 of the licensure as well as the PMA or 510(k).

5 So I just, I didn't want CBER to  
6 feel like we're looking to start implementing  
7 510(k)'s for all BLA submissions but  
8 essentially can we improve.

9 And I think we have seen recently  
10 actually some platforms that are being used  
11 for diagnostic in the licensing. Maybe we can  
12 learn from that. But I think if we can just  
13 try to -- and I think those communications are  
14 important. They happen, they don't always  
15 happen. Anyway, we can encourage that.  
16 That's all, I just wanted to clarify that.

17 DR. BUSCH: Thank you. We have 5  
18 more minutes.

19 DR. MARCHLEWICZ: Ben Marchlewicz  
20 from Abbott Laboratories. I'd like to return  
21 back to the question of kind of streamlining  
22 or smoothing the clinical and pre-clinical

1 studies. And kind of add on a couple of the  
2 previous comments.

3 Like Jeff had mentioned in terms  
4 of maybe bringing more testing in-house,  
5 especially for specificity, I think as you get  
6 to more and more fully automated systems, and  
7 a lot of systems we have today, the  
8 variability of the end user site type testing  
9 maybe becomes less of an issue when you have  
10 a fully automated site. If all the operator  
11 is doing is loading a rack of tubes and  
12 replacing reagents and disposables it really  
13 eliminates a lot of that end user variability  
14 that was seen in prior type technologies. So  
15 if we could streamline a lot of those high  
16 numbers of samples to be brought in-house by  
17 the manufacturer that would certainly add to  
18 the ease of doing some of these specifically  
19 studies.

20 Secondly, it was also mentioned  
21 earlier about special informed consent. Now  
22 that comment was in relation to special

1 populations. But having been involved with  
2 several of the recent PRISM assay launches the  
3 informed consent requirements that have been  
4 put on even for just random donors, normal  
5 donors coming in, I feel has actually  
6 introduced an unknown bias into the data  
7 because we see upwards of 50 percent of the  
8 donors opting out of providing the samples.

9 And especially when we were doing  
10 Chagas and you want to get a certain high-risk  
11 population the people who are most prone to  
12 choose not to have their blood tested were the  
13 potential high-risk donors. So something that  
14 could be done to ease, make it more generic,  
15 something to smooth the overall consent  
16 process I think would facilitate clinical  
17 studies.

18 And how that added to time and  
19 cost. It then takes twice as long to get the  
20 minimum number of samples if only 50 percent  
21 of the people agree to use their samples.

22 Lastly, in terms of some of the

1 discussion I had with Hira during the break  
2 also in terms of easing the overall cost or  
3 spread of new technologies. It was mentioned  
4 at one of the previous discussions of having  
5 some of these assays used as a research use  
6 only basis, or kind of test out the process  
7 for some extended period of time to see the  
8 viability of whether that marker is even  
9 needed.

10 I think from a manufacturer's  
11 perspective if there was some cost recovery,  
12 cost-sharing, risk-sharing in those early  
13 stages. We've heard from some of the other  
14 manufacturers that one of the bigger barriers  
15 is the unknown of whether or not this will be  
16 a viable product.

17 Well, if it takes 2 to 3 years of  
18 RUO testing to get there many manufacturers at  
19 least from the financial management side would  
20 not want to risk as was stated \$5, \$10, \$12  
21 million in development costs for something  
22 that's unknown. If we're going through an

1 extended period of research or IND and there  
2 was some cost-sharing or cost recovery for  
3 those reagents it might be more palatable to  
4 provide those reagents.

5 DR. STRAMER: Okay, not being FDA  
6 but having been involved in many of the  
7 clinical trials for Chagas I certainly felt  
8 your pain as having to have those sheets  
9 administered and deciphered for who gets --  
10 which tubes get tested and which not.

11 In more recent clinical trials  
12 we've used information sheets where we've gone  
13 back to the model of where the donor signs the  
14 blood donation record acknowledging that  
15 they've read, understood, have had time to  
16 answer questions related to the research that  
17 may be done on their samples. So we've kind  
18 of moved away from that.

19 I forgot the second point that I  
20 was going to make but I wanted to make a point  
21 that I made earlier.

22 DR. BUSCH: I think FDA was

1 helpful in that transition.

2 DR. STRAMER: Yes, FDA was very  
3 helpful in that transition certainly.

4 But as far as specificity testing  
5 and doing testing in-house I still, you know,  
6 get chills up my spine thinking that there  
7 won't be robust specificity testing prior to  
8 test kit licensure.

9 And even as we define, if you're  
10 defining a robust clinical trial as 100,000  
11 units which is huge for a clinical trial  
12 that's still 1 week of testing at the Red  
13 Cross. And it happens every single time we  
14 implement a new test that there are surprises,  
15 that they weren't seen in the clinical trials  
16 and we only pick them up in validations or we  
17 only pick them up in test implementations.  
18 And that's even on the most automated methods.

19 DR. MARCHLEWICZ: But Sue, if we  
20 were able to do it in parallel in-house, I'm  
21 not saying eliminate the clinical trials,  
22 could we do 200,000 or do more samples if some

1 of that could be done in-house.

2 DR. STRAMER: I mean, under an IND  
3 model, an open IND model like we had with NAT,  
4 I mean that was ideal because that -- we  
5 really, truly knew the performance  
6 characteristics of the test prior to  
7 licensure.

8 MR. SCOTT: Since you mentioned  
9 that these are FDA questions, while I can't  
10 speak for AdvaMed because we have not had a  
11 chance to discuss them I can take them back as  
12 an industry representative for response.

13 DR. BUSCH: Thank you. Okay, just  
14 a few quick last comments.

15 DR. KASARSKIS: Yes, very briefly  
16 here. Andrew Kasarskis, Mount Sinai Medical  
17 Center.

18 I just wanted to clarify what  
19 might be an incorrect impression actually from  
20 my talk. With next-generation sequencing it  
21 is actually incredibly accurate and precise in  
22 targeted areas.



1                   So as Dr. Meyerson and others had  
2 mentioned if one were to construct a targeted  
3 panel the chainsaw to a dandelion analogy is  
4 actually perfectly correct. If you get high  
5 coverage in a certain area you will have a  
6 very accurate and very precise answer, and you  
7 will know the answer to your question.

8                   So when people talk about the  
9 inaccuracies, and when I was talking about  
10 expanding into regions that one technology  
11 does not touch that's talking about trying to  
12 assay regions that no other technology would  
13 assay today. For things which can be captured  
14 in a panel and sequenced you will be very  
15 happy with the results. So just something to  
16 keep in mind that what they do detect they  
17 detect well.

18                  DR. BUSCH: Thank you. Steve,  
19 last comment?

20                  DR. KLEINMAN: Yes, I just wanted  
21 to turn back to the red cell antigen issues  
22 which are obviously not the focus of this

1 discussion today but which were presented this  
2 morning.

3                   So these genotyping of red cells.  
4 It seems to me that if it's -- it seems to me  
5 this is a simpler thing than what we're  
6 talking about today, multiplex ID reagent  
7 discovery. And I'm wondering, and maybe this  
8 is a conversation you have with the particular  
9 manufacturers, but it seems to me there should  
10 be a straightforward path for these things.

11                   And I'm quite -- it doesn't make  
12 sense to me as a blood banker to have all of  
13 these antigens determined genotypically and  
14 then find out you can't use the results, you  
15 have to repeat this by serological testing  
16 which I think we heard ample data is probably  
17 inferior to the genotyping.

18                   Now, I may be wrong, I'm not an  
19 expert in this area, but I would suggest that  
20 some ways to facilitate moving that product  
21 forward might be indicated. I don't know if  
22 any manufacturers are at the point yet.

1 Obviously you need to do a thorough review.

2 But what's the gold standard here?

3 It seems to me we're moving to a new gold --  
4 it seems to me what we're trying to put on the  
5 market is more of a gold standard than what  
6 we're comparing it to and that's where I have  
7 the problem.

8 DR. BUSCH: Yes, thanks. I think  
9 let's save that one for the closing session.  
10 That's a pretty obvious next step I think.

11 So let's -- moving straight into  
12 the closing session. No more breaks. So I  
13 think the new panel will be chaired by Sanjai.  
14 If those members of the closing panel could  
15 please come up.

16 DR. KUMAR: So if everyone has  
17 settled in we can just get started. So we've  
18 had 6 scientific sessions so far, 28 excellent  
19 presentations. We had two prior panel  
20 discussions. So what's the purpose for this?  
21 So I just want to make the intent clear what  
22 the expectation from this panel discussion is.

1                   So if we had to prepare a  
2       blueprint of a road map that would guide us in  
3       the future how to facilitate the development  
4       of these advanced technology-based multiplex  
5       platforms for donor screening for infectious  
6       agent as well as for red cell antigens or  
7       blood cell antigen typing, what that road map  
8       would look like.

9                   So while in the previous panel  
10      discussions we were discussing, we were  
11      talking, we were listening, so more of a  
12      learning scientific exercise. Here we would  
13      like to get some opinions and some sort of  
14      advice that we can take it with us really and  
15      which will help us to carry us further.

16                  So we have all these questions.  
17      So in the end we have to make sure with the  
18      time we have, and we have to leave here before  
19      6 o'clock or the NIH will call us. They'll  
20      number some money per minute which we don't  
21      have. So we have to leave before 6 here.

22                  So we have to go through these

1 questions, make sure. In the past panels some  
2 questions were hanging there. But you have to  
3 go through every question.

4 And if you can reach some sort of  
5 agreement on what the opinions are here.  
6 Obviously there's not going to be one  
7 consensus. But still we can get some  
8 opinions, so that's the idea.

9 So before we get started there  
10 just very briefly we have one more form there.  
11 So the previous panel chairs except for Mike  
12 who just gave his talk, if they can just  
13 rehash their sessions if 2 or 3 minutes. We  
14 were saying 5 minutes. So we just get to hear  
15 what was discussed there so we can get onto  
16 questions because the questions are very  
17 important to us. So let's get started with  
18 Charles.

19 DR. CHIU: Sure. So the first two  
20 sessions were concerned on blood safety from  
21 infectious agents, present and future. And  
22 also to discuss advances in technologies for

1 blood-borne pathogen detection.

2           And I think that there were  
3 several points that came as a result of both  
4 the talks and the discussion. One was that  
5 the challenge for blood bank screening  
6 includes multiplex detection of blood-borne  
7 pathogens, both detection of established known  
8 agents, re-emerging agents such as dengue and  
9 Babesia, as well as completely novel agents.

10           It was also the consensus of the  
11 group that establishing sample repositories  
12 that could be used for testing and validation  
13 is critical, that these repositories should  
14 contain a sufficient number of representative  
15 samples from all pathogens that are targeted,  
16 and they need to be well annotated with both  
17 clinical and epidemiological data.

18           We also discussed the need to  
19 actually standardize a set of samples that  
20 could be used for validation of assays, and  
21 that these sample collections could be  
22 available as resources for institutions and

1 companies that are looking to develop assays.

2 This will likely involve the  
3 efforts of several groups including groups  
4 doing epidemiology and field work such as Dr.  
5 Nathan Wolfe at MetaBiota, the FDA and  
6 academic research laboratories and blood  
7 banks.

8 We also discussed for a novel  
9 high-priority agent that may emerge in human  
10 populations that is highly suspected to be a  
11 blood-borne pathogen having any test, even one  
12 with reduced sensitivity and specificity is  
13 better than having no test at all.

14 On the other hand, for detection  
15 of established agents it is expected that any  
16 new multiplex assay should have comparable or  
17 better test performance as existing screening  
18 tests at least in the setting of blood-borne  
19 pathogen screening given the consequences of  
20 false negatives and to some extent false  
21 positives.

22 Tests ideally should be flexible

1       so that you can incrementally add new agents.  
2       And then other factors include cost,  
3       turnaround time and bioinformatics analysis.

4               We also discussed three ways that  
5       we can kind of move forward with respect to  
6       this. One way would be to introduce these  
7       technologies in the sense of doing selective  
8       screening of high-priority groups. Those with  
9       high likelihood, a priori likelihood of blood-  
10      borne pathogen infection. This includes known  
11      positive donors, deferred donors, or groups  
12      that have specific diseases such as hepatitis  
13      or significant exposures, or potentially  
14      individuals from pandemic hot spots in Asia  
15      and Africa.

16             And then the other thing that we  
17      also discussed was the possibility that we may  
18      need to do these -- this testing in parallel  
19      with existing technologies. And certainly to  
20      introduce new technologies would probably  
21      involve to some extent analyzing either  
22      selective sets of samples or doing these



1 analyses in parallel with existing tests.

2 DR. KUMAR: Thank you, Charles,  
3 that was excellent.

4 DR. WESTHOFF: Am I next?

5 DR. KUMAR: Yes, please.

6 DR. WESTHOFF: I have a set of  
7 just quick summary slides. So very much  
8 reiterating what Charles has said from my  
9 session I hope we're ready. We've had 6 years  
10 of parallel testing of blood group antigens  
11 with serology and molecular methods. So we  
12 hope this technology is ready for  
13 implementation and embracing.

14 And I'll just review really  
15 quickly the motivation here is our lack of  
16 antibody reagents, all the polymorphisms both  
17 in HLA and blood group antigens and the  
18 ability now with molecular to resolve fine  
19 specificities not possible with antibodies.

20 And it really circumvents this  
21 need to develop an expensive, sensitive and  
22 specific antibody which we don't have the

1 resources to do for all of the 300 blood group  
2 antigens.

3 And one thing we haven't discussed  
4 too much here is the problem with the protein  
5 assay approach with blood group red cell  
6 antigens. These have been shown to be very  
7 confirmationally dependent and many antibodies  
8 directed to red cell membrane antigens don't  
9 work once you plaster that red cell membrane  
10 on a solid surface.

11 And throughout the discussion we  
12 realized with HLA and blood group antigen and  
13 maybe even with bacterial pathogens the  
14 concept of high- and low-resolution testing  
15 certainly applies. There's two different  
16 levels of resolution.

17 So what's happening here though is  
18 we're talking about not only donor testing,  
19 we're talking about patient testing. And so  
20 the real power here to have a comprehensive  
21 antigen profile on the patient is very  
22 powerful. And I would argue it's part of our

1 process of providing a pure and potent product  
2 to our patient is to have this information  
3 also on the unit.

4 Because knowing what antibodies  
5 the patient can make is a new paradigm.  
6 Before we've looked at the patient as a black  
7 box. They can make 1 of 300 different  
8 antibodies. If we knew their profile that  
9 reduces it at least 50 to 60 to 70 percent of  
10 the targets. And this has been an RUO test  
11 now that's being used clinically and is  
12 improving transfusion practice.

13 The ability to give an antigen-  
14 matched unit eliminates these problems with  
15 auto-antibodies, giving a least incompatible  
16 unit. And we've seen it in these patients  
17 with hyperhemolysis syndrome. If we're able  
18 to give an antigen-matched unit, especially in  
19 the Dombrock system, we've got a solution and  
20 a better product.

21 And certainly in the donor arena  
22 we've got lots of -- you've heard all of the

1 arguments. We've got ability now to get rare  
2 units. We've got ability to resolve ABO and  
3 Rh NTDs, reenter some donors.

4 But like infectious disease  
5 testing we have some gaps. Not all silenced  
6 alleles are detected. Just as you worry about  
7 all strains we have allele dropout. We have  
8 the same issues that you do in infectious  
9 disease.

10 We have about the same number of  
11 targets on a multiplex. So we've got some  
12 synergy there. And we've got some systems  
13 that we probably still want to do antibody and  
14 DNA testing both for. So there's lots of  
15 synergy here.

16 We've got some contrasts in that  
17 the number of times we want to test a donor is  
18 not every donation, similar to Chagas. So  
19 that means there's less people, less  
20 manufacturers interested in supporting us.

21 The target copy though is very  
22 different. You're looking for the needle in

1 the haystack. We're amplifying the haystack.  
2 I think we can still do it from the same  
3 sample extraction, we just go different  
4 directions.

5 We won't be doing mini-pooling  
6 because we want to know the donor profile but  
7 the exception may be we may do mini-pooling to  
8 confirm the D negative donor status. So we've  
9 got synergy there.

10 But a little bit of difference  
11 here is that what we do for antigen typing out  
12 a donor and patient impacts the practice of  
13 medicine. And so we need some concordance  
14 across technology. In other words, the  
15 hospital may be confirming what we are putting  
16 on the unit. And you don't have to worry  
17 about that in infectious disease testing.  
18 Nobody's going to repeat your HIV or your  
19 screening test.

20 So the other common issues I think  
21 are where we've got to worry about new targets  
22 and pathogens just like we have to worry about

1 new alleles in different populations. We need  
2 a black box automation just as you do. How to  
3 deal with the single target failures, the  
4 control and test validation materials. We  
5 have those same issues. The population  
6 variations in admixtures, same issues. And  
7 same issues for confirmatory testing and  
8 reentry.

9 So I don't want to take too much  
10 time here. This is my last slide. I do think  
11 next-gen sequencing is certainly applicable,  
12 maybe sooner for us than for pathogens,  
13 certainly in the HLA arena for  
14 transplantation. They're certainly moving,  
15 will probably be the first to move I would  
16 assume to next-gen sequencing.

17 Certainly we are doing a lot of  
18 sequencing in blood groups for confirmatory  
19 and high-resolution testing. And again these  
20 are targeted next-gen sequencing. And so  
21 we've got a little edge there. Avoids our  
22 problems of silenced alleles and is for our

1 confirmatory testing.

2 And next-gen sequencing may allow  
3 us to actually do ABO and Rh where silenced  
4 alleles are high-risk for us. We'll have the  
5 same problem as you do, too much information  
6 for routine testing and what do we do with  
7 those polymorphisms that aren't associated  
8 with clinical presentation.

9 And so in summary, after 6 to 7  
10 years of parallel testing with a nice ability  
11 to confirm most of these things, serology and  
12 I think we've got the data to show these are  
13 robust and important technology, multiplex  
14 testing. Thanks.

15 DR. KUMAR: Thank you, Connie,  
16 that was very nice. Let's hear from Tom  
17 Slezak now.

18 DR. SLEZAK: So we heard that deep  
19 multiplexing of PCR and way beyond 20  
20 signatures are possible to detect known agents  
21 with high sensitivity and specificity.

22 There's a wide range of formats

1       that are being used and there's varying levels  
2       of sensitivity some of which is due to the  
3       various sample dilution effects depending on  
4       the formats.

5               Microarrays we heard provide  
6       detection down to a range from 10 to 100 copy  
7       level per millilitre. The type of  
8       amplification strategy that's used is highly  
9       dependent on that level that can be reached.

10              We also heard that the assays can  
11       provide some ability to detect unsequenced  
12       variants depending on whether probe designs  
13       are done to look at family-specific, species-  
14       specific and strain-specific levels.

15              We heard that next-generation  
16       sequencing can find everything, sometimes  
17       including things you didn't want to find.

18              But I think what was very  
19       interesting, we heard a lot about dealing with  
20       the problems of dealing with the data. We  
21       heard two types of solutions. We heard a lot  
22       about reduction of hosts through various



1 algorithmic means. There was also some  
2 mention of various targeted amplification  
3 strategies.

4 I guess my personal comment is  
5 that some combination of those two are  
6 probably most useful for blood safety -- for  
7 blood safety type of applications.

8 We also heard that bioinformatics  
9 is no panacea. I was amused by all the slides  
10 that kind of had, you know, help me, Obi-Wan  
11 Kenobi, bioinformatics will save us. It's not  
12 going to work quite that easily,  
13 unfortunately.

14 There are some hard decisions that  
15 need to be made on, for example, on  
16 thresholds, levels of concern. We heard from  
17 some speakers that per-assay or per-agent  
18 thresholds may be needed which makes it even  
19 more exciting.

20 There's certainly the issue of the  
21 false positive rate concern level that you  
22 might have. If you use sort of a when in

1       doubt, check it out strategy you're not going  
2       to have a whole lot of blood left after you  
3       look at it with some of these really highly  
4       multiplex techniques.

5               We heard that there's a lot of  
6       importance for the reference sequence  
7       databases that are used to be able to compare  
8       the sequence-based strategies. And we heard  
9       also that there's work being done on that.

10              We had several speakers mention  
11       that we need to have ways to be sure that we  
12       can update the software and the databases on  
13       a regular basis. Things change. We get new  
14       data in the databases. Assays need to be  
15       redesigned as we learn more about not only the  
16       things you want to detect, different variants  
17       that are now circulating, now have been  
18       sequenced, but also different near neighbors  
19       that may end up being a little bit closer than  
20       you used to think -- than your neighbors were.

21              We also heard that sometimes the  
22       algorithms need to evolve. So there's some

1 issues in terms of how static you can have  
2 some of these highly multiplex systems be.

3 Finally, I think the way I would  
4 summarize this is that I think we've heard at  
5 least from the technology folks that there's  
6 kind of a need for all of those involved in  
7 blood safety to sort of accept and embrace  
8 that there is a coming paradigm shift.

9 This has happened in many other  
10 communities in biology. When you bring in  
11 massive sequencing things change. And so the  
12 degree to which you can accept that this sort  
13 of change is needed and then work to try to  
14 minimize the hard impacts and maximize the  
15 benefits I think will be a good sign for how  
16 well the blood safety field can deal with the  
17 technology changes.

18 DR. KUMAR: Thank you, Tom. So I  
19 will just make -- just wanted to say one more  
20 thing. Then we'll open the floor for  
21 discussion or other comments and advice.

22 We had the panel up here but still

1 we would like to hear from the industry  
2 representatives also. But in some concise  
3 way, something we can take back for us what  
4 are the scientific barriers they see. And how  
5 you perceive that we can lower the barrier to  
6 facilitate the process. So with that let's  
7 just start with the first question.

8 I mean I don't need to read it.  
9 It's up here, really. Who would want to take  
10 the first cut at this? Maybe it's hard to  
11 turn around and read. The questions are there  
12 in your -- in the packet that you got also.

13 So the first question is desired  
14 performance characteristics (sensitivity,  
15 specificity, etc.) of multiplex platforms for  
16 donor screening. So what advice you'd give  
17 us, really. What should be the desired  
18 performance characteristics of these tests in  
19 terms of sensitivity, specificity, et cetera.

20 So I mean this question is not  
21 very different from what we have been  
22 discussing this session before or in many

1 other sessions. But what do advice you give  
2 to us? I mean we heard a lot of concerns,  
3 complaints, but what advice you give us now  
4 really. So we can --

5 DR. STRAMER: I would say even  
6 though we just heard in the last session a lot  
7 of changes could be made I think the process  
8 has served us well over time. So I would say  
9 we still want the same level of sensitivity  
10 and specificity in the assay, especially we're  
11 replacing assays. If we look at some type of  
12 microarray that contains HIV, HCV, HBV we're  
13 not going to want lesser performance than we  
14 have today.

15 And then for newer agents we're  
16 going to have to do what's possible. I mean  
17 remembering what Harvey said, that perfect is  
18 the enemy of good. So I'm not sure we're that  
19 far off track.

20 DR. NAKHASI: So let me sort of  
21 extend the question. We want to know from the  
22 technological point of view is it possible to

1       achieve that as a single plex versus a  
2       multiplex. What are the barriers? And if the  
3       answer is yes, we can, we are scot-free.

4               But then we need to also  
5       understand where are the barriers in that and  
6       if there are. So I think I want to hear from  
7       you as well as the manufacturers because  
8       that's the question.

9               DR. STRAMER: Do we have a test  
10       with 20, you know, different analytes on it so  
11       that we even know what the performance  
12       characteristics are?

13              DR. NAKHASI: No, but we have at  
14       the moment two or three together where we may  
15       --

16              DR. STRAMER: Right --

17              DR. NAKHASI: But now if we go to  
18       four or five which now that you heard what's  
19       our immediate need, what's the long-term need.  
20       Let's say if we have in the immediate need  
21       where we want to extend additional let's say  
22       dengue, Babesia and HEV would we still be able

1 to maintain that? So Jay, you had something.

2 DR. EPSTEIN: Well, I just think  
3 we need a little bit of clarity what we mean  
4 when we say multiplex. Because I heard some  
5 very different things.

6 I heard that one notion of  
7 multiplexing is, well, you can have more  
8 analytic channels from a common sample.  
9 Another concept of multiplexing was that the  
10 platform has many independent reactions.  
11 They're really just independent so the  
12 platform is multiplexed but the assays really  
13 are separable.

14 And then we have what I think  
15 we've generally meant which is that the assay,  
16 the analytes are studied as a mixture and then  
17 you extract independent results out of an  
18 assay on a mixture.

19 These are really different  
20 strategies. And I think that we haven't quite  
21 thought through the issue of, okay, we have  
22 assays that are in use now on platforms that

1 are in use now. Can we expand their use for  
2 additional analytes without drastic changes?  
3 Okay, that's one issue.

4 But that issue is really quite  
5 different for systems that in essence involve  
6 channels for different assays versus systems  
7 that involve making the mixture, the reaction  
8 mixture, more complex. So, and I think that  
9 the challenges therefore are different in  
10 those different contexts of platform. So I  
11 just think that before we answer that  
12 question.

13 But I would just reiterate, I mean  
14 from the regulator's point of view there's no  
15 incentive to go backwards with sensitivity and  
16 specificity for donor testing for the existing  
17 agents of concern. You know, we won't allow  
18 that. And so the challenge if you make the  
19 reaction itself more complicated is to show  
20 that you haven't denigrated performance for  
21 all the original analytes.

22 The challenge for completely new



1       assays is that it's the state of the art. I  
2       mean we do the best we can when we have  
3       emerging agents of concern, but then the  
4       implication is we expect progress over time.  
5       And so there's an inherent burden of looking  
6       at assay modifications, process modifications,  
7       reagent modifications. And we loosely call  
8       those generations.

9                       But the point is that when you  
10       start out with an assay for a new analyte  
11       which is suboptimal compared to our 99.9-plus  
12       percent sensitivity and specificity you have  
13       got to expect that there's going to be  
14       pressure to improve. And that means change  
15       and everything that comes with change.

16                      DR. KUMAR: Any other ideas,  
17       thoughts?

18                      DR. STRAMER: Well, I think to  
19       answer Jay's question, I think we need to hear  
20       from industry. Because you know, clearly --  
21       I don't think the blood bankers per se can  
22       answer that other than we want the best

1 performance, you know, we want state of the  
2 art.

3 DR. BUSCH: I think in principle,  
4 I mean we've clearly seen that at least two of  
5 the models Jay summarized, you know, the  
6 actual parallel testing and PRISM essentially  
7 puts samples in. They go through parallel  
8 serologic assays and some of those have two  
9 related agents, HIV-1 and 2, for example. And  
10 the companies have achieved that.

11 And then with the NAT assays both  
12 Roche and Novartis GenProbe, you know,  
13 multiplex with equivalent sensitivity if not  
14 improved sensitivity as they've moved to  
15 adding more analytes.

16 But when you take it to the full  
17 next-gen multiplexing, I mean, assays such as  
18 Charles. And we've heard several people speak  
19 to the fact that they are confident that they  
20 can achieve the same sensitivity as we're  
21 achieving now. But I haven't seen that data.

22 And I think it doesn't need to be

1 a fully fleshed out commercial assay, but I  
2 think it would be interesting to design some  
3 analytic panels or some challenge panels that  
4 would really target a few of these newer  
5 technologies to see if they can indeed achieve  
6 the sensitivity that we need.

7 DR. STRAMER: Just again to remind  
8 us as we talk about analytic sensitivity  
9 that's something different than the number of  
10 particles in a unit of blood. So even if you  
11 have 1 or 10 copy per ml sensitivity or  
12 whatever your endpoint is --

13 DR. BUSCH: But you've got to have  
14 the volume.

15 DR. STRAMER: -- you've got to  
16 detect -- you've got to have that in your  
17 sample.

18 DR. BUSCH: Right, right. And a  
19 combination of analytic panels and real  
20 clinical material, yes.

21 DR. SCHERF: So maybe I can add  
22 some additional information and experience

1       that we have. My name is Uwe Scherf. I'm in  
2       the Division of Microbiology at CDRH.

3               So we had the opportunity to  
4       actually see some of these assays. They were  
5       multiplexed. And we had the opportunity to  
6       see the ones that were just parallel testing  
7       and then you had the evaluation of the data in  
8       the software approach and so on.

9               But in addition to that we also  
10       had the opportunity to actually do this true  
11       multiplexing in a tube where you had the  
12       competition of all of these different primers  
13       and enzymes and components to later on  
14       generate the amplicon and generate the data  
15       and the signal.

16              And what I can share with you is  
17       from the diagnostic perspective with samples  
18       that actually are coming from diseased  
19       patients that if you are working with NAT  
20       assays, that's what we have really done in the  
21       last couple of years, they are very good  
22       performance observed.

1                   Now whether that is because the  
2                   sponsors have invested tremendous amount of  
3                   money and time to optimize it, I don't know.  
4                   But what we have seen is that there was not an  
5                   observed drop if you are moving from let's say  
6                   1 or 2 to 15 or 20.

7                   They were not always performing  
8                   the same. So if you are looking for maybe a  
9                   specificity of 99.3 for all of them I'm not  
10                  sure you can accomplish that. But of some of  
11                  them they were extremely well performing.  
12                  They performed in all of different specimen  
13                  types and sample types. But it's probably a  
14                  significant approach to actually get this  
15                  done. But it seemed to be possible for NAT-  
16                  based.

17                  If you are moving into antibody  
18                  approaches, antigen, I think we don't have  
19                  that opportunity yet to share with you.

20                  DR. KUMAR: Thank you. Let's hear  
21                  some from the audience. Yes.

22                  AUDIENCE MEMBER: I'm still from

1 the FDA. But one of the comments I have is  
2 the way I judge sensitivity and specificity as  
3 the statistician is by the lower confidence  
4 bound. And that is driven in part by sample  
5 size.

6 And so I get concerned about  
7 panels and how many specimens there are going  
8 to be on a panel. I just want people to be  
9 realistic about the estimates. And we think  
10 of the claim as being defined by the lower  
11 confidence bound rather than the actually  
12 observed sensitivity and specificity. And  
13 that's all I wanted to say.

14 DR. KUMAR: Yes, thank you. So  
15 unless there are any other comments about  
16 this.

17 DR. EPSTEIN: Just that, you know,  
18 we had a lot of discussion about CDRH versus  
19 CBER. But generally speaking in the medical  
20 environment where diagnostic assays are used  
21 you can tolerate lower sensitivity and  
22 specificity because the healthcare provider

1 can integrate patient data, can integrate  
2 results of other tests. I mean often we have  
3 only one test to qualify the donor to rule out  
4 a transmissible infectious disease.

5 And because if you are starting  
6 with clinical condition, you know, disease  
7 state the positive predictive value inherently  
8 goes up.

9 So you're up against two problems  
10 in the donor setting. First, that you're  
11 trying to screen a healthy population. I mean  
12 after all donors are selected to be  
13 asymptomatic in the absence of risk factors.  
14 So that's your first problem.

15 And then your second problem is  
16 that the operational requirement because of  
17 the management of a reactive result  
18 necessitates very high-level accuracy. So  
19 that's what drives the numbers. In other  
20 words, if you need to achieve 99.9-plus  
21 sensitivity and specificity you cannot  
22 determine that on population sizes that are

1       small. You know, hundreds won't do. You need  
2       thousands and tens of thousands. And this is  
3       what drives the complexity.

4               So you know, I think we need to  
5       discuss how far can panels take us and how far  
6       can in-house testing take us. But the bottom  
7       line is the setting drives the numbers.

8               DR. ALTER: Jay, I certainly agree  
9       with you, but in trying to think of economies  
10      or inducements to manufacturers if the same  
11      test could be used in the blood bank setting  
12      as in the diagnostic setting. I mean you'd  
13      have to up the sensitivity for the diagnostic  
14      setting.

15              But for instance, the agents that  
16      we want to look at in the blood bank setting,  
17      let's say malaria, Babesia, dengue, a couple  
18      of more, if they were also useful as a fever  
19      panel in a microbiology laboratory. If you  
20      could synchronize the two uses and put the  
21      sensitivity up real high so that it'll be even  
22      better diagnostically but it'll be okay for



1 the blood bank, that's one possible approach.

2 DR. GALEL: I have a comment about  
3 the expectation for specificity. Sorry, I'm  
4 Susan Galel from Stanford Blood Center.

5 And I think our expectations for  
6 specificity are driven to a large extent by  
7 what happens after a reactive result. That  
8 is, we're bringing information to the donor,  
9 we're permanently deferring them in many  
10 cases. We may do lookback of recipients. So  
11 if we could think out of the box a little bit  
12 in terms of what options we have for reflex  
13 testing or additional testing that might  
14 minimize the impact of -- or resolve the donor  
15 status enough that we don't have to bring them  
16 garbage information then maybe we can think  
17 differently about specificity.

18 For example, in this country if a  
19 donor has an individually reactive NAT result  
20 they're permanently deferred. In some other  
21 countries they, because there's a low pre-test  
22 probability of infection in other countries

1       they do repeat and duplicate. If the repeats  
2       are non-reactive that donor is not permanently  
3       deferred.

4               And so I think we can think about,  
5       again, I agree completely with what Jay said  
6       about pre-test probability of infection and  
7       how you evaluate results. But maybe we can  
8       also think about what options are available  
9       for reflex testing.

10              Certainly there are barriers. We  
11       haven't even discussed barriers to getting  
12       approval for confirmatory claim. You know,  
13       those barriers are so high that we don't have  
14       confirmatory assays for many of our tests and  
15       the donors are left deferred.

16              But if we can think -- rather than  
17       think in confirmatory claim language think in  
18       terms of reflex testing and use some sort of  
19       reflex testing to avoid permanently deferring  
20       the donor maybe we can relax some of our  
21       specificity considerations.

22              DR. KUEHNERT: Yes, I think that

1       what we're getting to is trying to use these  
2       tests at least initially more like diagnostic  
3       tests. And that's where it seems to be a  
4       niche for, for instance, donors that are  
5       positive but you don't know what to make of it  
6       and you need a reentry algorithm.

7               Also, organ and tissue donors are  
8       a different sort of type of assessment where  
9       it is a little bit more towards a diagnostic  
10      test although the tolerance of specificity, I  
11      think people want even higher specificity but  
12      maybe not so much emphasis on sensitivity.  
13      But there being even more importance on  
14      timeliness. So it's a different set of  
15      characteristics.

16             The other thing that I don't know  
17      if we're going to get into or not is  
18      concerning recipient testing. So we talk  
19      about how important it is to understand what  
20      disease an emerging pathogen is causing.

21             And I think this would be an  
22      opportunity to look at frequently transfused

1 patients that have unknown syndromes, unknown  
2 etiology and looking to see what it might be  
3 and whether it matches to anything that's in  
4 the donor population. So if you start with a  
5 hypothesis you can use these tests to either  
6 confirm or refute that.

7 So these are all probably to  
8 companies small-market things but they can  
9 lead to bigger opportunities through these  
10 sorts of very targeted purposes.

11 DR. EPSTEIN: Well, first of all I  
12 agree with what Dr. Kuehnert said, that we  
13 really need to understand outcomes in  
14 recipients to understand how to manage donors,  
15 and that studies have to be designed.

16 But that triggers the whole line  
17 of thinking about what exactly is the role of  
18 donor screening in the discovery arena. And  
19 I think that we've heard a lot of fascinating  
20 things about technology tools that can let us  
21 discover new agents. And we have to try to  
22 reconcile that with what drives testing

1 donors.

2                   And I think there are a couple of  
3 reasons that you want to do discovery in  
4 donors. One is simply that they're a good  
5 convenience population for a cross-section of  
6 the population. I mean you have millions of  
7 donations a year in the United States. And so  
8 you have samples of convenience but with the  
9 flaw that it's not disease-driven. They're  
10 all asymptomatic.

11                   But the second is, you know, it's  
12 the Willie Sutton idea. You want to find out  
13 what's in the donors because that's what's  
14 putting the recipients at risk. So it's  
15 logical to go there.

16                   But I think the tension then comes  
17 that you don't want to be doing routine  
18 testing of sort of a very highly intense  
19 nature because it will be inherently complex,  
20 cumbersome and fraught with spitting out  
21 answers for which -- I mean data results for  
22 which you don't know what to make of them.

1                   So I think that we haven't quite  
2                   sorted out how do we use the donor population  
3                   most logically as part of discovery and how do  
4                   we figure out what to come down on as routine  
5                   testing and with what technologies.

6                   So to me that's the dilemma about  
7                   these incredibly multiplex say GeneChip  
8                   approaches or next-generation sequence  
9                   approaches.

10                  I can't imagine that that's for  
11                  routine donor screening. I mean it just  
12                  strikes me inherently as illogical. And yet  
13                  wanting to do that on donor samples makes a  
14                  great deal of sense because we want to find  
15                  out what's there.

16                  And I would just plant one idea.  
17                  Could we use pools of donor samples to do  
18                  epidemiologic surveillance for the unknown in  
19                  the donor population?

20                  DR. CHIU: If I can comment  
21                  basically. Actually, it turns out that that's  
22                  exactly what my lab does. We already, we've

1 received like samples from Sue Stramer on  
2 deferred donors and we're already screening  
3 pools of deferred donors with acute illness.  
4 And also we're looking at cases of transfusion  
5 hepatitis, both donors and recipients, in the  
6 TTVS study from samples provided by the NHLBI.

7           So the goal of that, this is  
8 different than designing like validating an  
9 assay for screening. This is looking for --  
10 in high-probability populations to see if we  
11 can identify novel agents that we could then  
12 determine whether or not they pose a threat  
13 and whether or not they merit basically  
14 routine screening. So I mean, this is work  
15 that's already been undergone.

16           But I guess the question is  
17 whether I see there's a role for routine donor  
18 screening using NGS or microarrays. I mean I  
19 guess the question is if we can deal with  
20 these issues of sensitivity and specificity I  
21 certainly think there is a role simply because  
22 it's been very, very difficult -- for several

1 reasons.

2 But probably one of the most  
3 important reasons is I'm thinking back to 2009  
4 H1N1 where the outbreak occurred and it was  
5 actually estimated that you had about a 3-week  
6 time window where potentially we could have  
7 prevented a worldwide pandemic. And if you  
8 imagine that 2009 H1N1 if it had the severity  
9 of SARS, you know, we'd be living in a much  
10 different world right now.

11 And the basic issue is at the time  
12 that it came there was not a single FDA assay  
13 that was approved or even close to approval  
14 that could actually detect that at that novel  
15 pathogen. So I think that the rules have to  
16 be different for emerging -- there has to be  
17 a pathway for development of these assays or  
18 validation of these assays for detection of  
19 emerging, of truly emerging agents where time  
20 is a priority.

21 For routine blood screening I  
22 don't see, because with routine blood



1 screening I think to a large extent, I mean we  
2 appear to be pretty happy overall. I'm  
3 getting the impression that for sequencing  
4 that we've made many -- we've made tremendous  
5 advances in preventing transfusion-transmitted  
6 hepatitis, HIV, et cetera. So the question is  
7 how much better can next-generation sequencing  
8 or microarrays bring to that? Probably not.

9 So the only advantage of next-  
10 generation sequencing or microarrays are in  
11 dealing with novel agents, reemerging or  
12 emerging agents, or potentially in the setting  
13 of a multiplex platform.

14 And the question of multiplex  
15 platform is does it make sense to include  
16 agents that we're already routinely screening  
17 for such as HIV and hepatitis B and C, or does  
18 it make sense simply to try to work on  
19 multiplex platforms for rare, emerging agents.  
20 And I think that arrives at the crux of the  
21 matter.

22 DR. ALTER: I know nothing about

1 this, that's why I feel free to comment. I  
2 think these two things have to be for now  
3 totally separate. One is viral discovery,  
4 pathogen discovery which is a research or a  
5 CDC surveillance, but it is really not a blood  
6 bank issue. It doesn't become a blood bank  
7 issue until an agent is identified, proven to  
8 be transfusion-transmissible, proven to have  
9 bad outcomes in recipients.

10 So I think right now you have  
11 many, many groups that are looking for novel  
12 agents with these tremendous technologies. So  
13 for the next many years our focus has to be on  
14 multiplexing for agents that we know exist but  
15 we're not currently testing for them, or a new  
16 agent that comes out and suddenly becomes  
17 important like HEV may be now emerging as an  
18 important issue.

19 So what I looked at for this  
20 symposium was could we get a multiplex that  
21 wouldn't replace HIV and HCV the way we're  
22 doing them now. They work so well. But that

1 would take on the other agents, Babesia and  
2 dengue and malaria and Chagas and those  
3 things. If we had this supplemental platform  
4 to test for 10 of these agents so we wouldn't  
5 have to bring on 10 new tests over time that  
6 would be what I would like to see out of this.

7 DR. KUMAR: So let me ask you a  
8 question, Dr. Harvey. So you don't see the  
9 role of these multiplex platforms in  
10 simplifying the way donor screening is done  
11 right now. Just include these known  
12 established agents in the technology, use the  
13 opportunity to do it that way.

14 DR. ALTER: No, I shouldn't have  
15 quite said it that way. I have no problem  
16 that if you show non-inferiority of a  
17 multiplex HIV, HCV that's fine. And if you  
18 can add those, and if you can add Babesia and  
19 dengue onto that, that's perfect.

20 DR. KUMAR: Sure. Just take  
21 things further.

22 DR. EPSTEIN: I just want to add a

1 nuance to what Harvey Alter has just said. I  
2 think there are two postures that we could be  
3 in. One is we have potential agents of  
4 concern, we know what they are like hepatitis  
5 C. We're not sure how transfusion-transmitted  
6 disease they may be causing.

7 Do we want to go ahead and  
8 integrate them into platforms but sort of not  
9 have that channel on all the time? In other  
10 words, you use that channel as part of  
11 prospective research, you gather the kind of  
12 data that would allay the concerns that  
13 happened under Chagas. You figure out what to  
14 do with that assay. But you've already moved  
15 toward integrating it with a platform that's  
16 in place, in use, okay?

17 The other model is -- and that  
18 satisfies the need that's been articulated for  
19 rapid response because you're there if you  
20 need to be there. In other words you gather  
21 the epidemiological data and you decide to  
22 turn it on routinely. But you've already

1 implemented in the multiplex platform. So  
2 you're ready to roll if needed.

3 The other model is that you  
4 decide, well, we have an agent of potential  
5 concern so we want to get all the analytes  
6 ready but we don't know if we need to build an  
7 assay. And then if you decide you need that  
8 assay well you're behind the curve. You know,  
9 now you have this whole development and  
10 implementation and translation phase and you  
11 haven't yet done the epidemiology.

12 So I think that there's a little  
13 bit of a decision, and maybe it's agent by  
14 agent, I don't know, but there's sort of a  
15 philosophical difference between what I would  
16 call readiness and precautionary measures. In  
17 other words, how far down the implementation  
18 pathway should you go once you have a  
19 potential agent of concern.

20 DR. ALTER: You know, maybe so.  
21 They could still -- I could still see that --  
22 I mean we know right now the things that we

1 would like to be tested for, those could be  
2 put on first. And other things might come  
3 along.

4 But you know, I've seen -- you've  
5 seen TMA for instance. It can adapt very  
6 fast. So when something becomes a problem you  
7 can take that existing technology and tweak it  
8 and you have a new assay in less than a year.  
9 Now, if it's a disaster agent that's not going  
10 to be fast enough but there is flexibility in  
11 these systems.

12 And I don't know if you have to  
13 have every one on the standard blood bank  
14 panel. But on the side somebody else can be  
15 researching all these things and be ready to  
16 go.

17 DR. KUMAR: Although we have not  
18 exhausted all possible discussions, we won't  
19 have this benefit, all this gathering again  
20 anytime soon so let's try to get some comments  
21 on other topics also here.

22 So it comes to the issue of second

1 one, adaptability. So I think it relates to  
2 the flexibility what this technology offers  
3 really in terms of high-throughput cost, data  
4 handling of the multiplex platform for donor  
5 screening.

6 So let's see. I mean what are the  
7 possibilities in terms of all these things we  
8 have listed here. And what are the plus and  
9 minuses.

10 DR. SLEZAK: Well, I think we saw  
11 pretty clearly that in terms of cost and time  
12 that multiplex PCR appears to be the only  
13 player that's ready for prime time. I don't  
14 think that's going to change in the very near  
15 future without some major advances which may  
16 be coming.

17 DR. NAKHASI: I think, again, I  
18 just want to bring the manufacturers into this  
19 discussion. Because we may be sitting here,  
20 what toolbox I wanted. But the question is to  
21 the manufacturers how can they get that  
22 toolbox and what are the barriers. And I

1 think I would like to hear from the  
2 manufacturers small and large and big and  
3 medium size to really tell us what they -- you  
4 know, what are the barriers. I think because  
5 without that we may be all discussing for 10  
6 years and we still would not have anything  
7 here. The challenge to the manufacturers. So  
8 please go to the microphone and tell us.

9 DR. LINNEN: Well, I think it's  
10 been said several times already but the  
11 biggest barrier is really knowing if there's  
12 going to be a market. And so we do a lot of  
13 studies to try to determine if there's a  
14 market. We're engaged in a number of those  
15 right now. So for me that's really what it  
16 comes down to.

17 We have the systems in place right  
18 now. I think as people have recognized it's  
19 relatively easy to develop new assays, modify  
20 assays. Of course you heard earlier I'd like  
21 that to become more streamlined in terms of  
22 the validation and modification of assays.



1 But really it's knowing that you're actually  
2 going to be selling the test at some point.  
3 That's what it comes down to.

4 DR. NAKHASI: Well, I think if I  
5 can follow up on that. The question is being  
6 prepared versus when the need arises. When  
7 the need arises you definitely will have the  
8 market. But the question is to be prepared  
9 and will multiplexing provide you that  
10 opportunity to be prepared. And then when the  
11 need arises as Jay was saying, that if you  
12 have a channel which can be turned off and on,  
13 and then when the need arises you already --  
14 and there is a market.

15 DR. LINNEN: In theory that sounds  
16 very good. Essentially our assays are not too  
17 different from that. We can make  
18 modifications so that can become easier. But  
19 when you -- if we look at an example right  
20 now, or one from several years ago. When West  
21 Nile virus came on the scene we actually did  
22 experiments of putting it in with our Ultrio

1       formulation and it worked well.

2               But we had no idea really what was  
3       the future of West Nile virus and do we really  
4       want to change all of the work that we had  
5       done on optimizing the assay that we had so  
6       far for HIV/HCV/HBV even though that wasn't  
7       licensed at that point. So it's not so easy.

8               Now if we go to a case we're  
9       working on right now, HEV, we could add that  
10       to our current multiplex but it's really not  
11       the simplest route to answer the questions  
12       that we need to answer right now, what's the  
13       prevalence in the U.S. and then eventually is  
14       it being transmitted, is there disease, all of  
15       those kind of questions.

16              It's not the simplest route to  
17       answer those questions for where we are right  
18       now with the technology. Because when you  
19       make a modification to the assay you've got to  
20       put a lot of effort into the analytes that are  
21       already being detected to make sure that you  
22       haven't affected the performance for the

1 detection of those analytes.

2 DR. BUSCH: Jeff, while you're  
3 there, the complex of arbo-plex I know has --  
4 where you've got West Nile and we're concerned  
5 about dengue. Now you've got a standalone  
6 dengue prototype and then you've got  
7 Chikungunya. So creating a test.

8 Again, depending on the region of  
9 the world you might have all channels or some,  
10 but we sort of haven't heard much lately. Is  
11 that an example that --

12 DR. LINNEN: That is something.  
13 We do have a number of feasibility projects  
14 ongoing. That is something that we're looking  
15 at is a multiplex arboviral type test. Big  
16 question is exactly what viruses we want to  
17 include in that. But that's -- it's been on  
18 our radar for some time. We showed some very  
19 early feasibility of that assay. We have a  
20 different assay format that we're looking at  
21 right now. But it's something we're doing.

22 You know, there's a little bit of

1       hesitancy because just one of those we really  
2       don't know if it's going to go into -- it will  
3       actually become a licensed test and go into  
4       routine use in different places around the  
5       world.

6                       So that's -- it really comes back  
7       to what I originally said, that it's  
8       relatively easy to create prototypes but going  
9       beyond that we really have to have a business  
10      case.

11                     DR. KUEHNERT: I think this really  
12      does go back to burden of disease. I know  
13      that one panelist had said it would be great  
14      if there's a definition of what's needed in  
15      the field. And I think that rather than sort  
16      of picking a name out of a hat it would be  
17      good to have a priority list.

18                     And Dr. Stramer has mentioned a  
19      couple of times the effort that has been made  
20      in creating the EID list and the supplement.  
21      I think that is very useful. But I think we  
22      also need to actually look at transfusion

1 outcomes through hemovigilance and other  
2 surveillance to really make the case to  
3 everyone, industry and public health, that  
4 this is something that's worth investing in.

5 When I think about Babesia there  
6 are a number of deaths each year that comes  
7 across our desk at CDC and it makes me think  
8 there really needs to be an intervention here.  
9 And there aren't great solutions right now.

10 For dengue we just heard, I mean  
11 it's hard to find cases that really have  
12 impact in terms of transfusion-transmitted  
13 dengue for whatever reason that is. So I  
14 think when we look at the list we have to sort  
15 of try to stratify out and really look at what  
16 the impact is in terms of disease in  
17 recipients. And again I think the technology  
18 might be useful in recipients as much as it  
19 would be for donors. In fact, I think it's  
20 the place to start.

21 DR. STRAMER: I think we also have  
22 to be careful about what we put together

1       although in one assay. And if you can turn  
2       off the read of one virus versus another, one  
3       parasite versus another you may not be using  
4       all those agents in the same places.

5               We talk about selective testing  
6       models. We may be doing dengue in a different  
7       region or a different time than we do Babesia  
8       testing. So it's really hard because you may  
9       not know the absolute epidemiology at the  
10      beginning. So you want to keep the assay  
11      separate enough so you have enough flexibility  
12      to use them as needed.

13             I think it would be great if we  
14      could all have in our laboratories systems  
15      that have been validated with assays on them.  
16      And then we turn on the switch and then we're  
17      ready to implement the test as needed. But  
18      unfortunately that's not reality. And the  
19      cost and burden for doing that would be  
20      incredible.

21             I mean how long have we talked  
22      about Babesia? Sanjai, when was the Babesia

1 workshop? How many years ago was that?

2 DR. KUMAR: 2008, yes.

3 DR. STRAMER: That's one agent.

4 Here we're talking about 10 agents, 20 agents,  
5 30 agents. I still go back to the plea Rich  
6 Cable made. We talk about 1 agent, there's no  
7 question it's transfusion-transmissible and I  
8 mean I'll show you 18 cases that we've just  
9 recently had. We just had two Anaplasma  
10 cases. I mean these things are happening and  
11 we still can't really, you know, if it wasn't  
12 through Mike's efforts or through my efforts  
13 like strangling some of these small  
14 manufacturers we wouldn't even be doing  
15 anything now with Babesia.

16 DR. KUMAR: But what do you think  
17 then in multiplex platform does offer that  
18 opportunity? I mean somehow --

19 DR. STRAMER: Jeff hit the nail on  
20 the head, it's a business case. And it goes  
21 back unfortunately to Chagas. No one's going  
22 to build for 200,000 or 500,000 tests a year

1 no one's going to build a test.

2 DR. KUMAR: But somehow we are  
3 forgetting the power of technology here  
4 somehow. I think it's being somewhat lost in  
5 discussion.

6 DR. NAKHASI: Well, can I make a  
7 comment? So I think I want to go back to this  
8 concept which both Jay and Harvey put and  
9 which have been talking since yesterday. Can  
10 we have this two-tier type of system where one  
11 is basically doing this research type of thing  
12 like Charles is trying to do with you and  
13 others, to keep on doing that whereas at the  
14 same time -- because unless an antibody we  
15 heard just from the market, from manufacturers  
16 that they will -- they need to see market.

17 So can those two tracks be going  
18 simultaneously so that we do not have to then  
19 dig the well when the house is on fire kind of  
20 a thing. So you have enough information there  
21 and then we say.

22 And then also for people like



1 regulatory agencies it will be easy for us to  
2 make the recommendation at that time what's  
3 going on, you know, the disease aspect, the  
4 transfusion transmission and things like that.

5 So I know that there's a funding  
6 issue. Now the question is who is going to be  
7 funding that and all this which will come at  
8 the end of this, the last question. But I  
9 think maybe that is one of the models to be  
10 thought about.

11 DR. CHIU: Can I just briefly  
12 comment on that? So it's -- I mean in  
13 principle something like next-generation  
14 sequencing, assuming it can meet the  
15 sensitivity and specificity requirements could  
16 be essentially a pan-pathogen or at least a  
17 pan-viral assay in the sense that you could  
18 potentially consider using unbiased next-  
19 generation sequencing and validate a limited  
20 set of five to eight or just a few targets,  
21 and use that as an actual assay. And  
22 basically you would simply mask or ignore the

1 rest of the data, or use the rest of the data  
2 for research purposes.

3 The problem is we're -- in fact,  
4 early on in the original development of the  
5 ViroChip we were actually thinking that would  
6 be potentially one of the ways you could bring  
7 a pan viral assay like the ViroChip or the  
8 GreeneChip or the chip developed by LLNL.  
9 Potentially you could bring it as product, as  
10 a validated product would be potentially just  
11 validating it for a limited number of targets  
12 and then masking the probes or masking the  
13 remaining sequences but those could be  
14 potentially unmasked for emergency use.

15 Then I'm wondering whether that is  
16 a viable direction at least with respect to  
17 FDA approval.

18 DR. KUMAR: But Charles, the thing  
19 is these are investigator-driven studies and  
20 they will be subject to as long as the funding  
21 is there.

22 DR. BUSCH: But I think the

1 question though is the principle of amplifying  
2 sequences and potentially having something but  
3 you're just, you're not -- you're purposely  
4 bearing the bioinformatics, the detection.

5 DR. CHIU: Yes. And a good  
6 example would be, say, the Luminex platform  
7 where the Luminex assay has coronavirus probes  
8 but those probes, the data is not reported out  
9 because it has not been approved for  
10 coronavirus detection. However, the  
11 multiplexing does include probes for a virus  
12 as part of the assay. And this would be just  
13 on a much wider scale.

14 And the question is is that  
15 something that is feasible either with the use  
16 of microarrays or next-gen sequencing or some  
17 other kind of proteomics or any sort of highly  
18 multiplex platform.

19 DR. SCHERF: So maybe I can add  
20 something on this. So from CDRH perspective  
21 we've already done this. You described that  
22 Luminex for example has -- I think they have

1 a research version where additional probes  
2 have been made available. And in the mix  
3 itself, I mean all of these probes are in  
4 there.

5 But for the FDA-approved version  
6 or cleared version they are only allowed to  
7 report certain viruses. And the rationale  
8 behind that of course is that at the time of  
9 the clearance not enough samples were  
10 available so they couldn't get the performance  
11 of that.

12 So in principle this is absolutely  
13 possible. But I think it needs to be then,  
14 also be suitable for the different centers  
15 because you need to be aware. There could be  
16 very detailed and nuanced questions that need  
17 to be taken care of. But I think it can be  
18 done.

19 You can also consider a pre-EUA or  
20 something where you described it that FDA  
21 didn't have any assay available after the H1N1  
22 which is actually not really correct. Two

1 days after the declaration CDC had those  
2 available and public health labs were able to  
3 detect the virus. So FDA itself has made  
4 tremendous amount of efforts to actually be  
5 prepared and have avenues developed to  
6 actually address some of these points.

7 And I think it's nice to share  
8 with you that even with some of the newer ones  
9 that are coming up and coming to discussion  
10 it's already again in discussion how we can  
11 make this available.

12 But are there opportunities for  
13 additional people to help and contribute?  
14 Yes, there are. And I think everybody around  
15 this table is encouraged to do that because it  
16 helps us to actually get better and get faster  
17 to the next point.

18 But the possibilities are there.  
19 They might need to be tweaked because of the  
20 underlying analyte that you're looking into.  
21 But it's clearly doable to do that.

22 DR. KUEHNERT: To me this is not a

1 technology challenge, this is more a  
2 communications challenge and a real change in  
3 the paradigm of blood safety. Because what we  
4 would need to tell people is that everyone is  
5 viremic with something, both donors and  
6 recipients, it's just a matter of what you're  
7 exchanging.

8 (Laughter)

9 DR. KUEHNERT: And so this is not  
10 an easy conversation, I know, and I think it's  
11 going to take some time to adjust to that even  
12 for people who are experts let alone when you  
13 think about a donor collection center or  
14 hospital on informed consent. It really is  
15 going to require a change in informed consent.

16 And but I think in the end it will  
17 help better inform the true risk of  
18 transfusion. But it's going to take some time  
19 for people to adjust to that. And that I  
20 think is the bigger barrier than the  
21 technology.

22 DR. KUMAR: That's an excellent

1 point. So we are almost halfway through our  
2 time. So I would prefer to move onto the next  
3 topic here unless there are other comments.

4 Oh I'm sorry, I didn't see you in there.

5 Let's be quick so we can --

6 MS. CALLEJA: Hi, it's been a long  
7 day but really a good day. This is Khatereh  
8 Calleja with AdvaMed.

9 I just wanted to say a couple of  
10 comments. One is that I think it's really  
11 important that we're all in the room having  
12 this conversation. And to also let you know  
13 that industry is very committed to working  
14 through these issues.

15 We're new. There are a number of  
16 I think pretty challenging questions that have  
17 been posed today which we don't have immediate  
18 answers because we're just really hearing them  
19 today. So I think as an industry we can all  
20 get together, whether it's next-gen folks or  
21 PCR or some of the very important tests that  
22 we have on the market today and talk about

1       this.

2                   But I only wanted to reiterate  
3       that poor Pete Scott is up there. It's not  
4       that he's not interested or doesn't have a lot  
5       of ideas, we just haven't got together as a  
6       group to really talk about this.

7                   So I just wanted to share the  
8       commitment that we're interested but also  
9       raise a couple of issues that we're hearing  
10      that are important. Specimens is a real  
11      challenge. Coming up with flexible validation  
12      models.

13                  We understand the constraints but  
14      also that it's important. We have a good  
15      success with West Nile. We've all worked  
16      together collaboratively. We saw that time  
17      line really speed. If there's ways we can  
18      somehow focus on where, you know, and also  
19      meet -- you know, Sue's raised a lot of  
20      questions and other panels for user needs.  
21      We're thinking about the users, the customers,  
22      too. We have to meet their need.



1                   And that comes into consideration  
2           on what are those performance characteristics  
3           and what do they need and how many analytes  
4           and targets are we talking about. And you  
5           know, I think we don't want to throw the baby  
6           out with the bath water. There are a number  
7           of obviously well-characterized doing a great  
8           job in the blood centers.

9                   And really just kind of looking  
10          forward and having this conversation. So I  
11          think this is a good and really important  
12          first step. But just to kind of raise that  
13          these are some really tough questions and it's  
14          going to be technology-specific. It's going  
15          to depend on the use and the clinical need.

16                  So I guess where we can have those  
17          conversations and just think also there may  
18          not be one magic answer. I think that's why  
19          probably everyone's having a little bit of a  
20          challenge.

21                  I guess and the other thing is  
22          that we're open to looking at proposals. And

1 I'm delighted to see the agencies actually  
2 saying tell us, what do you think it looks  
3 like, what does the submission look like. So  
4 we're happy to look at that. As I said, this  
5 is just something that we'll have to give some  
6 thought to.

7 And maybe there are -- CDRH has  
8 presented some opportunities here too. We  
9 might look at that. We also might look at new  
10 ways. We've seen that in the past on some of  
11 these emerging areas and success models and  
12 ones that haven't been quite as successful.  
13 So thank you.

14 DR. KUMAR: Thank you.

15 AUDIENCE MEMBER: Yes, I wanted to  
16 just comment on Jay's model. You know, he  
17 said that -- which I agree with, you know,  
18 that we can go along doing what we're doing  
19 for known pathogens and then we need to have  
20 a kind of rapid response to new pathogens  
21 whether they be -- and as the panel said we  
22 have a group of pathogens that we already know

1       about.

2                   But I think you can't put funding  
3       on the bottom, you have to put funding on the  
4       top. That's the question because right now  
5       we've been -- we can take the current  
6       situation. We have one manufacturer and Jeff  
7       represents that manufacturer who's gotten up  
8       and said yes, we're willing to look ahead,  
9       we're willing to develop a prototype assay.  
10      We don't know that we can sell it. We're  
11      absorbing some of the costs and we're helping  
12      in the development.

13                  But you have -- there's a second  
14      NAT manufacturer, they're not even in the  
15      room, and they have not stepped up to the  
16      plate to do any of this developmental work.  
17      So it's partially voluntary and I don't know  
18      how we can sustain that because they have to  
19      make business cases within their organization  
20      as well.

21                  And so it's happening in a good  
22      way but I would say to the people who make

1       microarrays, are they ready to furnish these  
2       microarrays to blood -- are they happy just  
3       having them available for research purposes?  
4       They may or may not make money on this. They  
5       have to step up and say they're here.

6               So I mean the companies themselves  
7       have to make an investment. And they're not  
8       required to do so by FDA and they don't have  
9       a return on investment. So I think that's,  
10      you know, if we want to implement the model  
11      where is the money going to come from?  
12      Certainly blood centers aren't going to pay  
13      for that preparedness if they're not using the  
14      reagents.

15             DR. KUMAR: The question of  
16      funding where it comes is not lost on us. We  
17      did put in the end because you know the  
18      question will come to one person on the panel  
19      here only so we're being kind to her really.  
20      So we go through all these things and then --  
21      yes, exactly. Well, that's why I'm trying to  
22      push so we can get to the last question. So

1       okay, yes, Ralph, please. Yes, let's be  
2       quick.

3                   AUDIENCE MEMBER: Yes, there's --  
4       for fear we're not going to get through all  
5       the questions I'm down on question 5.

6                   A few minutes ago Hira Nakhasi  
7       raised the question to the manufacturers in  
8       the audience what are the barriers to  
9       development. And I would like to expand that  
10      same charge to the researchers in the  
11      audience. Because a lot of these products  
12      that we've talked about are not at the stage  
13      of being developed for manufacturing. They're  
14      still being developed.

15                  I mean we had 10 or more different  
16      platforms presented to us by some of the best  
17      researchers with some of the most advanced  
18      products from around the country. And as I  
19      look at them it would be very difficult to  
20      compare one to the other for their key aspects  
21      for applicability to the clinic. Throughput,  
22      turnaround time, cost potential.

1                   And so I want to know what are the  
2                   barriers to the researchers for doing the work  
3                   to demonstrate the applicability of your  
4                   product or your device as it might be applied  
5                   to a blood screening situation.

6                   DR. SLEZAK: My quick answer on  
7                   that is there are many valleys of death for us  
8                   in research. One of the things that we've  
9                   seen in the past few years is it's possible  
10                  with some of these devices to get ahead of  
11                  where the funding agencies are.

12                  And it's very similar to what  
13                  we're seeing just here in this particular  
14                  community. There's an entrenched way of doing  
15                  things. Disruptive technologies are very  
16                  difficult to bring into any new environment.  
17                  And that's what we're seeing now.

18                  A lot of us have been working on  
19                  these microarrays for 6, 7 or even more years  
20                  and we are just now having these discussions  
21                  of can we get them out of the research lab and  
22                  how. So there's a lot of problems. It's a

1 chicken and egg thing. The venture  
2 capitalists don't want to invest money because  
3 there's not a market. There's no market  
4 because there's no product.

5 I think discussions like this will  
6 help move things along but ultimately we need  
7 some of the funding agencies to step up and  
8 place some bets on at least general  
9 technologies and let us get them through to  
10 the next level.

11 DR. KUMAR: The onus in the end on  
12 the investigators will go only so far really.  
13 The funding agencies will have to take it to  
14 the next level. And then in the end industry  
15 has to pick it up obviously. So Lou, you have  
16 been --

17 DR. KATZ: Yes, Louis Katz,  
18 America's Blood Centers, Washington, but not  
19 really. I come from an area called the Silos  
20 & Smokestacks National Heritage Area. Appears  
21 to me that I'm in Iowa because I'm looking up  
22 at the top of a big silo.

1                   And I'm a recovering clinician as  
2                   some people know. And I'm going well, I've  
3                   got falls and medication errors and  
4                   healthcare-associated infections and on and on  
5                   and on at the institutions where I've taken  
6                   care of sick people over a long period of  
7                   time.

8                   And I want to know how this and an  
9                   additional X dollars on a unit of blood as  
10                  opposed to what we're being asked for now  
11                  which is it's got to cost less or we're going  
12                  to go down the street to Sue's operation.

13                  So, and this is kind of to bring  
14                  Jim Berger into the conversation because as  
15                  executive Secretary of the Advisory Committee  
16                  on Blood and Tissue Safety and Availability  
17                  they're really allowed to think about issues  
18                  of cost effectiveness.

19                  It's a zero sum game in the  
20                  hospital these days. So if it costs me five  
21                  bucks more to process a red cell it comes off  
22                  the top of something else that was going on or



1 was supposed to go on in that hospital. And  
2 I want to know what are the threats in blood  
3 safety, transfusion safety right now, ignoring  
4 what we all know is kind of an elephant in the  
5 room, the next big thing, the next bug. Why -  
6 - how do we justify consuming more resources  
7 in comparison to other priorities where the  
8 morbidity and mortality is substantially  
9 greater?

10 DR. DODD: Thank you, Sanjai. I  
11 was going to ask essentially the same  
12 question. I've been struggling for 2 days  
13 really to get a picture in my mind of exactly  
14 what is broken. Because we're talking about  
15 something that seems to be broken and yet I  
16 don't believe it is.

17 I think we've had some failures in  
18 the past. We've got societal problems and  
19 financial problems some of which that Lou just  
20 laid out that have delayed our reaction where  
21 we should have had one. But when we had a  
22 monster emergent infection in this country we

1       were on top of it within less than a year.

2       And you just heard from Jeff, you know, he was  
3       material in that. The tool is there.

4                       And I don't -- I haven't heard a  
5       real reason to angle these new technologies  
6       into this. Now, I'm an old dinosaur but could  
7       somebody on the panel tell me exactly what's  
8       broken outside of your imagination?

9                       DR. SLEZAK: I think some of us  
10      would probably think that a year is a pretty  
11      long time compared to what could be achieved.  
12      And we understand that there's all the  
13      regulatory issues that are behind that.

14                      Some of the agencies we're working  
15      with are actually trying to figure out how to  
16      go from a new disease to a vaccine in a month.  
17      And that's, you know, it's a DARPA kind of  
18      target but these are the sorts of things.  
19      It's a paradigm change all the way around.

20                      We're seeing the same issues in  
21      the vaccine safety people and the food safety  
22      people. There are a short list of things that

1       they have to test for and if you're one of the  
2       unlucky people who gets something that they  
3       haven't tested for you're wondering why.

4                   DR. DODD: Fair enough.

5                   AUDIENCE MEMBER: I would like to  
6       answer the question what's broken. Actually  
7       nothing is broken but we have the new  
8       technology at hand that has a huge potential  
9       for future patient care -- we should not use  
10      it.

11                   I did my doctoral thesis on  
12      monoclonal antibodies in blood groups.  
13      Everybody said this will never be applied.  
14      It's way too expensive, we don't need that.  
15      And they have so many problems. Well, that's  
16      all kind of true but of course the companies  
17      not investing in monoclonal antibodies are out  
18      of the market by now. And the monoclonal  
19      antibodies turned out to make it much less  
20      expensive.

21                   So this probably will also be the  
22      case with molecular technologies after some

1 investment. And we have to overcome this  
2 hurdle. The system's not broken but it will  
3 be much better once we have all these  
4 molecular methods in place.

5 DR. KUMAR: Well said.

6 DR. STRAMER: I would -- not to  
7 challenge Roger, goodness, I could be in big  
8 trouble, but I would say there's some aspects  
9 of our business that are broken, actually.  
10 I've referenced confirmatory supplemental  
11 testing before. That is broken. I mean we  
12 don't have new tests that are coming forward,  
13 that's broken. We have a Babesia problem but  
14 I feel like Rich Cable now, like harping on it  
15 repeatedly, but that's broken.

16 So I would like to see if we can  
17 bring some of these technologies into the  
18 blood centers even for confirmatory  
19 supplemental use. I asked that yesterday for  
20 some of the agents that we do test for. We do  
21 have consent to test donors for many viruses  
22 existing today. So I mean we could do

1 confirmatory testing and as part of that look  
2 for other agents.

3 It would bring technology in-  
4 house, it would bring the familiarity of that  
5 technology to the blood centers and then that  
6 way it would be a first step to at least  
7 introduce the technology. We could perhaps  
8 play with novel pathogens, you know, in some  
9 research studies.

10 And the reason West Nile even  
11 though 9 months may seem like a long time, the  
12 reason it was that relatively short time was  
13 because we did have the technology there. We  
14 knew how to use it. And this would at least  
15 introduce that paradigm.

16 Matt had talked about the burden  
17 of disease. Relatively speaking, and I know  
18 this is going to be heresy, transfusion-  
19 transmitted West Nile virus is not a big  
20 public health issue. Mosquito-borne West Nile  
21 virus is a big public health issue. So even  
22 though we responded and it took 9 months we

1       were responding to 23 cases in the year that  
2       there was the biggest arbovirus outbreak ever  
3       recorded in the United States. So it's still,  
4       you know, we felt it was important enough to  
5       really move it forward as quickly as we can.  
6       But in public health terms it's not a great  
7       deal.

8                   DR. KUMAR: In the next 2 minutes  
9       we have to really move on now. Okay, Harvey,  
10      please.

11                  DR. ALTER: Roger, I just want to  
12      say it's not badly broken.

13                  (Laughter)

14                  DR. ALTER: But it certainly could  
15      be better. And if there -- and the only thing  
16      keeping us from making it better is money. So  
17      the technology has come such a way and to not  
18      use the new technology only because we're  
19      limited by money when there are diseases like  
20      Babesia that could be prevented from blood  
21      transfusion. Even Chagas which was a failure  
22      in some ways. But I bet we prevented some

1 case of Chagas by just screening chronic  
2 carriers, not incidence infections. So I  
3 think that wasn't a worthless exercise to  
4 introduce that at some cost.

5 So let's pick the agents that have  
6 some clinical relevance that we could put into  
7 a platform and see how much it would cost if  
8 it was used on every unit of blood. And it  
9 doesn't mean we're going to do it but maybe we  
10 can work with manufacturers to see whether  
11 it's worth their investment. Because to go  
12 from where they already are to where we want  
13 to be is not that far if the regulatory  
14 requirements could be reduced to make it  
15 easier and faster to implement these.

16 AUDIENCE MEMBER: Sanjai, could I  
17 just ask one question?

18 DR. KUMAR: Yes, please.

19 AUDIENCE MEMBER: There's a  
20 transfusion transmission that we haven't  
21 talked about at all. Sue, you alluded to it  
22 a little bit yesterday I think when we were

1        talking about sensitivity and testing and the  
2        fact that we have bacterial contamination of  
3        platelets that's not addressed well at all.  
4        And whether this kind of technology could be  
5        useful for those kinds of organisms, the  
6        bacteria for testing for platelets.

7                    DR. KUMAR: I think Charles and  
8        Tom, I mean, you have entire programs looking  
9        at bacteria as well, right? You're sequencing  
10       bacterial genome and how do you apply that to  
11       platelets? Testing setting. I think it's  
12       just a matter of application like any other  
13       analyte.

14                   DR. CHIU: Yes. Basically we do  
15       metagenomic sequencing. So we're looking at  
16       the bacteria of fungi, parasites and viruses.

17                   AUDIENCE MEMBER: But the problem  
18       is you still need the bacteria in the sample  
19       and you need to wait long enough for it to  
20       grow. It's not an analytic problem, it's a  
21       time problem getting your product on the  
22       shelf. And I do agree that if you had your



1 approach it would be far better than the  
2 approach we have now.

3 But it is partially limited by the  
4 bugs have to be there. It's a sampling  
5 problem again. I'm sure you can find it. All  
6 you need is one bug in there to find it.

7 DR. CHIU: That's not unique to  
8 this obviously. But there is a sampling  
9 issue.

10 DR. KUMAR: I'm going to move onto  
11 the next question now. It comes to analytical  
12 issues.

13 And let me simplify the question  
14 here. We all know what pre-clinical and  
15 clinical validation studies require now when  
16 we're testing a single analyte. Now the  
17 question is when it gets -- we know how to  
18 review two or three pathogens. We have some  
19 limited experience on donor screening. But  
20 then it becomes multiple analytes and variant  
21 forms and so forth really. So the question is  
22 obviously they're going to do 20 pathogens on

1 a platform. We now are going to be 20 times,  
2 you know, validation studies. So what kind of  
3 validation studies?

4 And I think this really comes the  
5 question of lowering the barrier and changing  
6 the threshold a little bit so we can make it  
7 easy.

8 DR. STRAMER: I think it goes back  
9 to Jay's question about how you define  
10 multiplex. Because the definition of  
11 validation may be different. So if you have  
12 independent channels or independent -- you've  
13 segregated assays even if they're on one  
14 platform. I think the validation can be  
15 unique to that analyte. But if they're all in  
16 one tube and you're messing with that tube you  
17 want to go back and validate everything you've  
18 done in that reaction.

19 DR. NAKHASI: So are we then  
20 giving an advantage to one type of technology  
21 versus another technology? Because now  
22 already we are saying if there is a technology

1       where we have each analyte separately. And  
2       you know, you can do that whole study in one  
3       plate and everything is fine. But if there is  
4       a technology now, so the question is then what  
5       type of study. So we need to make a  
6       distinction there.

7                   DR. STRAMER: Well, you would --  
8       if everything is combined I mean your  
9       specificity studies and your reproducibility  
10      studies, you know, if they're very  
11      straightforward and you're validating  
12      sensitivity for each of the analytes.

13                   But again, if you're manipulating  
14      the analytes, the individual from CDRH said  
15      it, if you put five more analytes in it and  
16      it's all in one tube I mean I would think  
17      you'd have to validate everything in that  
18      tube.

19                   DR. ILLOH: So I'm here because  
20      I'm from the Division of Blood Applications.  
21      We're responsible for the review of HLA kits,  
22      immunohematology reagents, RBC genotyping and

1 all that.

2 What we tell our sponsors is we  
3 usually ask them to follow the recommendations  
4 in one of the guidance documents published by  
5 CDRH for which we share with them. And those  
6 guidance documents kind of outlines what they  
7 need to do, analytical studies, pre-clinical  
8 studies and all that validation.

9 However, we do recognize that  
10 there are challenges with some of the alleles  
11 or red cell antigens that need to be tested.  
12 And so we work with the sponsors individually  
13 to kind of develop a plan.

14 So I'm trying to take this  
15 discussion away from infectious disease for  
16 about 2 minutes. So if Connie has comments or  
17 anybody else from that industry can comment  
18 about that, about the challenges that we have  
19 with that that will be welcome.

20 DR. WESTHOFF: And I think what  
21 we're talking about here is the reality of the  
22 situation. The reality of the assay design

1       that you've decided to do. I agree, all  
2       primers in one tube means change that and  
3       you're, you know, everything is at risk.

4               But one of the things that have  
5       come up I think in the red cell world is if  
6       you have a low signal on one of the amplicons  
7       and a 35-plex or 36-plex does that, you know,  
8       what impact does that have on the  
9       interpretation. And so those are the kinds of  
10      things we're dealing with. If you've got one  
11      inferior amplicon in the whole mix what does  
12      that say about the total assay. And I think  
13      we're still struggling with that.

14             DR. BUSCH: Since we're talking  
15      about this immunohematology I think let's come  
16      back to Steve's question at the end of the  
17      last session. Why can't we drop serology  
18      confirmation?

19             DR. ILLOH: There's no licensed or  
20      approved molecular test. So we're encouraging  
21      industry to come in with submissions and we  
22      will review them.

1                   And like I mentioned a few minutes  
2                   ago we probably will follow the same paradigm  
3                   that we use for HLA kits, for example, using  
4                   the same guidance documents. And we recognize  
5                   the technologies are different. There will be  
6                   challenges. And I think we've been working  
7                   with sponsors to address those challenges.

8                   DR. WESTHOFF: But I think one of  
9                   the things that are important here the  
10                  technologies aren't really all that different.  
11                  It's not, you know, similar basis.

12                  And that's the other thing I'd  
13                  like to say about the infectious disease and  
14                  this arena also is I think we can't  
15                  underestimate the power of having a similar  
16                  technology to address all of these things. I  
17                  think regulatory-wise and process-wise and  
18                  implementation-wise I think we'll all benefit  
19                  from each other's experience across all of  
20                  these targets with the similar technology.

21                  DR. ALTER: Connie, while you're  
22                  looking for red cell antigens with molecular

1       technology can't you just look for a Babesia  
2       in that same red cell?

3                       (Laughter)

4                       DR. WESTHOFF:   Sure, but we'll  
5       have to change the multiplex, re-validate the  
6       multiplex when we throw those primers in.

7                       DR. ILLOH:   -- stuck to the red  
8       cell or something.

9                       DR. EPSTEIN:   If I could, this  
10      comes back to the sampling problem.   The  
11      problem with parasitic diseases is low-level  
12      parasitemia and for many of them high-cell  
13      association, you know, intraerythrocytic or  
14      inside leukocytes.   And so finding a sample in  
15      -- I mean finding the analyte in the sample is  
16      daunting.

17                      And I don't think we've quite  
18      talked enough about strategies to concentrate  
19      analytes.   And it was mentioned that in doing  
20      the genotyping for red cell antigens or HLA  
21      taking the leukocytes off the filter offers  
22      you a sample.   It's a research sample but it

1       also could be an analytic sample.

2                   I think that we need to think a  
3       little bit about getting a little bit more  
4       mileage out of that filter. I mean if that  
5       filter had ligands for analytes of interest,  
6       for example, red cell antigens expressed only  
7       in a malaria-infected red cell, or a Babesia-  
8       infected red cell you could use the leukocyte  
9       filtration process to concentrate the pathogen  
10      and then test it from the concentrate off the  
11      filter. So that's just one thought here.

12                  But when we say we've had this  
13      problem for Babesia. But the problem is that  
14      we haven't had a good technology to address  
15      Babesia. And even though as has been said at  
16      this workshop there are INDs now looking both  
17      at NAT tests and at antibody what's not being  
18      said is that that assay approach has a very  
19      high cost in terms of donor loss and that the  
20      association particularly of the seropositives  
21      with infectivity is in fact low which was the  
22      Chagas problem.



1                   So you know, you're paying for a  
2                   strategy that may create a safe unit but comes  
3                   at high cost in terms of donor loss. What  
4                   you're looking for is an assay that would  
5                   correlate at good enough sensitivity with  
6                   infectivity. And that's the thing that  
7                   nobody's devised yet. But it's fundamentally  
8                   a concentration problem.

9                   So I think the problem of  
10                  parasites is really not a problem of knowing  
11                  analytes on the organism. I mean for malaria,  
12                  and Sanjai knows this in chapter and verse.  
13                  I mean you have some gene targets that have  
14                  100 copies in one parasite. It's not a  
15                  problem. If you've got one parasite in your  
16                  sample you can easily find it with  
17                  amplification technology. It's a question of  
18                  getting the organism into the sample.

19                  So I think that where I'm really  
20                  heading here is that these different problems  
21                  don't all have the same solution. And yes,  
22                  there's something in common between parasites

1 in a red cell and doing red cell antigens, but  
2 don't forget you do the red cell antigens on  
3 the leukocytes of the donor. It's got nothing  
4 to do with testing the red cell. So, you  
5 know, it's easy to mix things up and I think  
6 that there's some thinking that just has to be  
7 case by case.

8 And it's an open question how to  
9 use these newer technologies to solve the  
10 problem of dengue or of Leishmania or of  
11 malaria or of Babesia. They're not all of a  
12 kind.

13 DR. KUMAR: Thank you, Jay. So  
14 maybe I can just focus this question in a  
15 simpler way also. Suppose there's a multiplex  
16 platform with the mainstream pathogens we  
17 screen for now. And then you have mixed the  
18 primer. Unless you -- if you're testing even  
19 one chamber you're mixing primers and probe  
20 everything, how they will interfere with each  
21 other, the hybridization to the other analytes  
22 are there. And what kind of sample size you

1 would need to look for, the effective  
2 sensitivity of one pathogen in relation to  
3 other. Or you look in the combination to each  
4 other. What sort of validation studies you  
5 will require to show that mixing of one  
6 particular probe. So you may have to go back,  
7 readjust your probe again. This probe is  
8 interfering with the detection of the other  
9 probe. So those sort of things just to put in  
10 mind really the scientific question how to  
11 address that.

12 DR. NAKHASI: I think that has  
13 been addressed in our multiplexing of the  
14 HIV/HCV/HBV. I think some of these NAT assays  
15 have.

16 But again it's two or three when  
17 it is now -- when the complexity or the  
18 multiplicity of it increases. Is it the same  
19 way to do it or there is a different way to  
20 validate? That's the question.

21 DR. SLEZAK: So I think that's  
22 exactly the point Peyton Hobson was making

1 too, that when you get to the higher levels of  
2 multiplexing you don't want to have this N-  
3 squared problem of testing.

4 Certainly there could be  
5 approaches for a large multiplex and to me  
6 large starts over 20 or 40 where if you're  
7 adding 1 more in there you rerun artificial  
8 tests against everything you had before, make  
9 sure that hasn't changed, and then perhaps  
10 take your new one and try that in concert with  
11 each of the others. So there's ways of  
12 reducing the complexity. You don't want to  
13 have to go back and do all of the combinations  
14 of all the things you already tested.  
15 Hopefully there's ways to collapse that a  
16 little.

17 DR. STRAMER: Well, couldn't you  
18 have panels to do that? And you have a  
19 standard panel and if there's changes you go  
20 back to your standard reference panel. And if  
21 nothing's changed then, you know, and those  
22 can all be in-house studies.

1 DR. KUMAR: Those are ideas we  
2 need to hear, really, standard panels, really.  
3 And having those panels available, the  
4 standard panels for everyone so people don't  
5 have to follow different standards, show  
6 different types of sensitivity criteria.

7 Okay, let's go to the floor area  
8 please.

9 AUDIENCE MEMBER: I work for  
10 Progenika and I just wanted to follow up on  
11 Connie's comments. Just to take one more  
12 minute for red blood cell antigens.

13 I would like to make a few  
14 comments that bridge some of those questions,  
15 in particular 1 and 4. With regards to what  
16 may be a reasonable validation study for red  
17 blood cell typing that includes additional  
18 antigens I just want to parallel what Jeff  
19 mentioned earlier.

20 It makes good sense if the  
21 reaction happens in a single tube that  
22 addition of a new analyte goes through

1 validation of the entire reaction and not just  
2 that particular analyte. But at the same time  
3 it may not be necessary to add to our pre-  
4 clinical study where you demonstrate  
5 performance of that new analyte. It may not  
6 be necessary to add another clinical study  
7 which may carry a larger burden of costs.

8 The second comment I wanted to  
9 make is with regards to the specificity of the  
10 assays. I'm not familiar with the infectious  
11 diseases field but for the purpose of red  
12 blood cell genotyping covering FDA standards  
13 have set a threshold that applies equally to  
14 all analytes. And that's the 99 percent that  
15 has been mentioned several times before.

16 Now, just by way of example let's  
17 assume that a small company develops a  
18 genotyping test that performs above the 99  
19 percent for 20 analytes. And let's say that  
20 the opportunity comes to one analyte, that  
21 test. Let's also say -- assume that there are  
22 no serology reagents for that analyte and

1       let's say also that the medical community  
2       would like to have some information about that  
3       analyte, that it would benefit their decision  
4       to know about that analyte.

5               Now, the company tests a new set  
6       of primers and probes for that analyte and  
7       reaches a 98.5 percent specificity. So  
8       between a potential benefit for the company  
9       and a potential benefit for the medical  
10      community stands a 99 percent threshold.

11             The final comment I wanted to make  
12      has to do with the economic implications. As  
13      Jeff mentioned before the point that a company  
14      is going to address first is whether they can  
15      make a business case about a particular test.  
16      And a business case does not mean only a  
17      market where I can sell my product. For a  
18      small company part of the business case is the  
19      cost of the validation study. And in that  
20      sense a standard threshold for everything that  
21      I have to be above may imply a burden that  
22      discards that option from the business case.

1 DR. KUMAR: Let's take the last  
2 comment because after that we'll have only 10  
3 minutes left before you give your concluding  
4 remarks. So, you have a question? A comment  
5 here please.

6 AUDIENCE MEMBER: A comment that  
7 lives off of Jay's note about the stochastic  
8 dilution of Babesia and being able to take a  
9 sample large enough to have one cell that you  
10 may detect or fail to detect.

11 There's been some debate going on  
12 here of the burden put on doing multiplexing  
13 in a single tube, the regulatory pathway  
14 burden of combinatorial re-validation if you  
15 were to add one more analyte to the tube. And  
16 the alternative being a linear problem of  
17 having 20 separate pathways for 20 analytes  
18 and adding 1 more linear pathway it's now  
19 21/20ths of the regulatory validation burden.

20 And there's a cost to that lower  
21 burden. One, it requires much larger sample  
22 size in order to provide sample of adequate



1 quantity to each of the 20 or 21 channels. Or  
2 it proportionately reduces the sensitivity for  
3 each of the analytes in those channels  
4 compared to the same volume of input going  
5 into a single tube with the multiplex  
6 amplification.

7 So I think because of that  
8 conundrum that drives the importance of  
9 considering alternatives to the combinatorial  
10 model and how could we justify leveraging such  
11 alternatives.

12 And I think one I suggested in the  
13 earlier panel this morning, the nucleic acid  
14 tests that are developed have shown over and  
15 over and over again in multiplexes going up to  
16 50 or 75 that if you take care in establishing  
17 those multiplexes there's remarkably little  
18 interference of one amplicon to another in  
19 those multiplexes.

20 And it's a very simple validation.  
21 Sue suggested panels to validate that all  
22 previous things are unaffected if you add one

1 more primer pair to a pot of 50 or 60  
2 amplicons.

3 And I think doing some strong  
4 demonstrations of the generality of that  
5 assertion will help to change the policy that  
6 right now is logged for decades into  
7 diagnostic assays, critically important to  
8 make sure they have high sensitivity, high  
9 specificity, but working with proteins,  
10 antibodies, antigens, things that are  
11 notorious for interactions that can lead to  
12 interference and sensitive to outside  
13 components in a clinical sample that can  
14 interfere with how they work.

15 But the simple hybridization, the  
16 simple amplification, the simple sequencing in  
17 nucleic acids is a remarkably more generic  
18 platform that could allow and justify a  
19 relaxed approach to combinatorial  
20 multiplexing. And I think that would be  
21 really an advantage and a good outcome for  
22 this group to consider as opposed to trying to

1 force-fit the old diagnostic validation  
2 pathways to the new opportunities for  
3 multiplexing.

4 DR. KUMAR: Okay, thank you. So  
5 if all agree maybe we should move to the last  
6 question here now, funding opportunities. So  
7 Dr. Glynn, would you like to enlighten us what  
8 are the possibilities here and what hopes  
9 these investigators and test developers might  
10 hold?

11 DR. GLYNN: Right, you should  
12 always be hopeful so that's a given. So, I  
13 just wanted to mention that NIH is only one of  
14 the major funding agencies that I think you  
15 can turn to. I'm thinking about Department of  
16 Defense and I'm thinking about BARDA, a part  
17 of ASPR. And of course CDC is another funding  
18 agency.

19 And we each have different  
20 missions. So I can tell you a little bit  
21 about NIH of course but I cannot speak for the  
22 others except to say that you should always --

1     you are welcome to always call me or someone,  
2     you know, in my branch at NHLBI and we'll be  
3     pleased to try to guide you in terms of what  
4     kind of funding opportunities we think might  
5     be available to you, whether it's at NIH or  
6     again through one of those agencies since we  
7     have strong collaborations with them.

8                 So in terms of at NIH I would say  
9     the major way to try to get funding when you  
10    are interested in developing a test is through  
11    the small business program that we have. So,  
12    and I think several of you have benefitted  
13    from that program.

14                You can apply for phase I, phase  
15    II and I think Dr. Busch has mentioned that  
16    before. You can apply for a fast track if you  
17    think your technology is advanced enough that  
18    it can directly go into phase II.

19                And we have been working actually  
20    at NHLBI in evaluating our program. And again  
21    we are very aware of this valley of death and  
22    we've been trying to think about ways on how

1 best to support that. So hopefully you'll see  
2 as we -- in the future some things that might  
3 be useful to you if you have a promising  
4 technology that you're interested in  
5 developing. So that's for the test  
6 development piece.

7 Our usual way of funding research  
8 is through of course the usual R01 grants.  
9 And for these we're looking really for  
10 innovative research, meritorious. And it  
11 usually has kind of a known practical aspect  
12 I would say which is quite different from the  
13 small business applications.

14 So if you have specific research  
15 hypothesis in mind and if through those if  
16 when you went through those you can at the  
17 same time develop an assay. That might be  
18 also a way of trying to get through that.

19 We certainly are funding right now  
20 some viral discovery programs with excellent  
21 research questions of interest. So that's  
22 always something to think about.

1                   We also fund resources. You've  
2                   heard about the large bio repository that we  
3                   have. We have about I think something like 5  
4                   million biospecimens that come from different  
5                   clinical studies that were funded by NHLBI.  
6                   They were done for heart disease, lung disease  
7                   and for primarily transfusion safety.

8                   So we have a program that you can  
9                   go on the website and you can look at the  
10                  different collections that are available. And  
11                  then you can request biospecimens if you are  
12                  interested. So that's also something that's  
13                  available to anyone who is interested.

14                 And then finally I would say for  
15                 the rapid response capability we have been  
16                 very lucky to have the REDS program which is  
17                 now in its third phase. And I would say that  
18                 if there is an emergent problem that occurs  
19                 and causes a lot of morbidity and mortality  
20                 then of course the program can be asked to  
21                 redirect some of its energy to evaluate some  
22                 research questions related to this agent.

1                   So I would say that's kind of in a  
2                   nutshell the -- but the major message is  
3                   please call, call me and then we can discuss  
4                   what we can do and work together.

5                   DR. KUMAR: Thank you very much.  
6                   I think this is what is going to drive  
7                   innovation and bring some things in the public  
8                   arena. So maybe we can mull the other  
9                   question now. Yes.

10                  DR. BUSCH: I just wanted to  
11                  follow up with Simone. There may be some  
12                  comments about how within the REDS 3 program  
13                  both the enhanced donor recipient linkage  
14                  piece and then on the international side the  
15                  large studies of obstetric hemorrhage in South  
16                  Africa and sickle cell disease. And how those  
17                  recipient populations and the ability to link  
18                  donor and recipient outcomes can help inform  
19                  the question and provide specimens to enable  
20                  addressing of risk and need.

21                  DR. GLYNN: Right. So essentially  
22                  we are launching some large studies. And we

1 are trying to concentrate our efforts more  
2 certainly on the linkage between donor  
3 donation and recipients, and doing some  
4 recipient-based studies of interest.

5 So what I should probably have  
6 mentioned is that we have a mechanism right  
7 now where you can apply for what's called an  
8 ancillary grant. And the idea there is that  
9 you have a specific research question in mind  
10 and you would like to tap in on a clinical  
11 study that's ongoing.

12 And you can apply for that  
13 funding. And it's very new. It's quite  
14 timely. And then you can therefore use some  
15 biospecimens or some of that information that  
16 we're collecting in other programs. So REDS  
17 is a program where we do studies but you can  
18 really tap in in any ongoing cohort or  
19 clinical trial that's ongoing.

20 DR. NAKHASI: So in addition to  
21 these which is very good the opportunities  
22 from the federal government and agencies of



1 the federal government. I would like to ask  
2 Sue because she is involved how the blood  
3 establishments and the small manufacturers  
4 have collaborated and how that collaboration  
5 has resulted into some kind of, you know, how  
6 those kind of opportunities may be existing  
7 there too. You have experience and I would  
8 like to -- maybe that could be explored.

9 DR. STRAMER: You mean the  
10 logistics about how that happened?

11 DR. NAKHASI: Well, you know, how  
12 the cost sharing and you know.

13 DR. STRAMER: Well, there is no  
14 cost sharing. We pay for it. I mean we pay  
15 for it through cost recovery. That hasn't  
16 been actually implemented as of yet and  
17 actually may be a very difficult proposition.

18 We found a partner if you will  
19 that's interested, has a long history in doing  
20 parasitologic and other research. It's a  
21 clinical laboratory obviously. You know, we  
22 just -- basically they had the experience. We

1 knew they were out there and we approached  
2 them.

3 But we tried the grants mechanism  
4 through an R01. We weren't successful.  
5 Unfortunately I think what Simone didn't  
6 mention is right now the success of R01 grants  
7 is, what did you tell me, 6 percent?

8 DR. GLYNN: Right. I did mention  
9 that, didn't I?

10 DR. STRAMER: Yes.

11 (Laughter)

12 DR. STRAMER: Yes. So I mean  
13 it's, you know, although you may be very lucky  
14 to get funding, Immugen didn't go through the  
15 SBIR mechanism and you know. The reason -- I  
16 had a question after I made my presentation  
17 yesterday why is the scope of your Babesia  
18 testing so small. And that's all I've been  
19 allowed to pay for.

20 And you know, the Red Cross is  
21 paying for this now, you know, at the tune of  
22 will be millions of dollars. And as Lou

1 mentioned we're losing market share. I gave  
2 a talk at Brigham and Women's and I asked  
3 them, well, how's your patient blood  
4 management program going? And they said  
5 great. We saved a million dollars last year.  
6 And they're our, you know, we provide blood to  
7 them. So that alone, that's one hospital.  
8 That alone is why funding research out of  
9 blood centers is particularly onerous.

10 I mean even getting money through  
11 the federal government, through NIH or other  
12 mechanisms, I mean the vehicles are there but  
13 they're very difficult to secure. So I mean,  
14 the financial pieces of this are extremely  
15 difficult to -- you know, it's not even a  
16 capacity issue. At Immugen, you know, I would  
17 be doing a lot more testing if I had someone  
18 to help me share the costs of it.

19 DR. BUSCH: We have that same  
20 experience with Immunetics. They did get SBIR  
21 and we're launching these studies where the  
22 NIH is funding the pivotal trials. And my

1 expectation was that the major clients who  
2 were part of these trials who are the limited  
3 screening that's funded for the pivotal  
4 trials, that they would want to go beyond that  
5 and there would be willingness to pay cost.  
6 There's no interest.

7           They know these are Babesia-  
8 endemic regions where they have cases every  
9 year but they do not have the money to pay  
10 even cost recovery to do anything more than is  
11 funded by the clinical trial through the SBIR.

12           DR. STRAMER: Well, we're not even  
13 getting the clinical trial. And everything  
14 you put in your R21 we're getting. I follow  
15 those Babesia-positive donors. We reimburse  
16 them. We want the data. We're following them  
17 once a week. We do like testing up the wazoo  
18 between Western blots and quantitative PCRs,  
19 enhanced PCRs, hamster infectivity studies.  
20 You know, we know basically what's happening.  
21 I mean we've already identified -- you're  
22 talking about just an antibody test. We're

1 going to need a PCR test on top of the  
2 antibody test. I mean, we identify window  
3 period cases.

4 And to your point, Jay, they can  
5 be found. I mean there are parasitologic  
6 samples and those in the window period don't  
7 look any different than you would expect in a  
8 viral profile. I mean we have cases with a  
9 million parasites or parasite equivalents per  
10 ml down to 18 parasites per ml. And they're  
11 detected in the absence of antibody.

12 You follow every single one of  
13 these donors and they seroconvert. They  
14 confirm. They're infectious in an animal  
15 model. And so I would almost argue going back  
16 to Babesia if we want to limit donor loss I  
17 mean we focus on that and de-tune if you will  
18 the antibody assays. I don't think we need to  
19 be picking up donors at 1 to 128 dilution on  
20 immunofluorescence that are antibody negative  
21 -- I mean that are PCR negative. We've done  
22 EPCR, we've done hamster inoculation. I mean

1 we can't find any parasites but we're  
2 deferring those donors. And then we watch  
3 them clear antibody over the next year or two.

4 But anyway, so there are ways to  
5 fine-tune Babesia, it's just we have to get  
6 more creative and look at where the important  
7 donations are.

8 DR. EPSTEIN: Just to clarify,  
9 Sue, the studies you're talking about are the  
10 studies that were needed to figure out what  
11 the safety strategies should be.

12 DR. STRAMER: Right.

13 DR. EPSTEIN: You know, when you  
14 roll back the clock 6 years we didn't know  
15 these things. And the available data at the  
16 time was that looking at index cases that  
17 there was a high rate of false negative PCR.

18 DR. BUSCH: You know, we're  
19 talking about the funding. I mean this is all  
20 good science and it's amazing but the bottom  
21 line is that in the very regions where they're  
22 reporting it they're not able to pay the

1 incremental cost of the testing.

2 DR. STRAMER: And this goes back to  
3 what Jeff said. I mean we need some kind of  
4 sustainable financial model to really support  
5 the ongoing safety of the blood supply. And  
6 without that this is all research.

7 DR. BUSCH: It just seems like that  
8 when we do recognize there's a threat somehow  
9 we get the job done. So I think what we need  
10 to do, it goes back to how do we identify a  
11 public health threat. And maybe that's  
12 something that is up to the public health  
13 service agencies to be consistent and say this  
14 is the number one threat. This is public  
15 enemy number one for blood safety and then  
16 stick with it until the problem gets solved.

17 Concerning unknown threats I think  
18 that's a lot more difficult and it's going to  
19 take a collaborative effort. We do it  
20 actually fairly frequently in terms of  
21 clusters of illness and transplant patients.  
22 We've seen rabies most recently, Balamuthia.

1 I worked it in, Balamuthia, and other causes  
2 of encephalitis in donors and recipients. So  
3 I think there I think particularly for the  
4 sequencing I think that could be a very good  
5 first success concerning this area in  
6 identifying possible pathogens in the future.

7 DR. KUMAR: Shall we close the  
8 session now so Dr. Nakhasi can deliver the  
9 closing remarks?

10 DR. NAKHASI: Yes, unfortunately  
11 we are having fun here having the discussions  
12 and I don't want to stop the discussion but I  
13 think we will be thrown out of the room I  
14 guess, is that right? Yes, I see.

15 So in the interest of time I think  
16 these 2 days have been very, very fantastic.  
17 We heard a lot of good things about the  
18 technologies, need for the technology in the  
19 blood donor screening. And what the  
20 challenges we have for those technologies.  
21 And obviously at the end of the day the cost.

22 But I'm really enlightened by



1       hearing that the industry that they are open  
2       to that. And I think they're open to new  
3       innovation and new -- they are interested in  
4       discussing with us.

5               And this is an opportunity for  
6       industry to come and talk to us and see how we  
7       can jointly along with the blood  
8       establishments solve this problem. I think  
9       that's a very important thing.

10              And I think for us the next step  
11       is to digest this 2 day's meeting here at  
12       least for FDA and to then come back and see  
13       how we can put together this discussion in the  
14       format of a publication or in future guidance  
15       or something like that.

16              So with that I would like to thank  
17       all the participants, all the speakers and  
18       everybody else here, audience, for a wonderful  
19       2 days. Thank you very much.

20              (Applause)

21              (Whereupon, the foregoing matter  
22       went off the record at 5:57 p.m.)

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In the matter of: Detection of Transmissible Agents  
in Blood Donations

Before: FDA

Date: 04-11-13

Place: Bethesda, MD

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