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AN INTERACTIVE DISCUSSION ON

MEDICAL CONSIDERATIONS OF 3D PRINTING

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Katherine Vorvolakos, PhD, FDA

P A R T I C I P A N T S

(Continued)

Dr. James Yoo, Wake Forest University

Maarten Zandbergen, Global Services Manager,

Materialise

TABLE OF CONTENTS

T A B L E O F C O N T E N T S

(Continued)

TABLE OF CONTENTS

(Continued)

P R O C E E D I N G S

Opening Remarks

DR. DI PRIMA: You guys are really good. That was quick. I want to thank everyone for joining us here at the FDA. I am Dr. Matthew Di Prima. I'm a materials scientist with the Division of Applied Mechanics in the Office of Science and Engineering Laboratories. More importantly, I am running the Additive Manufacturing Working Group with a number of other very talented people here in the room. And on behalf of the Working Group, I want to again thank everyone for being here and run through a quick -- some ground rules and some opening remarks.

So first of all, I need to point out I am not Dr. Steve Pollack. He is my office director. The office directors got called away at the last minute, so he will hopefully be swinging by a little bit later to mingle people but won't be able to give the opening remarks. That being said, I think you all know why we are here and how important it is that we're here to have this discussion.

So part of being here is we're really looking for an open discussion, so we want as much participation as possible. That being said -- you guys don't need to quite look at that yet -- everything that's said is going to be transcribed, and in the afternoon sessions there is going to be closed captioning. So I want an open and honest frank discussion. Just realize that everything you say is going to be open to the public. It shouldn't be a problem for most of you. I like making jokes when I'm at the mic, and that periodically gets me in trouble. So just be aware. We want you guys to talk, be open, honest with us. Just be aware there is going to be a record of what's being said.

Okay. In case of any sort of emergencies, we are going to exit out through the

doors. The gates are supposed to open, and our emergency assembly area is on the other side of the traffic circle. It is National Fire Safety Month, so just in case, I want to be sure.

All right. In terms of questions and discussions, this is solely focused on the technical workshop. We are not going to be talking about regulatory policy at all, that's going to be a whole separate discussion. So everything we are going to talk about is under the assumption that you are either coming to the FDA for some sort of premarket submission or you're going to be registered as a device manufacturer. So if you guys ask us any hypothetical questions, we're going to say either no or that will be for a different workshop. Today we just want to be focused on technical considerations.

The docket is live and we are going to have a link to it on many of the slides. You can get to it from the FR Notice and from the Workshop. There is a lot to talk about. We're not going to have time for all of it, so please understand if the moderator cuts you short or you don't get to speak here, please go to the docket and give us your comments. It's going to be open for a full month after this workshop. And this is going to be probably the best way for us to really gauge your opinion. And everyone who is online and everyone who is not even webcasting has access to that docket. So if you want to go back to your companies, your teams, your universities, and people have more ideas and thoughts, please feel free to share them. This is not a one-time event.

And lastly, a quick overview. Everyone should have a copy of the agenda. This morning we are going to have a series of brief talks hopefully to bring everyone up to speed on some of the aspects of the technology. The FDA is going to give some very brief overviews of our current concerns.

There is going to be some brief Q&A after those talks. Please limit your

questions to what the speakers touched on, and the aim there is for clarification. We have all afternoon and tomorrow morning for more open discussions.

We're going to take a break for lunch. When we come back, this room is going to be divided. The people with the red lanyards are going to be on this side; the people with the blue lanyards are going to be on that side. And that's going to be the breakout sessions. The way that is going to work is the FDA moderator is going to throw out a question. We are going to have a panel of I don't want to say experts because most of this room is full of experts, but we have a panel of people sitting up front who is going to facilitate the discussion with everyone else in the room to really sort of touch on all the topics and make sure that the FDA fully understands that concern, that question, how the technology is working.

So with that, I would like to invite LCDR Michel Janda and the first set of speakers up, and let's have a great day.

(Applause.)

Perspectives on Pre-Printing Considerations

LCDR JANDA: Good morning. My name is LCDR Michel Janda. I am currently stationed in the Joint and Fixation Devices Branch One. Today I'm going to present what is not considered regulatory policy but sort of where we are right now in software documentation in the premarket side.

So today I will be going over specifically orthopaedic patient matched guides and what the scope is and what I am trying to address here, why patient matched guides we consider to include software, points on existing FDA software guidance that might be useful out there for those of you that are looking to get into the market, and some approaches to producing that software documentation.

So patient matched guides are accessories to an existing orthopaedic implant system and are designed to implement the implant systems' recommended alignment in relation to identifiable landmarks on preoperative patient images within accordance to the implant's indicated use. If you are wanting to do something outside of those realms, we suggest that you come in and talk to us in a presubmission to obtain feedback from the Agency.

Patient matched guides are not regulated as standalone devices; rather, they are considered as accessories to the implant system itself, and subsequently take upon the regulatory classification of that implant system.

So why do we consider patient matched guides to also include the software? This is because as the design of the patient matched guides differ slightly between each patient, it is important to define the range of allowed designs and identify thorough process controls to ensure consistent and accurate guide.

So in general the design process includes the patient image acquisition, the image quality control and segmentation, patient modeling and anatomical definitions, preoperative planning and approval, guide design and patient match, feature definitions, and finally the guide construction. Each of these steps has the potential to employ proprietary and off-the-shelf software, and the software may be used by the manufacturer or even the end user. And software documentation is necessary, as the design of the patient matched guides is not static, it is essentially redesigned for every patient, and so we need to document the software that is being used in each stage. And in addition to that, each step is also subject to design controls under 21 CFR 820.30.

So the existing software guidance is out there to help you produce documentation for us. There are actually several FDA guidance documents that relate to

software. Some of those relate to the software validation process, human factors consideration, and a recently published final guidance on cyber security. Today these are kind of outside of the scope of today's presentation. The two guidances that I am going to highlight today are intended to aid in providing acceptable software documentation for orthopaedic patient matched guides. These include the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices. This describes software documentation recommendation based on a risk-based level of control. This document applies to proprietary software used by a manufacturer in the designing of a patient matched guide.

The Off-The-Shelf guidance document typically applies to third-party software delivered to an end user, but the same questions and principles apply to software used in the design of patient matched guide. It is important to remember that FDA guidance are intended as aids to providing the basic information needed by FDA to understand your device.

So using these software -- I'm sorry -- using these guidance documents, I wanted to give a few comments. If the software is proprietary, then the guidance for the content of premarket submissions would apply, and that's pretty straightforward. I think a lot of people are familiar with how to use that. What is a little bit different is if the software is off-the-shelf, the sponsor shall probably apply the off-the-shelf software guidance document, which doesn't seem to exactly tie into how this software is being used in patient matched guides. However, the guidance document does say that off-the-shelf software is defined as a generally available software component used by a medical device manufacturer for which the manufacturer cannot claim complete software life-cycle control. So this is the case that would apply here.

And the guidance documents intend to aid in the sponsor answering the basic questions and it should be applied with flexibility because of the unique nature in how the

software is being used in the design of a patient matched guide.

Parts of the recommended content that is outlined within guidance document may be applicable, and parts of it may not, but the general questions apply, and I've highlighted those. I'm not going to read through them, but these are the basic areas that the guidance document outlines, and this is sort of the expectations that we are looking for, for when you are using anything off-the-shelf in designing these products.

I wanted to highlight that when it comes down to asking the question or answering the question of, "How do you know it works?" sometimes that's as convenient as just it's off-the-shelf software that's already 510(k) cleared. That's simple enough. Sometimes you might be able to use a device master file, and at the last level, you would actually have to do some black box testing to show that the software is working as you would think for your purposes of designing a patient matched guide.

And then as a last point of emphasis, the guidance document also suggests that you provide a software hazard analysis, and that would also apply in this case.

So there you go. There were the questions. I apologize.

So I think we are holding questions until the end of each session, so if there are any clarification questions, I'll be happy to answer that.

I would like to introduce the next speaker. Martin Bullemer. He has been a business development manager at EOS since 2006. He has 20 years marketing and sales experience in capital investment goods with a high focus to develop solutions together with customers.

(Applause.)

MR. BULLEMER: Thank you. Ladies, gentlemen, good morning, everybody. I

hope you can hear me with the microphone. I want to give you an overview what a company like EOS is doing when it comes to perspectives of pre-printing consideration, and I will focus mainly on metal. However, some of our controls might apply for polymers as well.

I will give you a very brief overview about EOS, just one slide, I don't want to be boring, and then I will focus on the main topic.

So who is EOS? For those of you who don't know us, we are a family-owned company founded in 1989, so we are one of the pioneers in this pre-printing environment. We are located very close to Munich in Germany. And what we want to do is we want to offer solutions to our customers, solutions with an attempt to have high quality industry product out in the market and to bring it to manufacturing. This workshop is all about manufacturing and making it happen, and this is also the goal of our company.

Having said this, we want to have complete answer and solution wherever possible. We want to make it as easy as possible for our customers to jump into 3D printing and use it like it is.

The markets we are serving are mainly the high quality industry markets, like aerospace, medical, general industry, and also some others.

To just give you a number, last quarter we shipping more than a hundred systems just with a very high percentage of metal systems. Most of them are going into manufacturing already in the aerospace industry.

We are committed to innovation, to quality, and we believe that sustainability will be a major driver for us during the next 10 years because sustainability, I believe it can be something like we have seen in the '80s and '90s when we all had to have the right quality management in place. I believe this is coming up pretty soon.

So what do we do? We actually, as a machine manufacturer, we do not only produce machines. We produce machines, but we do materials at the same time, and we develop the parameter sets to run these machines.

And looking at these triangles, you will see that quite often in my presentation because this is how we think about the process. All these corners of the triangle, they depend on each other. If you change anything, and at each corner, you will have different results. And only if you have a stable triangle, a well-balanced triangle, you will get high-quality parts out of that. It's quite important to the few we have in our technology, so it's not only about one corner, however, I will focus on the metal corner, on the material corner, in that presentation.

When we do a metal powder development, we ask ourselves, "What do we need to have?" We need to have the right mechanical properties, we have to have the right chemical properties, we ask the ask the function of performance, what are the regulatory requirements for that. We do a lot of FMEAs of our suppliers, and about our own products, about the machines, and our processes. The outcome of that will be a chemical specification, the particle size distribution specification, the method, how we do it, and we have all the quality controls in place. That's all mentioned then finally for the end customer and the material data sheet.

So how do we come to that? Very simple. I think everybody in that industry knows how verification and validation works, and we do exactly the same control in our company.

What we get out of that, again the triangle, you get much more than a material data sheet out of that. You are getting a system, a software, and a parameter set specified at the same time. So it's not only about the metal powder itself that you get, it's about the combination of the triangle because that will result in a high-quality product.

So what do we do? We ask our supplier network, we tell them how we want to have the powder. We get the raw material batch and go the whole cycle, and I will go into details about that. We do the raw material quality control. We actually produce parts; I will come to that later. We do a lot of data collection, write documentation, and then we ship it to our customers, sometimes even in very small packages. We give it to our customers, and, of course, being a company selling this stuff, we are obliged to listen to our customer whether it's good or not good.

So what do we do? We first select the right materials supplier by just getting a lot of batches and testing them. Then we make a detailed specification about the powder, and we establish the intake control. We have a clear identification of the lot numbers we are getting in. And we have dedicated storages for all our powders.

We produce parts, and again have the triangle in mind. You only know what you are doing if you actually produce real parts. If you stop at just raw material intake control, how do you know that you get the right quality when you're building a tensile bar or actually an implant? So this is pretty important. And we do all the testing of the material properties to meet the specification and the material data sheet we created before.

Doing that, we create a lot of data. I think we have tons of data, about three printing processes of metal already, in our storage. We do the right documentation. And finally, when it comes to the market, which is now a little bit off topic, we have the possibility to have very small packages. We have a stock in-house to serve our customers.

And again coming to the triangle, we can be a single point of contact to our customers, whether it's the parameter, the machine, or the metal powder. It's quite good for our customers if they like it.

So you ask yourself, probably yourself, how can we do all this? And there is nothing miracle about it, you just have to have the right foundation for it, the right quality management in place, to do that.

We do our metal powder development and all the sourcing and all the testing we do at our subsidiary, 100-percent-owned subsidiary in Finland, it's EOS Oy, and this subsidiary is certified according to ISO 13485, so that definitely gives a good foundation to all these controls. And we have the certificate according to the medical device directive in Europe.

So what do we do in detail? Just a little bit of insight what we do. When we do the raw material approval, we have a work order traveling going through the material, with the material. We are building quality samples. We have a separate record for that. We do internal quality testing, and I will come to that a little bit in detail. We have separate measurement protocols. We do the quality approval. We have a bill of materials going with that. Label printing, packaging. We look at if we have deviations. All the controls you have to have if you want to have a high-quality product.

How do we do the quality assurance? Like I mentioned already, we actually build parts, and again I really want to emphasize if you want to be sure you have high-quality parts, you have to build them. You have to have a machine under the right conditions which is serviced very well. You have to have stable parameter sets. You are not allowed to play with these parameter sets every day, you better lock them down, and then you produce the parts.

What we do in our office, we just build tensile bars in each directions. We will have a discussion later on whether it makes sense to test X, Y, Z directions. We test all of it, and especially when we build vertical bars, these are the most critical ones, we want to see what is the outcome of them.

Then from each of these lots we are getting in, we are checking the chemistry, we are checking the chemistry of the powder when we have the intake control, but we are also checking the chemistry of the build parts to exactly know when we write down on the material data sheet or in the mill test certificate that we are sure what we are delivering to our customers.

Whenever we can't do the testing ourself, we do the mechanical testing and the chemistry testing at certified labs and again use a contract partner who actually really can do the stuff according to the right controls.

The things we do internally, sample preparation, density measuring, microstructure analyze. We do also according to GMP, and good GLP regulations, otherwise, if you are not established to that level, you better do it outside at the right partner.

And that's all we do here. And the result of that is that the materials is definitely a very important part to that triangle, but it's not all. All of the discussion we are having today will be about the printing in the machine and how to develop the parameter set. And some of us here in the company, they call these triangle "magic" triangle, but if you have everything under control, what I have seen here today, it's nothing magic about, you just have to work on it and have the right controls in place.

Thank you.

(Applause.)

LCDR JANDA: Thank you. The next speaker today is Maarten Zandbergen. Martin leads Materialise's Global Clinical Engineering Team with responsibility for all surgical planning, guide development, and surgeon interface.

MR. ZANDBERGEN: Thank you. Good morning, everybody. I would like to thank

the FDA for giving me the opportunity, or giving us the opportunity, to speak here today. And I will be giving some insights into perspectives on pre-printing considerations, also a little bit about printing and post-printing as well, and then the experience that we've had at Materialise over the past few years.

And I would like to start by introducing these two gentlemen because I think they're a very good example of what we try to do at Materialise. It is within our mission statement to create a healthier and better world through additive manufacturing and its applications. The two gentlemen that you see here on the left side is Dr. Daniel Buchbinder, a long-term user of our technology, and on the right side is his patient, Carmine, from New Jersey, who at a certain point in his life was diagnosed with oral cancer, cancer in his lower jaw, and I'll talk about it, his case, to give you an example basically how we helped this patient together with the surgeon.

So by giving a little bit of background about Materialise and where we started. Here you can see Mr. Fried Vancraen, who is our founder and still to date our CEO, who founded Materialise in 1990 after he saw his first 3D printer, or stereolithography, in a research institute, and basically in the position that he held at that point, he wasn't able to get a lot of traction to purchase such a machine at the Catholic University of Leuven. At that point he made the bold decision to start his own company to what has become Materialise to date. We have grown to a global company. We have offices all over the world. And earlier this year we hired employee number 1,000 for the company, which was a pretty big milestone for the company.

Just to give a little bit of detail about the Materialise structure, we're active in various fields, for instance, in industrial production, in development of 3D printing software,

and then the medical field as well. And I will be giving a little bit more insights in what we do at the medical side of things.

Even from the very beginning, from when we had just had that first machine, we were already active in this medical field and started to produce anatomical models. This was one of the first models that was produced at Materialise, a skull model that would help a surgeon to prepare for his surgery. And we've come a long ways since then. And here at the bottom, you can see the typical workflow that we follow for every single case, every single patient, that is treated with our technology.

It basically all starts with scanning a patient, that's the first step, and over the years we've worked with scan centers with radiologists to make sure that when patients are scanned, when images that we receive that we get in, that they have sufficient quality, making sure that the end product, which will be determined by what you get in, by the input that you get, is of sufficient quality.

And then we have developed software, software called Mimics, that has grown to be the industry standard for medical image processing that really converts the stack of 2D images that comes out of a CT or MRI scanner and turns that into a virtual 3D model, which gives you an accurate representation of the patient that you're treating.

With Mimics, you can do a lot of different things. Here you can see an example of a subject where different parts of the anatomy are being segmented. You can see the spine, the whole skull, the lower jaw. That is all segmented throughout the software. Not only hard tissue structures can be segmented, you can look at soft tissue structures as well. Here you can see the face and then the skin. Nowadays hearts are also being segmented and anatomical models of hearts are also being used.

You can take it even one step further, add another layer of complexion, and map it with 3D photos. It's an example you can see here. At Materialise, we're quite cost conscious, so we don't use any attractive models, we use our own employees as models, as you can see here.

(Laughter.)

MR. ZANDBERGEN: But also Mimics really does that, so it takes your stack of 2D images and then turns it into a virtual 3D model, and based on that, you can start to do a lot of different things, what we define as engineering anatomy. So based on your virtual 3D model, you can start making measurements, you can make designs. An example here of a cranial plate design. You can link your designs or your anatomy or your implants that you design, you can link that to FEA or CFD, CFD analysis.

Another thing that you can do and that we do routinely, again going back to our workflow, is based on our virtual 3D model, we can then use that to start and plan surgeries in a virtual environment. We do that for a lot of different applications. The example you see here is a craniomaxillofacial case. This is actually Carmine's case. You can see on the right side where we planned the resection, so planned the part of the bone that is going to be taken out of the lower jaw.

And in the craniomaxillofacial fields we plan these surgeries in interactive planning sessions, so we have teams of clinical engineers that go into these online planning sessions and plan the case together with the surgeon. We have certain scripts and protocols that we follow to make sure that every single aspect there is covered for every single surgery.

For other types of procedures, like total knee replacements, we developed softwares where surgeons can log into and plan their cases on their own, so there is not a direct

interaction required with a clinical engineer, so that they can go in at their own time, fine-tune a surgical plan, and basically approve that and to then initiate the design and production of the surgical guides.

So once a surgery is planned, we go ahead and design these medical devices. Again for different types of applications, you have different types of surgical guides. On the left side again you can see the models in white, which are the surgical cutting guides that will guide, at the end will guide, the surgeon in the OR that will help him to transfer the surgery that was planned in the virtual environment to the OR. In the middle you can see an example of guides that are being used for a unicondylar knee replacement and on the right side guides that are being used to assist in a shoulder replacement, so a total shoulder joint that is being placed.

Once those devices are designed, the surgeon sees those and approves those before we go ahead and produce them. We use different types of manufacturing techniques. One is laser sintering, which is routinely used for the production of our surgical guides, which are produced in polyamide, and then we use stereolithography for our anatomical models. The resin that we use has the unique feature to color specific features of the anatomy. As you can see here with the skull model, where teeth and the nerves can be selectively colored so that the surgeon has that in his hands either before stepping into the OR or even in the OR.

To make sure that every single case follows the same process, as I said, every single case is unique yet you want to follow the same process and make sure that all required and necessary quality checks are being performed. Specifically for the production environments, we saw the need to develop a platform to make sure that everything comes together in one system. The platform that was developed is called Streamics. We use it daily at our medical and industrial production, and it really follows every single part throughout its

whole case flow, so you go from data preparation from the time when an order is created through build preparation to tracking the actual build of your part, of your machine, to post-processing, making sure that your part, when it comes off the machine, the required actions are taken to make sure that the accuracy and the quality is sufficient to then ship it out to the physician.

So then at the end, our surgical guides, they are medical devices that are being shipped to the OR or to the hospital. They are sterilized locally with steam sterilization techniques and then autoclaved, they're being sterilized, and then being utilized in the OR to help the surgeon transfer what he planned in the virtual environment to the OR.

As I said, we are active in different fields. We have developed solutions for craniomaxillofacial surgeries, some of the guys that I showed you to assist in craniomaxillofacial surgery. We have guides for complex osteotomy treatments, for hip revisions, and oncologies. The majority and the largest volume that we see today is for joint replacement guides and for total knee, shoulders, and hip implants. And then we've also started, through our daughter companies, we started to design and produce implants as well, so not only the surgical guides that are used in the OR but not implanted, but also the implants itself, so for the craniomaxillofacial implants and then implants that assist for hip revisions as well. Those are currently not available in the U.S. market, though.

Over the past few years, we have helped more than 150,000 patients with this technology, so more than 150,000 surgeries that were assisted with these 3D printed medical devices. And then coming back to our patient Carmine, who was a very successful surgery, here you can see the virtual 3D model. In blue you can see his lower jaw, where at a certain point he was declared cancer free, but unfortunately due to all the irradiation, his jaw and the bone in

his jaw was becoming so weak that there was a high risk of fracture under normal load, and that's where Dr. Buchbinder made a decision to use this technology, to plan this case virtually, to assimilate the osteotomy so he could accurately see where he wanted to make his osteotomy, make his cuts.

Here you can see again the design of the devices of the surgical guides that would guide his osteotomy planes and it would also predrill screw holes for the plates that he would put in place. Here the defect that was going to be created would be replaced with a fibular bone graft, so the fibula, one of the bones in your lower leg where bone is harvested, so healthy bone that is harvested and then replaced or to basically fill the gap to give sufficient support again for the new mandible, for the new jaw, that is created.

And something that brings everything together is a plate, patient-specific plates, that is then manufactured by our partner, DePuy Synthes, that then really brings everything together. So with the surgical guides and with the patient-specific implant, everything fits together. In this case, it was a very successful surgery.

And this is Dr. Buchbinder and Carmine I believe 4 weeks after his surgery, so quite a severe surgery, and a very successful result. And I just wanted to share this case, I think it speaks to the mission that we want to bring to the world in creating a better and healthier world.

So thank you.

(Applause.)

LCDR JANDA: Thank you. I would like to introduce the next speaker, Andy Christensen. He joined 3D Systems as Vice President of Personalized Surgery and Medical Devices earlier this year. Before that, he was President of Medical Modeling, Incorporated, in

Golden, Colorado.

MR. CHRISTENSEN: Thank you, and good morning, everyone. Let's see here. It's really a pleasure to be here today. You know, in front of this group, it's a pleasure to be here with peers and colleagues, with those in the FDA that are setting a policy on this, I think it's really a timely thing about just 3D printing in general. It's been around for a long time, but it's timely that we're here today, and I'm pleased to be here.

I joined 3D Systems by way of acquisition about 6 months ago, so I'm here as a user of technology as well as now a producer of technology. And a lot of kind of what I hope to spark conversation is focused on my basis as a user of technology. And we have a lot of experience in plastics over the years, and some in metals.

This morning I've been asked to give some discussion points on pre-printing considerations for plastics, so that will be my focus.

Going back, I wanted to take a brief minute to talk about, as the other speakers have, I think it's important that we get some idea of where we all come from. 3D Systems started with an idea and started with this part, so this is circa -- not circa, this is March 9, 1983, the first stereolithography part that was ever printed. This started, this was done by a guy named Chuck Hull, who is created by many as being the inventor of 3D printing. Chuck is the CTO of -- he founded 3D Systems at that time in the mid-'80s and is currently still very active with 3D Systems as our CTO, and he's a guy that's not sitting around. I think at one point he tried to retire and I believe came back to work because he found that that wasn't for him. So I give a lot of credit to him in the past and a lot of credit today. He's very active and not sitting around as a figurehead but actually there doing the work.

I thought today, you know, interesting that we're all here. I think a lot of the

technology for plastics is focused on personalized surgery, so it's an area kind of very near and dear to my heart, near and dear to 3D Systems' heart. This image as well is an interesting image, and many of you in the room would recognize it as some kind of a radiology, you know, some kind of a medical image. It's actually the first clinical CT image done about 43 years ago this last week in the UK, and, interestingly, done of a patient with I forget the issue, but they had some kind of a frontal -- there's an issue in the frontal lobe there on the patient's right. And this guy, Sir Hounsfield, was the guy that developed that technology, and I think it's interesting that this goes back 40 years, Chuck Hull's invention goes back 30 years. Those two together really formed the basis of today, giving us the tool, you know, giving us the basis of tools that are available for personalized surgery.

So as I talk a little bit about 3D printing, 3D printed parts, again focused on plastics, I'm going to show some what I think are fairly dry slides of some text talking a little bit about I guess questions, you know, and me trying to raise questions for all of us. I think this is a great spot to have as a discussion point. I would want to start off by saying that 3D printed parts and 3D printing as technology isn't new, you know, and it's been around for a long time, it's been around in the medical device field for a long time. I think that even in the FDA's archives there would be devices going back more than 15 years ago that had some 3D printing aspect to it, which I think is very interesting.

But these are, you know, today you would find them used as medical devices and you would find them also used as indirect parts to be used to construct medical devices or as some part of a design chain to be used for medical devices. And I think that depending on which of those they are, the controls and all of this, the considerations to be done, pre-printing, during printing, post-printing, very much they need to be driven by the actual use.

I also feel like I would agree with the colleague from Materialise talking about the fact that you can't look at these in isolation, so you can't look at pre-printing and mid-printing and post-printing kind of in isolation of each other and that you've got to look at a product and you've got to look at the intended use and you've got to look and see what process and what material and what workflow you need to use to get to the whole -- you know, the end product that meets your needs.

In this case, I'll talk a little bit about we do similar work. Materialise and 3D Systems have some similarities and as collaborators and competitors in different ways. I'll talk a little bit about some of our history in using models and using guides and guided surgery and kind of where things have evolved to today, and some considerations surrounding how you would look at these from a plastics printing standpoint.

So I liked Martin's presentation a lot from EOS. I think focusing on the fact that you have inputs and you have a process and you have controls, really a lot of it for us comes down to raw materials. And on the pre-printing side, you have to look at what you're putting into a process and then what you want to get out, and you have to choose that material in that process quite carefully, and I think that looking at controls on the front end and controls of the process can give you a controlled output, and that's being shown time and again today, and I think that, you know, we talk about -- Materialise showed some numbers about tens of thousands, hundreds of thousands of patients. I think we all could talk about large numbers of patients that are being helped by these technologies. So they aren't novel, and they're here and they're controllable processes, and I think that's an important thing for all of us to kind of think about today.

When you think about which material, there are many -- you look at strength,

you look at resolution and accuracy, and you look at biocompatibility, all of these things, you may have different requirements for your product, and I think in the room we have obviously got a lot of industry, and so looking at this from a plastics standpoint, most folks would be thinking about 3D printing for guidance. And there are some here to talk about 3D printing and plastics for implants, and that's a whole I think different discussion, and I know Severine will do a good job of leading that discussion later.

But talking about plastics and talking about guidance, many times you need -- you know, you have certain requirements for accuracy and you have certain requirements for what the material feels like, what it looks like. And you can't just choose any material. So I think most everybody in the room probably understands that, you can't choose a material A and a process B and put them together and hope that they work. So you're kind of choosing both at the same time. You're either led to choose a process and then you have the material that comes with that process, or you're led to choose a material, and you get the process that comes with it, or vice versa.

At 3D Systems, this is a small grouping of our different types of platforms, and each one of them would have multiple materials that can be run, there's a lot. You know, we have something -- across the company I think we have eight different print engines, so it's a lot of different ways to print things, and I think for medical devices and for plastics specifically, we're talking about very few of those processes being used, and probably a wide range of them used in different ways. So we would see researchers using every type of equipment.

When you get into real production settings, you would really be finding yourself with multi-jet modeling, you would find yourself using stereolithography, you would find yourself using laser sintering, and you would find yourself using maybe color jet printing in

different ways. All of this realm, you know, you're talking about machines that literally run from hundreds of dollars to millions of dollars, and there is a lot of difference in there.

So I'm not going to talk to all of that, but just to give you some idea of the scope, materials, as we talked about, are tied. Formulations, I found this as someone outside of the -- you know, as a service provider and as a business trying to provide parts, formulations are very -- you know, are kept as trade secrets, and I think it's a little bit of a challenge, you know, on the plastics side.

Now, I think on the metals side, it's different. The metals have established standards, and you've got established ASTM standards for kind of conventionally manufactured parts and materials, so you can look at titanium alloy and you can find an ASTM standard for a raw titanium alloy for both a conventionally manufactured part as well as an additively manufactured part, and you've got things like chemistry to be able to test completely, and you know what should be in there.

On the polymers side, it's different. So we have to look at polymers from a user's standpoint as kind of like a black box, I mean, almost like software where you can't know exactly how it's working, and the same way with materials. You have to test them and you have to test them a lot because you don't know exactly what's in all of those materials because they're trade secrets.

In that way, contracts with your suppliers, as a user, are really important. And things like change, Martin mentioned change and the fact that you can't just decide to change a software version today or a material today, it's really important. Obviously, choosing materials, there would be all kinds of different things to talk about, you know, for how they look. Some of the things we've done in our past can look like a lot of different things. Stereolithography here,

primary the translucent parts, although you see many opaque parts as well today, and processes like color jet printing and multi-jet modeling and many others that are used. Some of these processes allow you to selectively color certain areas. Some of these parts are things that can be cleaned and sterilized; others are meant to really be kept outside of the OR. So there are different kind of levels.

Components, I've talked a little bit here about how these are used. As we move forward, I think what we've seen in the industry is a movement from in the beginning the use in medical was really for anatomical modeling, and that's moved to then using data in a digital format to design custom implants, was kind of the interim step. The step today is then using that data to plan surgery and to get to outputs of things like templates and guides. So you're not really just outputting a facsimile of somebody's anatomy, but you're using it to guide the actual surgery.

And I think from there, you know, there's a whole step ahead which is actually creating bioprinting parts, which I think is potentially outside of some of the scope of this group, but I think it's a really interesting kind of future step as well where you've got 3D printing as a good application to produce living parts.

Certain industries, like the hearing aid industry, have moved to being almost 100 percent digital, and many in the room technology-wise have been part of that. You know, Materialise played a role in that, EOS played a role in that, 3D Systems played a role in that, helping take an industry that used to be very analog and moving it to being digital with a digital output by additive manufacturing.

So talking about batching and recycling, I mean, I think some of this, like all of the processes are different, you know, so they're all different in what you're going to do and

how you're going to control laser sintering versus stereolithography versus multi-jet modeling, they're all going to look a little different, and I wouldn't be able to go into detail, but I do think that you need a -- many of these processes require some baseline amount of material, and then you add material to it. So they're good questions about, how do you do that? and how do you recycle powders? how do you recycle resins? how long do you use things? Some of these things come with shelf life or expiration dates, and you've got to contend against it, and I think it's an interesting question.

Validations have been talking about. I think we would treat in our way the same. You would have to look at what you can, validate, and look at what you have to verify or what you want to verify, and there are some -- you know, for different devices, you may have ways of validating most all of it, and for other devices, you may be left to verify because it's very hard to validate, and I think that as a user, again, you'll find a way that best suits your needs in compliance with the regulations.

We talked a little bit about -- I think Materialise touched on this a little bit, you know, just for the application of the knee, there is a lot done today for planning to guide cuts to place standard implants for the knee. So total knee arthroplasty done with Materialise and us and many others supporting products on the market, many devices and many tens of thousands of patients per year are getting treatment, getting better treatment than traditional techniques, using additive manufacturing as the way to get parts out, and I think additive manufacturing for these applications is really a perfect fit.

Quality control -- so I switched from like interesting slides to a lot of text -- so quality control and things like CFCs and testing of materials before you even put them in a machine, testing of materials when you put them in a machine, how to do that, you know, I

think we've taken an approach that there are a lot of times you can put a material in a machine in a quarantined state, produce test samples, put it back in a quarantined state, test the test samples, and then clear or release a batch of material. There are many ways to do that. Sometimes you can pass that on to the supplier of the material and there are sometimes when you're going to have to do that yourself, and I think that depending on your need, depending on the supplier, there are many different ways of doing that.

And then again quality control. I think differently in plastics, many of these materials are novel, you know, they're not typical plastic materials, they're used in kind of the additive manufacturing field. And in metals I think it's different, where you have very established standards for metals and you know what that metal is. In plastics, it's different. So again kind of looking at it from that black box standpoint and looking at things like mechanical testing, dimensional, and biocompatibility, which really are the three kind of key areas.

You've got other things like design. This is kind of a future idea for creating braces using technology. So you've got a combination of taking data -- and I think I talk about preprinting software here for a second -- but we have a concept that we call the digital thread, which is kind of that hole in between, you know, from the patient getting a CT scan or an MRI and then using that data to guide treatment, all the things that happen in the middle, and there is a lot that happens in the middle. So I appreciated the conversation earlier about software. There are a lot of pieces that have to work together. Some of those may be custom pieces, some of those may be off-the-shelf pieces, some of those may be pieces from who knows where, and put together, they all kind of have to be together as a system.

So, again, looking at these products and these ideas is you can't look at pre-printing and during printing and post-printing the same way in the digital piece; you've got to

kind of look at all of the pieces together and how they all flow.

I'm going to show a similar case to what Materialise showed, just the concept of our product called VSP reconstruction, which is a product that takes and guides and mandibular surgery, so reconstruction surgery like we had seen earlier. The concept, though, you know, really this clinical transfer concept, so using a graft from a leg and transferring that plan to the patient using guides, you know, and in this case, I found it interesting earlier, the I think the concept of systems that are software-based and hard -- you know, the software and the parts and all of the pieces that go together as a single tool we have as well found, and these things are used. This you could think of like a miter box, you know, where in the end those cuts are going to form that mandible, and I think the next slide is a little bit of blood, but in surgery those parts being used and being used in the real world every day for applications of reconstructive surgery.

So I appreciate the time. I'm really looking forward to the rest of the discussion. And thanks again for having this meeting.

(Applause.)

LCDR JANDA: We do have some extra time, so if there are any clarifying questions.

(No audible response.)

LCDR JANDA: If not, we can save that time for lunch and move on to the next session. That will be fine.

Perspective on Printing Considerations

LT COBURN: Thanks very much, LCDR Janda. My name is LT James Coburn. I am a researcher in the Office of Science and Engineering Laboratories. And I am also helping with

the working group that is leading this conference. Thanks again for coming, everybody. And I will have some brief, also texty, slides. We'll see how that goes. All right.

The goals of my talk are twofold. One is to summarize our current approach towards 3D printed devices and 3D printed guides. Hopefully, I will get some of that done. The second goal is to introduce our speakers. That one should be easy.

The first thing, as was alluded to earlier, this is not a 1-dimensional process, this has, as Martin mentioned, three corners, where you have your material, your processes, and your devices, and through printing, the software control is one of the major aspects that we look at. Who has control of the software? Are all of your parameters controlled by the vendor? Are they controlled by the person who is making, say, the medical device? Are they configurable by the users? Where are there limits? Where are there not limits? And then also for these different kinds of processes, especially ones that require extraneous support material, powder-based processes included, who decides where the supports are, what the fill algorithms are if you have a polymer process, and how does that affect the part of the device? So who is controlling that and how does that affect your final product? Is that under the control of the device manufacturer or is it under the control of the user?

As was talked about in the last session, materials obviously play a big part in this depending on the kind of printing you're using and the material that it takes, you could have different powder size distributions, if you're using a filament distribution system, you can deposit that at different speeds with different heating. Inside there is basically a convection oven, and how does that affect the deposition and adhesion of those different polymers or of the melting of the metal?

And as I mentioned, it's probably a simple analogy for this group, but often this

works very well, is, do you think of it as an oven inside and the build platform is your baking sheet there where every part of your oven may or may not have the exact same heat distribution, may not have the exact same properties? So in this case your rolls might come out a little underdone on one side and a little overdone on the other side. And the things that affect that are your beam intensity for your electron beam or your laser intensity, the speed at which it scans, obviously the environment inside the machine, and then any kinds of local changes in chemistry because a lot of these processes create a lot of heat, and that can change your material and it can change your part as it goes. So really the question here is, how many of those things can you monitor, how do you monitor those things? can you monitor them as the process goes on or do you have to verify afterwards? can you validate these processes? And documenting and knowing what you can validate versus what you have to verify is very important when you're trying to determine the safety of a medical device.

Which leads us, of course, to quality control and the things that really are necessary to establish that you have been able to verify, been able to validate, or know exactly what's going on in your process, flow diagrams, reproducibility. Obviously, as EOS said, they test a lot of their material just to make sure that everything falls within the parameters. And everybody has mentioned that verification and validation is an integral part of their industrial processes.

But then, of course, there is also the question of, when do you have to revalidate? When you have an installation at a medical manufacturing facility, what constitutes a change in the process? If they are supplying their own material and they get a different supplier, do they have to revalidate the process? What other aspects require revalidation?

Then, of course, the other question is, how do you identify problems that crop

up during each run if you're not verifying every sample?

So that was a quick overview of what we are thinking about that, so hopefully we'll have enough time for some questions after this. As Matthew mentioned at the beginning, the workshop has the comment period open at the *Federal Register*. There is also additivemanufacturing@FDA.hhs.gov., which is the e-mail address for additive manufacturing here. And I would like to acknowledge the working group, who has done a lot to put this together.

With that, I would like to introduce our subject matter experts, which, as, again, Dr. Di Prima said, everybody in here has some level of expertise, but these are the people that will have a microphone at the moment.

(Laughter.)

LT COBURN: So Jon Cobb currently serves as the Executive Vice President of Corporate Affairs at Stratasys. He joined Stratasys in 1995 as Vice President of Marketing, and he has held a variety of positions, including Vice President and General Manager of the Low Cost Dimension Printer's Business Unit.

Jon?

MR. COBB: Okay. Thanks. Thanks very much. I appreciate it and I appreciate the FDA letting us come in here and talk a little bit about Stratasys.

As mentioned, my name is Jon Cobb. I've been with the company for about 19 years, so a long period of time. When I first started with the company, there were those people that were questioning whether or not 3D printing was good for prototyping, and now we've moved a great deal from that particular area.

The way I look at it is Stratasys is really an enabler, if you will, as far as working

with a wide variety of customers. As a company today, Stratasys really started with the idea of utilizing the FDM technology, that's the foundation of the company itself, and if you look at Stratasys today, it's the culmination of a merger between Stratasys, FDM, Eden Prairie, and Objet Technologies about 2 years utilizing the Polyjet, and then MakerBot acquisition about a year and a half ago. So as we look at it, we have a wide variety of technologies, a wide variety of systems, that are available for 3D printing, servicing a wide range of applications.

If you look at the opportunity -- and it was mentioned here a couple times, so I'll be a little bit repetitive -- it's all in the idea of the personalization, and the personalization really comes in that area of not only the design flexibility that you have, but then also in the manufacturing flexibility. And I look at manufacturing flexibility and take maybe an example from the aerospace industry where you look at various wing designs now on UAVs at this point in time that utilizing 3D printing with the various support mechanisms that we have at this point in time allows for very, very lightweight, really innovative designs.

So you're really starting to look at, if you will then, promoting different manufacturing techniques, and obviously an opportunity for cost reduction and better quality parts.

There is also I think from an FDA standpoint, as has been mentioned here, there are a lot of issues, and the first one is in fact the personalization. From a Stratasys standpoint -- and it was mentioned earlier here -- we look at the way we manufacture the product. The products themselves are manufactured to design specifications at the initialization of the process of building, and then the products themselves are manufactured to those specifications, and then at the end of the production area, of course, tested to those specifications. I'll get into a little bit of detail on that, as I was asked to do.

So really the validation of the design all the way through our manufacturing process, and then we will assist a wide variety of companies that are using our products, both material products, because we manufacture material, and then also the system products as well in the validation of that process, and then looking at and evaluating the new materials and potential new build processes.

What I will focus on here in my next 10 or 12 minutes is really a quick look at the technologies that Stratasys has. I'm sure most of you are familiar with it, but a couple new pieces to the story that I wanted to talk about. A quick company update. And then a couple of slides then on the flexibility, if you will, of manufacturing with FDM, some of the parameter changes that can in fact be made, and then look at our process for the material development that we have.

First of all then, if you look at Stratasys, we've been in the business for a little over 25 years, 24 years as a public company under Nasdaq under SSYS, really began the company with the printing of wax material and then moved very quickly into the production of real thermoplastics, which I think if you look at Stratasys -- and this would be the Eden Prairie or FDM type of technology -- thermoplastics are really what I think put the company on the map starting with the ABS material and then followed really from that point very quickly with the idea of a soluble support, so getting the capability of very, very fine feature details that could be wiped away, if you will, with a soluble support.

That was kind of the way the company was. If you look at it today, it's more than the FDM. We talked about the thermoplastics in the start with the ABS material. Since that time, we have added a polycarbonate material. We have polyphenolsulfone material. We recently added ULTEM about a year ago, and then early last year a nylon material. Now, all

these are for the utilization of FDM.

Then you get into Polyjet, which is a resin printing, if you will, so utilizing the inkjet technology. And here you really have that multi-material, multi-color. So you take anywhere, utilizing Connex technology, from a very rubberized type of material all the way to what we call a digital ABS material. And then just like you blend colors in a color inkjet printer utilizing your three primary colors, we would take that very pliable rubberlike material along with the very durable ABS material and any blend in between of course then you could get.

Now, recently we did add the capability of color palettes on top of that, so in each one of those stories I just explained you would also have a continuum of about 40 colors that could be added to that as well.

The final piece of the technology is what we call smooth curve printing. Probably less people are familiar with that, but that's from the Solidscape product. And the difference with that, it is a jetting type of process, it's a singular jetting type of process. We call it high-precision wax. The reason for the high precision is that you have the jet and then you actually come and mill a layer off, so you get very, very fine detail particularly used for the jewelry industry as a company, probably if you look at 3D printing in jewelry, somewhere in the 70 to 80 percent market share, but then you also start to get into some medical device as well, and again you're using investment casting wax, so it allows that secondary process.

So if you look at it, those are the different technologies. Obviously, I mentioned MakerBot as one of the companies. MakerBot uses the fused deposition modeling, which probably most of you are aware of.

So that really covers the technology for the company.

In addition, we got really involved in the services business in a real significant

way recently. The company has always had a component called RedEye, when I say "always," about the last 8 or 9 years. Recently we added two components to that, one being Solid Concept, which up until the acquisition that we made of that particular company, was the largest independent service bureau in the U.S.; and then Harvest Technologies, and Harvest Technologies primarily focuses on the manufacturing of end-use parts primarily in the aerospace and to some degree automotive industry as well.

But really now, if you look at the services component of Stratasys, it's quite a significant component of our product. And I talked about the three components as far as different processes, different products, that we have, but with the acquisition of these two service companies, we have the exposure then to all the different technologies utilizing again through the service bureau.

If you look at the company itself, this year looking at a projection anyway of around a $700 million company, somewhere in the range of about a 35 percent growth every single year. We have about 2,800 employees, most of them based in the Eden Prairie, Minnesota, office, which serves as one of our dual headquarters. We have the Eden Prairie office and then we have Rehovot as well, and, of course, that came from the merger with Objet Technologies. We utilize a channel partner, so most of our sales are in fact through a reseller organization.

And, of course, there is a huge focus on the different vertical markets for us. And the one thing that we all know about 3D printing, it does in fact service a large industrial base.

Aerospace and automotive is really how the company got started and continues to be a big piece of our business. Included in there would be military obviously.

And then if you look at today and the focus of today's activity, really in that medical and dental area as well. I mentioned jewelry, which is really a Solidscape product.

But as we go forward, we start to really look at the idea of bringing the solutions, being that enabler, if you will, and starting to really focus on these various vertical markets. Hence, our excitement about being here today because, as I talked before, the medical and dental area are in fact areas that we do have focus on, not necessarily in our particular case, as we heard from a couple other of our fellow competitors, building products ourselves, but really offering the expertise and the opportunity for other companies to come and work with us, understand the processes that we use, and work with them to build products, and I'll talk about that in just a second.

And it really starts with the manufacturing with FDM. And I was asked to talk about how in fact you can enable the product, enhance the product, going forward. So I'll talk a little bit about some of the components within our software product and then talk a little bit about our material development as well.

If you look at manufacturing with the FDM area, anytime you want to build a part, there is a simple process that we call a green flag, and if you hit that green flag, you can print any particular part that has been sent to the machine. Obviously the information that you print is only as good as what you get in. But utilizing the insight of the product -- and now I'm talking specifically about Fortus Systems, which are the domain of the FDM -- you do have some capabilities. You have some capabilities of changing the various layer thickness up to .007 to .013. You also have the capability of changing the bead. So a layer is going this way, the bead is giving you your thickness this way. So plus or minus 40 percent can be a change layer-by-layer that you can actually induce, if you will, in the software by layer.

We also have the capability of what we call a material mix, and I mentioned the wide variety of thermoplastics that we have as you move up, if you will, into the Fortus product line, which starts at about $50,000 and moves up to about $450,000. As you move up into the price range, you get more and more variety of materials. So as you move into the higher priced products, you will get into all of the materials that I mentioned starting really all the way at the ABS material and going into the ULTEMs and into the nylons.

So in addition to that capability of the various materials, you also have the capability of alternating the build and support. So if I have a specific product, oftentimes I'll say I would want to build it in a thermoplastic, ABS, but for some reason, let's just say like for a soluble core or something like that of the manufacturing process, I could reverse that and then build my base material, if you will, out of the soluble and then utilize that soluble to say maybe wrap carbon fiber around it or whatever else and then pull that core out using the soap and water bath. So you can adjust it that way as well.

And then in my opening remarks, I talked a little bit about the raster fill patterns, and there is a lot of interest at this point in time in the aerospace and the military area specifically about the various raster fill capability that you have. If you look at the structure that is required to actually add the support and the strength on some of our parts, we have the capability of doing a sparse fill. That's an automatic setting, but if you want, you can go back into the software using InSight and actually segment or delineate where you want your support material and utilizing that fact, you're able to get very, very high structural strength with very, very light weight, which obviously is important in the aerospace industry. It could be interesting I think in the FDA area as well, but it goes back to this idea of looking at 3D printing, and there has been a lot of discussion about different uses of 3D printing where it can come in

and replace things that are being done today, there is probably a whole other area out there, which you really take the idea of the design and the capability of manufacturing of 3D printing, and you have a total different way to go about doing things. That's probably a different frontier than what this focuses on, but it's something that certainly is out there, and what I'm talking about here is a way to start to do that, and hopefully I've given you a couple of examples, maybe not from the medical field, but certainly in a high-tech area like the aerospace.

Finally then I wanted to finish with the idea of talking about material development. Material development for Stratasys has been a key issue both for the FDM area and then also for the Polyjet area. As I mentioned the Connex product line, which gives that wide flexibility of soft pliable material all the way up to a digital ABS material. It's a key company focus really defined by business units.

So the way our process works, we get material in from well-known suppliers, and all that has to be validated. There are specifications that we have. We look at that. Then when we actually manufacture our filament, if you will, in the case of an FDM, we have our own processes that we look at, and we have five critical measurement points that we consider to be company secrets at this point in time, but it really looks at utilizing the capability of that filament with a specific machine and understanding different shrinkage factors that are going to be inherent in the idea of building, say, an ABS part versus a nylon part. They're different. We test. We measure to that. So we look at the CAD file that comes in, we measure that, and then print the part itself, if you will, and match it with that exact figure.

Then you start to look at the manufacturing portion of the machine itself. Same idea. We would take that information from the machine, we build an oven, if you will. We divide that oven into quadrants, and then we control those particular quadrants. Now, we have

specific controls that we use today. The controls could be narrow or could be more open than they are today depending upon who the customer is and what the expertise is, but we do in fact look at that build chamber, if you will, in quadrants, and we look at utilizing a heat mechanism in there and, of course, a wide variety of fans to actually control that specific environment.

We test this out obviously from an engineering perspective, and then we test that out on every single machine that leaves the line for us. So that's tested to an exact specification. Again, we have our own specifications. They could be higher, they could be lower, depending upon what the ultimate manufacturer is looking for, but that's the way we test.

So if you look at the way we control things, since we manufacture the filament to exact specifications, we manufacture the systems to exact specifications, you have a wider control over that area. And again some flexibility, like I talked about, that we have with the Fortus system line and the Polyjet system line to build the certain components that you need from a material standpoint and from a quality standpoint.

The kind of examples that I have here is again from an aerospace manufacturer where we in this particular case guarantee and control filament. We actually serialize that particular extrusion process with that prescribed filament, and then we control the distribution for that specific vendor. So we supply that specific vendor controlled parts based on their requirements that they have given to us, which are different than the standard customer, if you will. So that can be done from the material standpoint as well.

A quick summary. Obviously, 3D printing, new opportunities, from the design, certainly from the manufacturing standpoint, there are a lot of opportunities utilizing different

manufacturing processes. The customization is really the new frontier out there. It means a lot of change.

And kind of in closing, we're a 3D printing technology. We have a lot of different technologies out there. We look for change, that's what the company has been focused on. But we also look at ourselves as a good partner, partnering with our resellers and partnering with companies, government, and educators to deliver positive change. And that's the interest in us being here today.

Thank you.

(Applause.)

LT COBURN: I actually have one question for you to clarify, and if anybody has a question, I think we have a couple minutes, we can do one or two.

The question I have is, when you have the controllable support or internal structural material, through InSight you said you could do a sparse fill?

MR. COBB: Mm-hmm.

LT COBURN: How does the software determine the structural stability of that part, or does it, or does the user have to do that? Because it seems like it's a user-controlled process.

MR. COBB: It would be a user-controlled process. So my example that I talked about, the wing particular piece, that customer that was involved in that did some experimentation, so they obviously had some specifications that they were looking at in that particular area, so what they had to do through an experimentation process -- and it's more, they knew some information going in, so it wasn't just totally wild-ass, you know, kind of guessing -- but based with that, then they went in and then actually built that structural support

and then tested it to make sure that it complied with what they were looking for. If that answers your question.

LT COBURN: Yeah. Thank you very much.

MR. COBB: Thanks.

LT COBURN: All right. Our next speaker is Ernesto Rios, who is Director of Manufacturing Operations at Renovis Surgical Technologies. He joined Renovis early in 2011 to support the company's effort in designing their first hip implant, or launching their first hip implant. He was instrumental in the acquisition, installation, and validation of their additive manufacturing equipment. So please welcome Ernesto Rios.

(Applause.)

MR. RIOS: Thank you. Good morning. Thank you for the opportunity of being here. It's a great opportunity to speak to you about our company and what we do in medical devices. This is the first time that we've had the opportunity to participate in this event, but I think it's very, very useful for the community to grow.

Sorry, I have to be in front of the microphone.

Just to give you a little bit of an overview of the company, I'll go with the agenda like this. I'm going to tell you a little bit about Renovis and what we do. I'm going to make a comparison of traditional manufacturing versus additive manufacturing. I'm going to kind of go into some of the details and what exactly what is what we do. I'm going to talk about the staff requirements that we have. Now that we have additive manufacturing, what are the specific skill sets that we are looking when we have people working in this environment as well as the learning curve that we have been through, some of the process monitoring that we do, and the lessons learned. And I guess we will do a Q&A if there is time.

So Renovis was founded in 2009. We're a medical device company. Our headquarters is in Redlands, California, but we have an engineering office in Austin, Texas. Austin has become a big hub for medical startups. We were a startup a few years ago, and now we consider ourselves a full-blown company. We have twelve 510(k) clearances, and we have two of those 510(k) clearances are for medical implants that are with additive manufacturing technology.

When I see the other presenters early today, they were talking about a lot of the plastics and the different materials that they use. We basically pick one technology, one material, and we stick with that, and that makes things a lot simpler for us because we are able to stay with that technology, maintain it, and the implants that we make are just that simple. I mean, we don't really try to come up with many materials because, I mean, what we do is make the medical implants, and it's very critical for us to be consistent in our quality.

We do have 3D printing for hard plastic. We use that just for pure prototyping just to touch and feel, just to see how the implant is going to look, but basically the metal implants is our business.

Our portfolio just very quickly. We are in the big joint business. We have a knee. We have a hip and acetabular. We have an offering on the acetabular cup that is made out of additive manufacturing using EBM technology. And we have trauma product, spine product. One of those spine implants is an ALIF cage that is also made with additive manufacturing, and those two have been cleared by the FDA, and one has been launched and the other one will be launching very, very soon. We also have pedicle screws and the instrumentation to support all of these systems.

I'm talking about product flow comparison -- process flow. Basically when we

have traditional manufacturing and additive manufacturing, we really don't see that it's a different technology or it's a different set of requirements. We do have very strict requirements that are very similar to traditional manufacturing. Some of the steps that involve the manufacturing of these products change because of technology, but in terms of controls and people's skill set, I mean, we do have some specific requirements.

Traditional manufacturing for an acetabular cup, which is what we have on the screen, this cup is made with additive manufacturing. If we go to traditional manufacturing, it will be kit material, which is the titanium alloy bar stock. Like I said, we only use Ti64. We don't work with any other metals at this time.

We forge the material into that shape, and we machine the outer diameter. If we have to apply the porous coating and sinter right after that, then the mechanical test, machine the inner diameter, clean, and pack. Those are kind of like the traditional steps that are taken for an acetabular cup, one that is porous coated. If it was plasma sprayed, it will change slightly just on the coating on the shell.

In additive manufacturing, instead of starting with the bar stock, we start with powder, with titanium powder, and when we put that powder into the machine, we produce the parts, which is we melt the parts, that's how we call it, we melt the parts in the machine with additive manufacturing technology, and we have post-processing, in our case, it's hot isostatic pressing, or HIPing. We do mechanical and chemical tests. We do it for every build despite that we have a very extensive validation, which I will cover in a minute. We still test and we machine the inner diameter, clean, and pack, and the rest is pretty much the same.

So the fact that we have additive manufacturing does not mean that we are able to just produce an implant that is ready to go into clean and packaging. A lot of people think

that because we have this machine, we can make implants very quickly and we can just have them made to size or very personalized. We are not that type of -- we're not in that business. We do have very standard sizes that we create. The technology -- we see a lot of advantages with technology for customization, we're just not in that stage, we're very early into the technology. What we see is how we can really customize the implant characteristics of the porous structure. We can get it as optimized as we want it, and that's what we did with this implant. So it's not that we are trying to do a lot of things with the technology, we're trying to get the best out technology for our purposes.

Some of the advantages that we see in manufacturing, additive manufacturing, is that in the case of the shell, we eliminate the forging, we eliminate the other steps like porous coating and the sintering that goes with it. We are also able to reduce the project lead times because, yes, we were able to get away from doing forging tools or the old lead time that is involved with that. It reduces the implant lead time, we're able to make implants that are implantable grade much sooner. Also, because we are able to get those implants quicker, we are able to reduce inventory levels.

So from the manufacturing standpoint, we do see a lot of advantages, not just the (inaudible) but also the manufacturing. But we keep it very, very simple. We see that this technology can provide us access to some other faster growing markets such as the revision market. We're still not there, we're still working through the few 510(k) clearances that we have and we're still trying to develop those products and getting them to market. But we see that this can enable flexibility for the design and we can also reduce the waste materials since we are able to reprocess a lot of the powder that is not used during the melting of the parts.

From the product designers' standpoint, we see that it eliminates flaking, and I'm

talking about a shell that is either porous coated or plasma sprayed. We see that this interaction of the substrate to the porous coating, it's not there. We have a porous structure on the part that is integral to the substrate. It is all one piece. We have done plenty of testing and we find that this is very, very strong just because it is made at the same time, and that improves the quality of the product substantially, and that's what we have been focusing on. So we have been able to enhance primary fixation by giving the different levels of roughness to the porous structure, and we have been able to provide control of the porous size and percent porosity. So this is something that has been key for us, which is what we are able to optimize that design of the porous structure to get all the characteristics that we look for in terms of pore size, the mean pore size diameter, of rolling porosity or gradients of rolling porosity through the porous structure. So those have been the advantages for us from the product design standpoint.

Some of the considerations that we have for additive manufacturing, which it's some type of disadvantages. We see that for the manufacturing operations, it's a substantial capital investment. We are a relatively small company and very new, and we started developing our implants 3 years ago with additive manufacturing. So 2 years after the company was founded, we were already looking into making parts with additive manufacturing. We purchased a piece of equipment, which was a big leap of faith for us, but we saw that this was definitely, definitely the future of manufacturing, and we wanted to be part of it.

Again, we are probably not playing with all the different materials that a lot of my colleagues are doing. That's their job. I mean, we were here to make sure that once we have that material established and there are standards established for it, that we develop the best implants that we can within those parameters. We are able to follow the ASTM standards

and meet the ASTM standards. We work very close with the additive manufacturing committee to make sure that we are on top of the regulations and all the guidance that they provide for the standards, ASTM standards.

But we do see that it is extensive validation. What we have done with the piece of equipment is we work with the OEM of the machine and basically we work with selecting the themes that we prefer based on the characteristics that we wanted to meet and the material properties that we wanted to obtain, and we pretty much froze those parameters. I mean, we got those parameters, we validated the machine, we validated the tank, the volume of the tank and all its various different directions and X, Y, Z, all the different directions, mechanical, chemical, microstructure, all the way throughout the tank. Once we did that, we pretty much lock it. We are not changing. We are not trying to come up with the new latest material. We just lock it and that's what we use. So our machine has the themes, and those are locked, those are very well controlled, very similar to traditional manufacturing, nothing different. I mean, the way the programs are released or the build projects are released is very typical in our industry and in our line of work. So we do follow all those same standards and we don't deviate from that.

But this machine in particular, I mean, it has intensive preventive maintenance. It's a complicated piece of equipment that we have come to learn and to love after so much work that we have put into it.

There are a lot of different things that we also have learned, like the raw material degradation, or titanium ELI, mainly because of the oxygen pickup. So there are a lot of things that I will share with you what we have done in order to kind of work this through so we can get the chemical properties as well as the mechanical properties on every build.

Like I said, on product design, some of the surface finish, it can be good, some of that cannot be that good, so we are still not in a stage where we can say this implant, as it comes out of the machine, we can use most of the surface as melted. I mean, we still have a lot of traditional manufacturing that has to be done after the part is melted. Hopefully in the future we have better surface finishes and we can just reduce traditional manufacturing, but currently, I mean, we try to get the best out of the technology, we don't try to do it all with it because we know that it still has some limitations, and what we are trying to do is just tailor those surfaces that we want, and the rest we use traditional manufacturing.

Staff requirements. So we try to kind of keep it similar to traditional manufacturing. We actually call them process engineer, a programmer, and operator. I don't know if that's standard throughout the industry. But basically what we need is a process engineer that is very experienced with validations. The validation of this machine is very time consuming and it's very expensive as well because there are multiple testing -- mechanical, chemical, microstructure -- throughout the tank when we did the validation.

So I just highlighted the ones -- the ones highlighted in red are the ones that I think are very specific to additive manufacturing, such as establish the powder routines. This is something that is not typical in traditional manufacturing, but here we have to be careful of how we recycle the powder. When I say recycle the powder, that was not sintered or melted in the machine we are able to recycle that powder, but we have to have very tight controls of what lots we're using. We don't mix lots, and we do a lot of things just to keep the integrity of the powder.

Determine the post-processing requirement. That's also part of the process engineer's task. We conduct cleaning validations, very intensive because of the porous surface

that we see that as an issue. We want to make sure that the part is cleanable as well.

We also conduct powder residue studies to make sure that our powder recovery system is working and develop process to remove support structures. So support structures is something that is not desired but is necessary in order to make the parts, but we put it where we need to put it. We work with the programmer.

One of the tasks that I have in red, it's to develop the necessary support structures in conjunction with the process engineer. It is necessary that we know how to remove those structures every time that they come out because they might -- many different designs of support structures might work for the implant, but not all of them are removable or as easy to remove.

From the operator's standpoint, we need a person that is detail oriented, organized, and physically strong in that there are a lot of parts that need to be moved around, builds that need to be taken in and out of the machine as well as preventive maintenance, but mainly the main thing here is that the person has to be very detailed. That person will recover the unused powder, which is kind of new for an operator that has never been exposed to additive manufacturing. They need to maintain low work area humidity. This is because we're working with titanium and its affinity to oxygen, we are very careful how we maintain our powder.

We also segregate and identify witness coupons. We do build witness coupons with every single build. We have a machine that is validated. We have validated the tank all across. We have witness coupons in a specific location within the tank to verify that everything has been -- that the build was in control. We also maintain powder integrity, which is just make sure that we have a traceability of powder every time that we build, the chemical composition

is there. And I will talk a little bit about how we monitor the process.

Learning curve. When we went to the training, we definitely learned a lot about the machine, but I think that at the time when we were challenged with doing the validation is the time when we start asking the tough questions to the OEM about certain parameters of what we need to be monitoring throughout the process during the build, and this validation is where we see our proficiency go up significantly just because we are able to really question how the machine works. So during the training you are just being told what you need to know about the machine, how to set up the machine, how to program, but during the validation, you start really questioning, "How can I make sure that this machine is going to produce the parts that I need?" So that validation period I think is the most intensive learning that we have just because of the nature of the validation is very complicated, it's time consuming, but once we have it, we don't move it much.

In terms of production, we still keep learning, we still try to participate in the committee, so we learn about technologies and what we need to do to incorporate them, and this is something that we are very interested in and we want to keep working on.

From the process monitoring standpoint, we do monitor the raw material, which is the titanium that comes in. We work with our suppliers, with the OEM as well, to make sure that the powder meets their requirements and the chemical composition that is required. And we also work in a build report, so we have developed this report that comes out of the machine every build. That build report is identified with a work order and has all the different aspects to have traceability, and it gives you a summary of all those parameters that you want in control.

We have established windows that we work with the OEM, and those windows are the best thing that we could have, which is if something goes out of control during the

build, the machine will stop, it will interrupt the build. This is not a way -- the machine will not ask you in the future, "What do you think about this layer that was not melted properly?" If the control, all the parameters that we have determined, which is current speed or whatever the parameter is, if it is out of control, the machine automatically will stop. And we have had that in the past, but it is a good thing because we want to make sure that the quality is built into the product.

Dimensional reports. We do maintain some of the dimensions as melted, not all of them. Like I said, we still do quite a bit of traditional manufacturing, and that is why we do the dimensional report right after the machine post-process, we do HIPing, and we control, we have certs for all of that. And to summarize kind of like the quality of the build, we still do chemical tests and mechanical tests on every single build, and that's a way for us to make sure that we have verified the quality of that build, and then we still use the validation as our support for the entire tank.

Some of the lessons learned that I would like to share with you is we need to be selective with the product. Not all product is conducive of additive manufacturing. For us, there are specific characteristics that we are looking for to introduce in the product, and not all of that can be made with additive manufacturing. So we try to exploit it to the point where we see those benefits.

We optimize product design, so once we have identified those characteristics that we want to put into our product, then we definitely optimize those characteristics, and I mentioned like mean porous size and volume porosity, which we have done extensive animal studies with the best -- really, really good results, so that's where we spend our time, trying to get those characteristics the way we want them.

Optimize build size. This is probably something that we should definitely -- that we needed to learn probably earlier. At this point, we have work into our builds and we have put together those builds, and they are probably not optimum, and we want to go back at one point and start creating new projects and new builds. We need to go with a shorter build, denser build. I think that's where we get the most efficiency. Reduce the number of layers but get as many parts as we can as close as they can be.

Maintain raw material integrity. This is definitely something that we have to develop, which is the process to recycle the powder and maintain the low humidity in the area. As well as traceability. I mean, we are very strict with traceability of the product.

Minimize number of operators. This is a process that it's a little bit complicated setting it up and retrieving the material. And despite the complications, I mean, you can -- sometimes it's difficult to realize you have a work order and that operator can just pick that program. He doesn't know what he's going to be making and the next day there is a part that is out there, he is just following the work order and which program he needs to be. So from that standpoint, it is very, very flexible, but we really want to have somebody that can take ownership of the equipment. This equipment is very complicated, at least the one that we have, but once it's running, it does great things. And emphasizing equipment cleanliness.

And that is all I have. I don't know if we have time, but thank you very much.

(Applause.)

LT COBURN: Thank you very much. That was very insightful. I like the lessons learned. One question I have would expand on that a little bit, which is, in your material selection and material control lessons, can you share maybe a best practice on what you've learned from recycling your material and then how to determine when the oxygen uptake is too

much and how much recycling is possible?

MR. RIOS: Mm-hmm. So what we have done is we -- first of all, we approve our product with titanium ELI, which is a very low oxygen content, and that has been difficult to maintain, but we have been able to do it. The way that we do it is we continuously refresh the powder with virgin powder, and we do note how much virgin powder has been added versus the reused powder. Once we have that batch, we pretty much fill up the machine with the powder, and we sample that powder. We always sample for oxygen at that point because we know that is the main element that will change, and we will do a full chemical analysis at the end of the build.

So we basically create new batches and we put into the machine and we try to obtain several builds out of that batch, and that's how we -- the longer we maintain the powder inside the machine under vacuum, the better it can be preserved. So that is how we do it.

LT COBURN: Great. Thank you. Oh, there's a question. If you can come up to the mic, please. It's in the front. And please identify your name and affiliation.

MR. TAGGEL (ph): My name is Sunil (ph) Taggel. I'm with Curative Technologies. One of the cross-sections you showed for the cup showed a very intricate porous structure. Do you have issues with cleaning the powder out of that after you have done the build? How do you clean the powder from those pores?

MR. RIOS: Yes, we do the powder recovery, which is we blast the powder, and after that we have a tumbling system to make sure that we get the powder loose out. But we do HIPing, and that also compresses powder in the part.

MR. TAGGEL: Thank you.

LT COBURN: One more?

MR. BINKLEY: My name is Peter Binkley. I'm here with e-NABLE. You talked about -- and forgive my ignorance -- but you talked about surface porosity as being a desirable?

MR. RIOS: Mm-hmm.

MR. BINKLEY: Can you explain the purpose of surface porosity?

MR. RIOS: Yes. So it's a porous structure. It's mainly for bone growth and in-growth, so basically what we want is a rough surface that can become attached to the bone really quickly mechanically, and over time we want that -- there is a specific pore size that you want to hit where the histology has shown that the bone can grow into much better. So that is why we want the porosity. We don't want porosity throughout the part, through the part, we want porosity on the surface of the part. Yes.

LT COBURN: Thank you very much. I think we don't have enough time for one more, but we will have all the discussion in the afternoon. So please save your questions for that.

Thank you again.

MR. RIOS: Thank you.

(Applause.)

LT COBURN: Our final talk of this session will be Dr. Scott Hollister. He is a professor of biomedical engineering and mechanical engineering at the University of Michigan where he directs the Scaffold Tissue Engineering Group. He and his colleagues first developed an approach for laser sintering polycarbonate in 2004 and his work on a bioresorbable tracheal splint with Dr. Glenn Green was given *Popular Mechanics'* 2013 Breakthrough Innovation Award.

Let's see. Dr. Hollister.

DR. HOLLISTER: Okay. Thank you, James. It's a pleasure to speak here. It's a very interesting meeting. As being the first academic to speak, not only will I give you text slides, but I'll give you very dense text slides, so hopefully we can get through them okay.

(Laughter.)

DR. HOLLISTER: What I'm going to talk about is some of our experience with laser sintering of the resorbable polycaprolactone splints for treating tracheobronchomalacia. I would like to acknowledge my co-authors, Colleen Flanagan, who does the build in my laboratory; David Zopf and Robert Morrison, they're otolaryngology residents that worked with us; Richard Ohye, who is Chief Pediatric Cardiac Surgery at Michigan; and Glenn Green, my colleague on the splint who is a pediatric otolaryngology surgeon.

So what I'm going to do in the talk today is I'm going to just briefly talk about the clinical condition we are looking at, which is tracheobronchomalacia, how that motivates our clinical goals and our design goals for the splint. I'll talk about how we laser sinter the splints and the parameters we use. I'll go over briefly some of the clinical uses and outcomes for the splint in the three patients we've treated so far, and then I'll try to talk a lot about the quality control parameters for laser sintering PCL not only for the splint but for other implants as well.

So tracheobronchomalacia is a condition especially in children where you get compression of the airway due to malformation of vascular structures, and in severe cases it can actually cause complete collapse on the airway on expiration. The current clinical gold standard for treating TBM is giving the child a tracheostomy, putting the child on a ventilator for 1 to 2 years. This treatment itself has significant complications on morbidities including death, and so there is obviously need in some cases for surgical intervention to sort of basically prop open the airway. Stents have been tried in children; they have basically failed. Many

people now believe that the best surgical approach is to place an external splint on the airway to keep it open. However, there is a need for patient-specific implants in this case because obviously the length of what we call the malacic segment and the diameter of the airway will vary from child to child. And this basically shows for our first patient the compression of the left bronchus due to a malformed right pulmonary artery.

Here is the first dense slide, but I'll just highlight a few points.

(Laughter.)

DR. HOLLISTER: Based on the fact that we wanted to create an external split to provide patency for the airway, we came up with a number of design goals for this splint device. We basically split those into mechanical, biomaterial, and surgical requirements. Some of the basic things mechanically we want the splint to do is obviously to hold the airway open for a period of time under arterial compression and inhalation and exhalation pressures. We believe that the splint should provide support not permanently in children but for about a period of 24 to 30 months because we believe as the child grows, the airway itself, due to Berdili (ph) effects, will become more open. Also, the splint itself should allow growth. And, of course, it should be biocompatible. And basically because we want to splint the airway open, we want the splint to have holes so the surgeon can actually suture the airway wall and suspend the airway inside of the splint.

So this just shows an example of the design we came up with. It's a bellowed open-cylinder design with the suture holes spaced periodically through the splint. We make it bellowed -- you can make it either bellowed or not bellowed -- to allow flexibility of the splint.

And we have a number of design variables we can change, there are about 10 different design variables we can change, and we can generate these designs automatically

using a special custom-written MATLAB program. And there are about 3 million different design perturbations for the splint.

And I think both due to the complexity of the design of the splint itself as well as the fact that we're actually sizing the splint to the individual patient, we use Mimics to make a digital model of the patient and we actually size the splint to the patient's airway. This is the reason that we need to 3D print the splints.

And the other nice thing, as you can see, the sort of spiral design here, that allowed us for the second patient to place splints bilaterally. We actually, Glenn Green and I met on a Wednesday, we did the design on a Thursday, and we built it on a Friday, and then we sterilized it and planted it about a week later.

So these are the ways -- this is the design parameters for the splint and how we designed the splint.

So obviously due to the complexity of the splint design as well as the fact that we want to make the splint specific for each patient, that really requires the ability to 3D print the splint, or in this case we use laser sintering.

This just gives you a brief outline of the process. This is our design process. We get a 3D scan of the patient, CT scan. From the parameters, we measure on that scan, we design the splint. We then again use Mimics to fit the splint digitally to the patient, and then we generate an STL file for the splint.

We are manufacturing the splint from polycaprolactone, so we receive the raw material. We store it. We have to have it milled to the correct powder size. We use a small amount of hydroxyapatite as a flowing agent for the process and then we go ahead and build the splint. We test -- we look at the geometry and the mechanics of the splint, we package and

we label it, and then it's sterilized.

This just shows the process, and hopefully this video will work. It's just going to show you our system. We're using an EOS. And this is Colleen. She's describing the process, but it's just showing the spreading of the powder inside the machine thanks to GoPro. And then you'll see actually the laser basically sintering the splint designs. We can build about 100 to 200 splints in a build in about 4 hours. That's the polycaprolactone material. And then we get the splints from the build.

You'll see here Colleen is actually taking the splints out. And then this is the final product of the splint. You can see the bellow design, you can see the suture holes, as well as the open cylindrical structure.

So there is actually quite a bit of literature published on laser sintering of polycaprolactone. In fact, I would refer you to Partee, et al., 2006. This was our work, and basically we did a whole design of experiments where we looked at different laser sintering parameters for the splint and these are all published. And this was actually for the material we used, which is the CAPA 6501 polycaprolactone. We have to have this material cryogenically milled. There are a variety of vendors that do this: Jet Pulverizer, Fraunhofer, Evonik. Our target particle size for the laser sintering is between 25 and 125 microns with a median particle range of 40 to 60 microns. And as I mentioned, we use the EOS P100 system, although now I think the current version of that is the P110 system.

As I mentioned in this sort of foundational paper, we discuss a design of the experiments looking at a variety of laser sintering parameters. These include the bed temperature, the laser power, the laser scanning speed, the scan spacing, the hatch spacing, and the beam offset, and these are published not only by us but a number of groups

throughout the world. Basically laser power for sintering PCLs range between 1 and about 5.4 watts. We typically use about 4 watts. Bed temperatures range between 38 to 56 degrees Celsius. We typically use between 50 to 56 degrees Celsius. Laser scanning speeds, we'll see that has some impact on the quality of the part. Have range for PCL from 9 to 1,800 millimeters per second. We typically use 1,000 to 1,500 millimeters per second. So this is the basic process we use to build the splints or any PCL implant that we build.

So I just want to talk briefly about the clinical application of the splint and the outcomes. As I mentioned, we have used the splint under emergency use; in fact, all children were in a life-threatening situation. This was cleared through the FDA and our own IRB.

The first case, which was actually published in the *New England Journal of Medicine*, was a collapse of the left mainstem bronchus. You can see the implantation of the splint here.

The second case was very interesting. It was a 16-month-old child. He had never been home from the hospital. He had bilateral collapse of both bronchi. So this was a case where we designed actually a spiral splint to accommodate both splints for each bronchus without overlap.

And I would like to mention that the first child is now 31 months post surgery. The second child is 8 months. And the third child, done at the end of March, with a left bronchus collapse, is now 6 months post surgery.

This just gives you an idea of what it looks like on the exhalation CT scan pre- and postop. Preop you can see in the first patient complete collapse of the left bronchus. You can also see a hyperinflated left lung.

We also see that in the second patient, complete collapse of the left bronchus,

hyperinflation of the left lung. You can see post surgery that the airways are now patent, both airways in the case of Patient 2, normal size lobes for both lungs.

This is bronchoscopy done on Patient 3 preop. You can see this is the left bronchus here completely collapsed on exhalation and then post surgery with a splint that this left bronchus is now open.

We track these patients with CT and MR looking at the patency of the airway.

For the first patient, as you see here, the dotted line is actually his normal right bronchus. The solid line is the treated left bronchus. You can see that preop the opening of the bronchus -- and I believe this is on inhalation -- was only a millimeter and a half, and that over time we can show that even with the splint on the bronchus, that the bronchus grows pretty much normally as compared to the untreated bronchus. He was 3 months old at surgery.

The second child, who had bilateral splints, airway diameter initially about 2 to 4 millimeters, now about almost 5 to 5-1/2 millimeters.

And the third child, again this is the untreated control right bronchus, this is the treated bronchus, a huge difference preop, and then postop they're pretty much the same.

And we continue to follow these children.

It's one thing to look at the data; it's another thing to actually look at the patients. So these are all the patients we've treated, both their preop condition where they're actually -- all these patients actually had a tracheostomy, were on the ventilator. These are all the patients postop. This is Kaiba (ph), he was the first patient. This is his second birthday. This is Garrett, he was actually on NPR, he's famous now. This is him sitting up for the first time. He's been home now since about a month after the surgery. And this is Ian, he is the third patient.

(Applause.)

DR. HOLLISTER: So the other question, of course, when we make these splints, we have to look at the parameters we are trying to hit in terms of the design, the stiffness of the splints, their geometry and so forth, and we have to have a way to assess that when we do the builds, so like everybody else has talked about, quality control is a huge thing. In academics, we're not necessarily known for quality control, but we're trying to learn quickly.

(Laughter.)

DR. HOLLISTER: So basically there is an initial quality check that we do for the build. We look at the powder when it comes in, we make sure it has the right particle size. We do a visual inspection of the powder. Obviously, this process is very sensitive to humidity. August, because it's very humid in Michigan, and January, because it's very dry, are the toughest months to build; they either curl up or clump. But we basically try. We check this with a hygrometer to have relative humidity between about 10 and 35 percent for the powder.

We then do inspections both in the build log from the machine and visual inspection to look for part dragging. It's always a bummer when you come in the next morning and you see a big trail of powder across your parts, you know that they didn't really build well. We look for sintered islands and things like that. So those are sort of visual checks we do on the quality of the build.

We also do caliber measures. We do that currently for the splint, but we're also looking at implementing micro-CT nondestructive evaluation of parts because that gives us not only the geometry of the part but the density of the part. And we do mechanical testing as well.

So this is some of our geometry quality control. As I mentioned, we do caliber

measurements, but we're also implementing micro-CT measurements. We haven't done this for the splint yet, but we've done it for some other parts where we do topology optimization, and there essentially we're optimizing the distribution of material and then we're converting that to an STL file and building that, and the nice thing about micro-CT, you can actually look at different feature sizes of the microstructure.

These are topology optimized microstructures with features down to about seven to eight hundred microns. And what we do is we actually scale these microstructures. And we can see that obviously as you get closer to the build resolution of the machine, you have more difficulty replicating the features that you're actually designing. So here we're down to about that .7 or .8 millimeter range. And, in fact, that's showed by the scaling here.

Actually, these structures are built by what we call unit cells that we repeat in 3-dimensional space, and the smaller the unit cell, in other words, the smaller the feature size we're trying to build, the larger the deviation we see from the actual design geometry, but once we get above that, about 1 millimeter threshold, we can build the parts with pretty good reproducibly both in terms of the struts that we design here as well as in terms of the throat areas. So that's one way we look at quality control in terms of the dimensionality or the geometry.

The other thing we do, of course, is we do mechanical testing. This is a very difficult thing, especially if you build heterogeneous parts with different feature sizes. So we test both on one range, the actual solid material, the solid cylinder, typically an ASTM standard 16-by-8 millimeter cylinder. We've looked at a lot of parameters and they affect it, including laser scanning speed. You can see that has some effect on the modules here, about a 20 percent variation.

As others have noted, because it's a layering process, we get some anisotropy in the properties, and these are our results. The X and Y dimensions are fairly equal, but they're a little bit stiffer in the Z dimensions for the cylinder.

Of course, on the opposite end, we have these microstructured implants that we design using topology optimization where we try to optimize material layout to give us a compromise between stiffness as well as permeability. This just shows some of the STL files for that. We build these parts, we test them in compression, and we compare the prediction of modulus or the measurement of modulus from the test to an actual prediction from a numerical analysis of the idealized part. And again what you see here is a plot of the experimental modulus versus the numerical modulus.

Ideally, you would like to have -- it's probably hard to see -- but a 1-to-1 correspondence with the dotted line here. And once we can get above sort of that minimum feature size, we can get almost a 1-to-1 correspondence between our experimental parts compared to our numerical analysis, but as we get closer to that feature size and it's hard to resolve those features, we see a larger deviation of the measured modulus from the numerically predicted modulus. So that's another thing we look at in terms of quality control of the stiffness.

For the splint, again we have also derived some design targets for the stiffness. On one hand, it has to have fairly high stiffness in compression, or relatively high, to protect the airway from vascular compression. But on the other hand, in an opening sense, we want the splint to be able to open to allow for growth. So we've made some calculations based on some numbers in the literature, and we believe that the opening stiffness, the geometric stiffness, should be about 2 newtons per millimeter or less, but the compressive stiffness should be at

least 10 newtons per millimeter, and probably higher. These are the results for replicas we built of the first patient's splint. You can see that the opening stiffness is about 2.8 newtons per millimeter. The compression stiffness is about 128 newtons per millimeter. And similar ranges for the second patient.

We have also done some testing of this splint in a pig preclinical animal model, although we did it in the reverse way, as you should do, we did the patient first and then the animal model. Should do it the opposite way. But basically also we found that the pig is a fairly rapid growing animal, and the split does allow for growth in this situation. Again, the numbers were pretty close to what we predicted we would need to protect the airway as well to allow it to grow.

I think going forward in the future, as I mentioned -- well, actually I don't know if I mentioned it, but these splints are resorbable, polycaprolactone is a resorbable polyester. It's a very slowly degrading polyester; it takes about 3 to 4 years to totally resorb in the body. So I think going forward there is a need to understand not only the static stiffness properties and strength properties of what we build with 3D printing, but we also need to understand the degradation properties and the fatigue properties, and obviously those are coupled in a very complex way for resorbable materials. We have started to look at both of those.

We have looked at sintering specifically in terms of how it affects the molecular weight of both the raw -- when you get the raw material, it has a certain molecular weight. We measure the molecular weight after we sinter it. And in this case, this is a spinal cage, a resorbable spinal cage, that we have tested in a pig model, and you can see that over time the material resorbs up to 18 months by about -- it loses about 40 percent in its molecular weight.

We don't know, honestly, how different sintering parameters may affect

degradation. We haven't done that test. I think it's a very critical test to do.

We have also looked at the same type of resorbable spine implant with some colleagues at UCLA as per the ASTM, I think it's 2077 fatigue testing. We have done fatigue testing of these resorbable polymers. We know that they can withstand pretty much the high range of cervical spine loads, and we've run these 3D printed resorbable materials out to about 5 million cycles. They can easily withstand that at about 60 to 80 percent of the ultimate load. And the interesting thing about PCL, it doesn't really fracture, it just sort of smushes around, and you can see that with some of the implants here.

So in concluding my talk today, what I want to do is just present you some of the work we're doing on laser sintering of resorbable PCL patient-specific splints for treating tracheobronchomalacia. We've had some success in three patients. We're working with the FDA to develop a clinical trial to test these resorbable splints. We have also been able to use laser sintering to fabricate what can be very complex topology-optimized scaffolds.

We've shown that at least on the static tests that our design targets of an opening stiffness of about 2 newtons per millimeter or less and at least 10 newtons per millimeter in compression, that we can meet that using laser sintering.

Obviously, the laser parameters, I think what those establish are the base properties that you can get with the material, but then, of course, it's the interplay with the design and these base properties that will ultimately determine the performance of the implant, and a critical factor there is how close the feature size of the implant you're trying to build is to the resolution of the machine. And obviously I think going forward we have to understand how these 3D printing parameters affect degradation properties for resorbable polymers as well as our fatigue properties in vivo.

And with that, I'll stop and acknowledge my co-authors as well as the funding for this work.

Thank you.

(Applause.)

LT COBURN: Thank you very much. Unfortunately, we don't have any time for questions on that one, but he will be in Room 2 in the characterization breakout session as well this afternoon.

Keynote Address

LT COBURN: So now it is my pleasure to introduce our keynote speaker, who is Bryan Sivak. He started his career as founder of InQuira, a successful knowledge management company, and he then turned to civil service where he became the CTO of Washington, D.C., the Chief Innovation Officer for the State of Maryland, and for the last 2-plus years, he has been the Chief Technology Officer of Health and Human Services helping to foster technology advancement and innovation in this Department.

Bryan?

(Applause.)

MR. SIVAK: So thanks, everybody. Good morning. I appreciate the invite to be here. I know we're running a little bit behind time, so I'll try to keep this relatively brief.

One of the things that I find somewhat interesting about large organizations, especially having come from sort of the smaller side of things, is that the bureaucracies and the way that these organizations work tend to challenge employees in a number of different ways, and they challenge employees, as many of you who have probably worked for the government here understand, challenge them due to bureaucracy, challenge them due to red tape,

challenge due to hierarchy, command and control infrastructures, things that sort of prevent in many ways the ability for folks in those organizations to actually experiment with new ideas, kind of bring things forward, to try things in different ways.

Government in many ways is sort of one of the worst offenders in this world, and I think that this causes a problem because we exist in a world today where things are moving incredibly rapidly. I mean, that last presentation was fascinating. And as I'm sure many of you in the room are a part of this world, you will recognize that as the institutions that sort of look at these processes, regulate these processes, sort of fall farther and farther behind in terms of how quickly they can process things, how fast the bureaucracy can move. We lose a lot of speed and effort and efficacy in terms of what we're trying to do.

So the question that we ask quite frequently is, how do we take such a massive siloed, command and control oriented, hierarchical, red tape filled, risk averse organization and translate it into something that's more risk aware, more modern, more agile, more flexible? And this is why, as a result, we created something within HHS called the IDEA Lab. We're a government institution, so we had to have an acronym. I don't think they allow you to create anything without acronyms. So IDEA itself is an acronym; it stands for Innovation, Design, Entrepreneurship, and Action. Each one of those things has a very specific meaning to us. I just want to touch on that actually very briefly.

So we throw around this word "innovation" a lot these days. It's one of those words that I used to have it in my title in Maryland. I've decided that I don't love this word anymore. In fact, it's sort of aggravating to me in a lot of ways. I think that really got hammered home to me the other day when I was walking down the street and I passed a sandwich shop that was touting its most recent sandwich innovation, and I thought, you know,

we're getting to a point where this word is becoming a little overused.

(Laughter.)

MR. SIVAK: But, you know, it does set a frame of mind. And so we figure if we're going to use it, we may as well define it, and the way we define it is very simple: we say innovation is a direct result of the freedom to experiment. And if you think about that within the context of a large organization like government, what that really means is pretty straightforward. I can teach you how to experiment; right? I can teach a scientific method to a bunch of bureaucrats; right? I can teach them to develop a hypothesis, to test that hypothesis, generate some metrics, look at those metrics to determine whether or not that hypothesis was valid or invalid, and then apply those learnings to the next iteration of that test.

What's also nice about this word "experiment," especially outside the context of science, is that it really encodes this idea of a unsuccessful experiment; right? And one of the things that we've learned over time is that in order to move anything forward, to really progress in terms of discovery or invention, we need to fail many, many times before we actually succeed, and we need to learn from those mistakes. We're not so good at the failure piece in government, we're not so good at the learning from mistakes, but that's one of the things that we're trying to encourage.

And then finally this word "freedom" is really important. One of the things that's really struck me in the government jobs that I've had to this point is that the stereotype that people have about government employees is actually I think for the most part fairly false. We have 90,000 or so people at HHS across the board, maybe three times that if you count the contractors, and for the most part, all of these folks are real smart, they are here for the right reasons, they're dedicated, they are motivated by the mission, but they lack the freedom to

actually execute in many cases on some of the good ideas that they have. And so if we can provide freedom and we can teach this concept of experimentation, we believe that this thing called innovation will result even in some of the larger bureaucracies.

Now, the question is sort of, how do we do that, and what does the IDEA Lab actually create in order to make this happen? There are really three different areas.

First, one of the things that's incredibly important, especially across an organization like HHS, which is both diverse and focused at the same time, you've got lots of different silos of interesting things happening, but they really are silos, I mean, they're like concrete walls that you kind of have to break through in many cases to get people to kind of work together. And what's interesting is that when you look across the organization -- one of the benefits I have sitting at the Department level -- is that you get to talk to a lot of people, and it turns out that a lot of people across the Department are actually working on very similar things or things that could be related to each other.

So one of the things that we believe is very important is trying to figure out ways to break down these silos to connect people who could potentially benefit from knowing each other at all different levels of the organization. I'm not just talking about the top; right? I'm talking about literally sometimes even the lower level GS-10s that are bench scientists at an institution. But if we can get those people together and working together, we believe that interesting things can happen.

So one of the things that we do is leverage the ability that we have, as part of the Secretary's office, to create these communities across HHS where we pull together people from different areas and kind of allow them to work together outside of their day-to-day jobs on a specific topic that has some relevant cross-departmental import.

We have some requirements for the characteristics of these communities. Number one, there has to be a defined and accountable leader. We want somebody to be in charge, somebody to point out and say, "This is your responsibility, make sure it gets done," but also we need a very clearly articulated mission statement along with some very specific and measurable time-bound goals, things that people can look at and say, "Yes, you are achieving what you set out to achieve," or, "No, you're not. What are you going to do differently in order to accelerate this?"

I think a good example is maybe the prototypical example of one of these communities is something called the Health Data Initiative, which some of you here might have heard of. This is an effort that we spooled up about 3 or 4 years -- or 4 years ago now or so, which is designed to basically look at all of the data that we have across HHS and make that data available to the outside world in machine-readable format so that people can do interesting things with this information.

What's kind of interesting about that story is when it started, it was really just an idea. We thought the data would be interesting and useful, but we didn't know for sure, and we have now I think proven through a bunch of different mechanisms that this is absolutely the case. Four years ago the default setting at HHS for data availability was most certainly closed; right? The data existed in these silos, they existed in these systems, nobody even gave two thoughts to putting them out there for people to use. But today we get calls all the time for people who are building new systems, who are experimenting with new things, asking us how -- what the best mechanism is to make this data available and put it out there for the world to use.

We see this in things like the Health Datapalooza, which is an annual conference.

We used to run -- now it's transitioned to the Health Data Consortium here in D.C., and this past June we had 2,000 people show up from around the world to spend 3 days talking about nothing but health data, which is kind of amazing to me, especially considering the first Health Datapalooza, which happened 4 years ago, was literally 40 people around a table. You know, so when you look at the growth, that actually says something.

And then every day I see new startups, new companies, that are leveraging the data that we have put out there in some way, shape, or form to change the way our health care ecosystem works, and it's been absolutely fascinating to watch. So I think that's a great example of how we can bring people together across the board from different levels in the organization to do something that is sort of bigger than everybody but can have a very sort of dynamic and interesting impact in the world.

Now, second, one of the other things that we realized is that while we have a whole bunch of really smart people in government who have got a lot of great ideas, we don't have all the answers, and we don't know everything that exists out there in the world, and not only that, we don't have some of the skills that we need inside in order to help drive some of these things forward.

So as a result, we created a couple of what I call in residence programs where we bring people in from the outside world, we recruit folks, to come and work on time-limited projects in the Department, that in one case, in the case of our HHS Entrepreneurs Program, is either our sort of discrete, one-off, relatively complex problems that need to get solved, and we bring somebody in from the outside world for 12 months to solve those problems. Now, it turns out the 12-month piece is important. If you only have 12 months to solve a problem, you almost by definition have to do things differently, you can't follow the standard bureaucratic

processes.

And what's really interesting is that there are sort of two goals to this. One is obviously to solve the problem. The second goal, though, is to actually teach people who are hosting these folks that there are different ways of doing things and that you don't have to be somebody special to come in and be able to change the way certain things work. And we're actually seeing some of these things take effect.

A really good example of this is one of our first HHS Entrepreneurs. He went into HRSA. One of HRSA's functions is to manage the organ donation transplant network, and one of the things that they had become aware of was that there is a big safety issue essentially with the fact that -- and this was a huge shock to me when I learned this -- but when organ procurements happen, the surgeons and the nurses that are performing the procurement end up having to write 70 to 100 labels for those organs by hand. And these are not simple labels; right? These are things that contain lengthy numerical alphanumeric character strings that are patient IDs. They are things like blood type and a whole bunch of other stuff, and they write them literally with a Sharpie on a label and slap it on a container.

And so they thought, wouldn't it be interesting if we could maybe somehow -- they actually -- it was interesting, they thought the problem was shipping and tracking of these organs. So how do we RFID tag a package, scan it on exit, scan it on import, and then we know that this organ got to the right place? When we brought in our entrepreneur, his name is David Cartier, and he was a UPS employee for 25 years working across the board at UPS. We figured, hey, who knows shipping better; right?

He did something really smart, and he actually watched a whole bunch of organ procurements, and he realized that it wasn't the tagging and tracking and the shipping that was

the problem, it was actually much earlier in the workflow, which is literally, why do they have to write labels in the first place?

And so he developed a mobile printing solution, really straightforward stuff, nothing terribly complicated, but it's interesting to see how tricky it is to get a very simple solution like that integrated into a somewhat status quo oriented system like the organ procurement operations.

But he's had amazing success, and he is now in the process of conducting a number of different trials in the field across the board. There are a bunch of data points, which is indicating that this is a successful solution, but the best sort of anecdote is when they did a pilot at one of these organ procurement operations, and it was I think a 3-week-long pilot, they then took the system away and the surgeons revolted. They were like, "No, come on," you know, like, "You gave this to us, you can't take it back." And so I feel like there is no better evidence than that to indicate that it's a good idea and a good system. And this is something that he created in 12 months -- right? -- from start to finish, really doing the right kind of work, you know, user field interviews, all kinds of stuff like that.

The second program in this bucket is something called Innovator In Residence. This is an initiative that we have which allows nonprofits who have a similar interest to HHS to fund a 2-year position within the Department to actually recruit somebody to come in and work on that topic. What's interesting about this to me is that we don't specify the details of what those people are there to work on, we just say, "Here's your topic. You figure it out."

And so we have a couple of really interesting folks that are in right now. One of them -- actually he is one of the more remarkable people I've ever met -- his name is Nag Murty. He is an entrepreneur. He's a Stanford D.School graduate, started a company called

Embrace, which some of you might have heard of. Think little tiny -- they look like little tiny mummy sleeping bags, designed for premature babies in the developing world, and the idea is that incubators, sort of modern incubators, are hard to use in the developing world because you don't have access to constant electricity, you don't have access to spare parts when they break, and so they developed this -- it looks like a sleeping bag, but it's got special material in it that essentially heats up quickly but loses heat slowly so that you can put premature babies in them, keep them warm for lengthy periods of time without access to electricity or any kind of fancy machinery. And so we found him, he applied to join the program, and he's been doing some remarkable work on the topic of patient engagement. I don't really have too much time to go into it, but a lot of this stuff, by the way, I should say is detailed on our website, so if you go to HHS.gov/idealab, you can check out all of these things.

And we have another one right now who is working on a topic called -- or the topic of Patient Match. Many of you might know that we are by law prohibited from developing a national patient identifier. One of the big problems in our health care system today is that we don't have a national patient identifier, so Bryan Sivak with an "i" and Bryan Sivak with a "y" at the same hospital look like two different patients, which is a huge problem. And so we have recently brought a couple people in to essentially work on the problem of matching patients, which I don't think is -- it's interesting, it's not an intractable problem, but it's a pretty difficult one when you look across the different numbers of systems that exist out there, the different types of data that are collected, and things like that. So that's the second piece.

The third piece I think is one of the most important, and what we realized is that we needed to invest in our employees, we needed to invest in the people that work at HHS in

order to let them sort of realize some of these ideas. So one of the things that we've created is -- you can think of it probably best as a internal accelerator, much like a Silicon Valley accelerator. Teams apply to classes. The ones that are selected receive 3 months of time, up to $5,000, which actually it turns out is the least important thing. Many of the teams don't even use the money. And, most importantly, training on methodologies that are designed to help them explore the problem in, let's say, a more private sector type way. So we teach them things like lean startup, business model canvas, human-centered design, design thinking, processes which we never teach in government but which actually allow these teams to go out to their, quote/unquote, "customers" and understand quickly whether or not their ideas are good, whether they need to be tweaked, whether they're going to work or not, and then actually test them and generate some metrics to prove or disprove that hypothesis.

One of the teams that was in our first class of HHS Ignite, which happened last year, was a team from the National Institutes of Health, and they wanted to create a -- and this is relevant to you guys -- they wanted to create a 3D printing library for biomedical files, and so they used the Ignite program to kind of test out this idea, and they created this thing called the NIH 3D Print Exchange, and basically it's not just a library, what they also created was a set of tools, freely available web-based tools, that allow anybody to upload 3D models that can automatically be created into 3D printable files, so people can then download those files, throw it into their machines, and come out with a model of something.

They came up with this idea -- actually, it's sort of interesting -- and, by the way, I should just say before I go into this that I'm not either -- I'm not a chemist or a biologist, so if I say something incorrect, don't fault me for that, but basically they were telling me the story about how one of their researchers was looking at a flu virus, a 3-dimensional flu virus, on a

computer screen, sort of rotating it around, and they were trying to look for potential pathways to find a vaccine for the flu, and somebody had the idea to 3D print it.

So they printed this model, and as soon as they picked it up and started looking at it, they actually discovered a channel in the virus that they could use as a receptor -- this is what they told me -- that they could use as a receptor for a potential vaccine.

So the idea was just by holding this model in their hand, they saw something different that they had never seen before in the 3D image on the screen, and that's what kind of led them to this idea.

Now, the team found through the pilot that we sort of gave them the space to look at, that this was a valuable idea and a viable model.

And then one of the other programs that we have in this bucket is something called HHS Ventures, which you can think of as a venture fund to sort of invest in ideas that we think have promise, that have shown some potential, but might be still a little bit too risky for the standard pathways of funding to take on, and so we actually funded them to continue their work along with actually another small chunk of funding from NIH to push this forward. And they're doing great. They were at the White House Maker Faire a few months ago demonstrating some of this stuff. They've been I think doing some really remarkable work.

So I want to close with sort of one thought, which is that we know through the course of history that most great inventions kind of come not through these eureka moments but through either serendipitous collisions of people who are working on interesting things that happen to get talking about stuff or through just sort of the collection of different ideas over time. Many of you guys might have read some of Steven Johnson's books. He kind of explores the history of invention and the history of innovation. And he's got a new book called "How We

Got To Now." And one of the pathways that he chronicles here is how the development of Gutenberg's printing press led to the development of reading glasses because people needed to read the printed material, which then led to the development of microscope lenses, which obviously blew up biology, which then led to the invention of telescope lenses, which obviously changed the way we look at the universe.

And he's very sort of vocal about noting that there never really is this eureka moment -- right? -- it's sort of a collection, a collection of things, that happen over time, networks and collaborations and contexts. And he's got a quote which I like. He says, "It was not a sudden epiphany or light bulb moment but something much more leisurely, an idea taking shape piece-by-piece over time, or in other words, a slow hunch."

And I think in many ways this represents kind of where we are today in the 3D printing world. You know, the solutions that we're seeing here and some of the things actually that were in that last presentation, they come from diverse fields -- right? -- and different people working on different things that solve problems around time and cost and speed and materials and all kinds of stuff like that, and, you know, I think when we can place sort of basic information like this and like what the NIH 3D Printing Team is doing into the public domain and allow people to sort of take the fruits of this labor, crowd source it, work on top of it, we actually see interesting outputs and directions that these things can go.

Just as one story to kind of end on, many of you guys might know the story of Richard Van As. He's a carpenter in Johannesburg, South Africa. He lost his right hand in a table saw accident and he was browsing the web one day and he came across some YouTube videos by a guy named Ivan Owen, who is a special effects puppeteer in Bellingham, Washington. And these YouTube videos basically showed some really interesting things that

Ivan was able to do with micro-fine wire and metal digits. And so they started Skyping together, these two guys, and they actually ended up creating a mechanical hand for Richard.

Now, one day Owen flew to South Africa to visit with Van As, and while he was there, he got a phone call from a woman whose child was born with a birth defect which caused an improperly formed hand. And so they started working together, they connected with MakerBot, who offered the use of a 3D printing machine, and now you have these prostheses that are being created on an incredibly rapid timeframe across the board. There is actually a website where you can go to and check out the process, actually order one, and it's kind of amazing how that collaboration came to be.

And so that's really the thought that I kind of wanted to leave you guys with today, that with this world that we live in today, we have this power of ideas that are able to connect at just this incredible speed, people working together in ways that they never thought they would be able to across different disciplines to create things that have massive and interesting and important long-term lasting value.

On that note, I don't know if I have time for any Q&A or anything, but if not, thank you guys very much, I really appreciate the time.

(Applause.)

LT COBURN: Thank you very much, Bryan.

And with that, we have a break. I will say 10 minutes for the break, which according to the clock here, would give us 10:53. So try and be prompt because we will be starting a couple minutes late already. So 10:53 be back here.

(Break.)

Perspectives on Post-Printing Considerations

DR. DI PRIMA: All right. So, so far we've covered some pre-printing perspectives and thoughts, and then we did some printing, and now we're going to discuss some perspectives on post-printing.

So some of the workshop goals on this topic. So, first of all, not all devices or additive manufacturing technologies have the same risks or degrees of concern. I think that's already been mentioned. We sort of look at things as load-bearing, non-load-bearing, implantable, non-implantable, patient matched versus standard sizes. So as we're discussing these concerns and what testing is necessary, please keep in mind that there is not going to be one size fits all, and we are going to be looking for some specifics based off of device and technology type.

What we're really looking at is what needs to be considered during the design process and, most importantly, what needs to be communicated to the FDA. You know, in the FR Notice we did mention that we're hoping that what we get out of these conversations is going to inform a guidance with the hope that we will let everyone in the room know what we're looking for when it comes time to submit an additively manufactured device. As I'm sure many of the companies here never like getting surprise deficiencies, so the hope is that we can sort of level the playing field and make sure that people know what we're looking for.

So, again, this is a conversation. We just want to get a sense of what people are doing, what works, what doesn't, so we know what questions to ask intelligently in the future.

So a lot of the questions we're going to be asking we're going to be looking for, have these already been addressed? how are you doing it? and even more importantly for us, what are we missing? People have been doing 3D printing for 25-plus years. What's working? What doesn't work? Are there some parameters that are key that we haven't mentioned?

So more specific post-printing considerations. So these are going to be the concerns related to device performance that are relevant after the printing process is complete, and they include, but are not limited to, mechanical properties, physical properties, cleanliness of the finished product, sterility, and pyrogenicity.

So in terms of mechanical properties, the difference between additive manufacturing and traditional manufacturing is now the layering process, and we're concerned about the interface between the layers and, based on your technology, you can have anisotropy in terms of mechanical properties. Now, I did some digging, and the absolute worst case of anisotropy I could find was published in a 2002 paper specifically looking at how you tweak -- how the mechanical properties of an FDM component can be changed by changing printing parameters. Their worst case there is Z print direction had only 15 percent tensile strength as the raw material. Believe me, this is not typical, but this is the worst case, and we're always worried about people tweaking some design parameters that they're not supposed to and leading to some mechanical issues.

There have also been a number of fatigue studies performed to investigate the effect of build direction on fatigue strength, especially in metals. As Dr. Hollister mentioned, they're working on that with some of the degradable polymers. And with the change in chemistries on the polymer side as well as the effect of this print direction, and probably even more on the polymers where you're polymerizing no longer on another melt, but you have a solid, and making sure you get that right interface, that's a potential concern.

In terms of medical device performance, something like a spinal cage can experience complex in vivo loading conditions, and that can lead to sort of challenges in the conventional testing of fatigue if you're just doing rotary beam fatigue on one direction and

you're not accounting for that print direction on your final mechanical behavior, there might be a mismatch there.

And sort of the last point here is patient matched devices lead to greater challenges in determining the best print orientation for mechanical performance because if you can imagine for a complex shape that you're sort of always tweaking to match the patient's anatomy, your worst case loading orientation on those print directions could change.

So these are all sort of the questions we have been kicking around here and hopefully will be addressed later this afternoon.

So continuing, traditional manufacturing, casting, it's been around a long time. Lots of tricks. People have figured out how to optimize your microstructure and mechanical properties. We lose a little bit of that with 3D printing. So in terms of some of the polymer systems, you have to add a lot of additives to an SLA to get the resolution you want. We want to make sure that those additives aren't negatively impacting mechanical performance. I've talked with quite a few metallurgists who aren't always thrilled with 3D printing because you lose a lot of your microstructure control and some of the tricks that have been developed over time. So these aren't necessarily concerns, but they're something that you need to consider in making sure that you're going to have the mechanical properties you need.

In terms of physical properties, we're always concerned about microporosity and getting fully dense parts. This may lead to fatigue crack initiation sites. We're also interested in ensuring that you don't have incomplete consolidation from pathing or some sort of material solidification problem because that may reduce your mechanical strength.

And we're also really intrigued with the engineered surface features, especially some of what Ernesto showed us on the design porosity. There are some really fascinating

designs we've seen in academia and even proposed in terms of medical devices with really sort of fascinating either through porosity or alternating from a fully porous region to a fully dense region, and we just aren't totally sure how that's going to -- features like that will affect the function and mechanical performance. So these are all sort of questions we're looking at.

Cleanliness. This has been mentioned a few times. So generally additive manufacturing has access material you have to remove. You have to remove all the powder in a powder bed system. If you're doing an SLA system, it's suspended in uncured material. And several of these will have sacrificial support structures that either need to be physically removed or are going to be chemically removed. So you have your part, and we need to make sure all of this extra material is removed because in terms of at least medical devices, we don't want excess material being introduced into the patient in terms of the materials, we don't know what the uncured or partially cured material is going to behave, so we need to make sure that we can clean these. And the challenge again with where we're seeing this in medical devices is going to be these porous components. If you have a printed porous coating, if you have the porosity integral to a solid piece, how do we make sure that we get everything out of that porous region, especially if you have porous regions connecting to a solid piece?

So again porous coatings may serve to track and trap excess printing materials. And since this porous coating is going on before the final machining process, we also want to make sure that any lubricants or debris from final machining is also able to be removed.

So sterility and pyrogenicity. So again we're going to look at the sort of complex structures and porosity. And we have a talk by STERIS talking about some sterilization techniques, but we have concerns that if you pick sort of the wrong sterilization technique for your device design, you might not be able to sterilize all the way through that porous coating.

Then, conversely, you might also be trapping sterilant in there. We also are very curious about how to validate the sterility of the internal surfaces and the porous-to-nonporous interface. So again usually when you do that sterility assessment, you pick what you would consider the worst case spot and measure it. Now, if that worst case spot is a couple hundred microns to a millimeter to inside a porous coating, how do you make sure that that's actually sterile?

And we're also worried about endotoxin and bioburden risks within these complicated devices, and again making sure that in this porous region you can pull it out.

So if you've noticed, all of these concerns are features of a device, not a specific technology necessarily. And, again, if you are printing something fully dense, a lot of these concerns are minimized. So again this is going to be a function of your technology and your device in terms of what we're worried about.

So I have a series of subject matter experts who are going to talk more about this.

The first one is going to be Greg Morris of GE Aviation, and he is going to be discussing their process of taking the additive manufacturing process to full production.

Greg?

(Applause.)

MR. MORRIS: All right. Thank you, Matthew, and good morning, everyone. It's good to be here. Let's see.

All right. So, no, I didn't take a wrong turn and miss the FAA and come to the FDA; and, yes, I am with GE Aviation.

So prior to GE Aviation I was with a company called Morris Technologies. We also got involved in the medical business. GE Aviation acquired our company, and we really

became aviation-centric.

So, look, the reason I'm here I think in part is to give a perspective of a different industry, and perhaps some of the similarities and maybe more so the similarities and some of the differences between what you do in the medical world and what our experience has been in the aviation world, and specifically around additive metals is where I am going to concentrate a lot of my effort.

So the first two things, I think it's fair to say in two primary observations that we would make at GE is that, number one, when you're designing for additive, every element of the design process needs to be thought about differently. So we've kind of touched on that. We've heard that from a few presentations already, but this is really an important point. You can't generally take, at least in our world, we have found you cannot generally take a design that was meant for castings or fabrications or machining and think you are going to just be successfully producing the same part with an additive technology. So we've learned that lesson very well on one of the parts I'll show you here today.

The other one is that from our perspective at least -- and this would of course be through the FAA -- that the qualification of additive is really no different than qualification of any new cast or forged alloy. That's a pretty significant statement from our perspective because what we're trying to say is we don't believe that the process itself should be certified, we believe still that the components we produce, the engines, should be certified, and that's a very important point for a lot of reasons. There are cost reasons and there are regulatory reasons, but at least in our world, that's how we view it, and we think and we hope that the FAA views it in a very similar way.

So let me just go through a little bit of our pedigree of where we've been with

additive and some of the things that we use.

So in our facility we actually have a number of different modalities. This is kind of an eye chart. But we deal a lot with the direct metal laser melting, which is a laser bed powder-based process, but we also have the electron beam process, we have cold spray, we have powder flow. We do quite a bit of different processes throughout GE, but also through GE Aviation.

Now, when we look at how we work with this technology, we have our Global Research Lab. They typically are involved in the early TRL/MRL levels, and they are the ones who create new materials or use certain materials and help to characterize them.

And then we also have our whole new materials area. We have a design area. We accelerate all that with some of our entities, just like Morris Technologies and AvioProp, which are the acquisitions by GE Aviation in 2012. Those are specific additive organizations that are now integrated within Aviation, and so we're pushing the technology not just on the R&D side of it, but we're pushing it into production.

And then we work with a number of organizations on the outside, like America Makes and Oak Ridge National Labs, Lawrence Livermore, various universities, and other industry partners.

So in the interest of time, I want to go through quickly some of -- the fuel nozzle story because that's one of our big success stories that we've been talking about recently, and we have a number of other parts that are in the pipeline, but this one is coming up relatively soon.

So the first thing I would tell you is this technology tends to be thought of as new, and there's a good reason for that. I think the media, the press, has really latched onto

this technology, being additive or 3D printing, in particular probably over the last couple, 3 years, but the industry, of course, as was earlier discussed in Andy's presentation, really began probably around the mid-'80s, but from our perspective on metals and metals specifically, we look at the technologies that we use today and we say the foundations of those technologies have actually been around for around 30 years, 25 to 30 years. And when I say the foundations of that technology, I mean metal powder and lasers combining together to do repair on flying hardware that's been in existence for 25 years. And then the 3D CAD modeling capability and software; that certainly has come a long way and matured very quickly in the late '80s, early '90s.

But a lot of that got packaged together to what we now think of as today's modern additive metal machines, whether they're electron beam or laser, but in reality, if you really break it apart, from our perspective, these are things we've been working with, we understand, we've characterized, and we know very well for the past 25, 30 years.

Now, as it relates to the technologies as we think of them today, such as direct metal laser melting or the EBM process, we've actually been working in those technologies for probably the last 12 years or so, when you look at GE Aviation and you look at Morris Technologies. So we have actually been working with these technologies very aggressively to characterize, to further them, to understand the science behind it, to improve them with in-process monitoring capability.

So if we look at all of that and you combine that into a product like our fuel nozzle, we started down the path of designing a new fuel nozzle back in the early 2000s, and GE at that time immediately leveraged this great new technology called direct metal laser sintering. And then we basically were helping them to accelerate their product design cycle, so

we pulled schedules back to the left. Whereas normally you see schedules bleed out to the right, we were able to pull schedules in, we were able to create hardware much faster and actually much less expensively than traditional means.

And then what happened along the way is that I think a lot of the engineers and designers that were working with us, they realized that, hey, we can get incredible complexity in this technology, so we started to build in the complexity. And where we sit today is we're now approaching our entry into service for the LEAP engine.

So speaking of the LEAP engine, the LEAP engine is the successor to our CFM56 engines. So for those of you who flew over to Baltimore or Washington for this meeting, you may have been on a narrowbody airplane and you may have had a CFM56 engine powering that airplane. It's actually the most popular commercial engine in the world. It's flown over 650 million hours of flight hours, so it's a very well-proven engine. And, of course, this is a joint venture between Snecma and GE. So it's the CFM56.

Our next generation engine is the LEAP engine for that specific style of airplane, and the LEAP engine has a lot of things it's going to bring to the table, a lot of technology that we're pushing in the engine. So we have things like ceramic matrix composites and additive in the form of the fuel nozzle. But we have aggressive goals to meet about a 15 percent reduction in fuel consumption and a bunch of other things that we have promised to our customers. And the entry into service for this engine begins in 2016. To date, we've sold over 7,500 engines, and that means we have a -- it's a great story, we have a huge backlog, but now we have to deliver and we have to scale, and that's really unprecedented in the aviation industry, to have that number of engines presold and to have this kind of technology that we're pushing into the engine.

So why the fuel nozzle? What are we doing with this? Well, we're trying to reduce our nitrous oxide and some of our emissions basically. We're also trying to get a fuel savings as we push these into the engine. So we've gone through multiple iterations from where a little tube used to be sending the fuel into the combustion chamber to where we actually got involved in more lean-burning fuel nozzles.

So there has been an evolution of design, and the last evolution really has taken advantage of additive, and that's been the Twin Annular Premixing Swirler, what we call our TAPS, fuel nozzle. So a very complex piece of equipment that is taking this complex mixture of air and fuel and it's giving us really the ideal scenario so when it injects into the combustion chamber, we get a very lean mix and we get a very efficient burn and efficient engine.

So why are we looking at additive? Why wouldn't we just go to some kind of traditional methodology? And there are a lot of reasons, but basically it's very simply stated as better, lighter, and cheaper parts and systems. So we've been able to combine multiple components into one. We've been able to get more life and more durability. We've been able to demonstrate we can produce these less expensively, faster, and we can iterate more often, especially in the prototype phase.

So the other final one I would say on this list is the capital equipment reductions. We can reduce the amount of capital equipment that we have to expend in order to ramp up and build thousands of these components.

So if I'm looking at some of where we do our things, again our Engineering and Design Group is embedded with our Additive Development Center, which was the Morris Technologies facility. We also have what we call Lean Lab, so we do a lot of R&D and we scale the process, industrialize the process, in facilities in Cincinnati.

In July of this year we announced where we will have our first production facility for additive, and that's going to be in Auburn, Alabama. So at the Auburn facility we will be placing multiple machines that will be additively producing fuel nozzles.

And throughout all of this cycle we continue to rely upon our Global Research Centers and some of the other businesses that are getting involved in additive as we share information and help to characterize materials in general.

So some of the highlights about why we went down this path. Number one, we took 20 pieces, what used to be 20 pieces, to make up this fuel nozzle, which were castings, machine components, they were brazed, they were welded, and now we can grow a very complex structure. We were able to achieve around a 25 percent weight reduction compared to the GEnx engine. We have about 30 percent lower cost and we are about five times more durable.

So how did we get to that durability? If you look up at the couple of little squares going around there, you'll see in the fluid dynamics and the thermal design arena that we were able to design -- and you see just little pieces of it, I can't show you the whole thing -- but what we were able to do is design to the process and design around some of the debits that we see at a surface finish, which are typically low cycle and high cycle fatigue debits, so we were able to design around some of those things that would have reduced the durability of the fuel nozzle. And with this really brilliant design, we are able to give a performance that we otherwise couldn't have seen in a traditionally manufactured component. So designing again to the process, leveraging all of the capability of design, is really, really important.

Now, if you think about it, if we had 20 different components that we were making in other forms or means -- so let's assume that you had machining or let's say you had

castings coming together, all of those had to be brazed, they had to be welded, et cetera, they had to be transported, you can see that we start to cut down on the vast number of complexity of supply chain issues that we have. So instead of having 20 different areas, a machining center or a foundry or what have you producing individual components, now we can just have one machine, if you will, multiple of these, but one machine growing the same component. So there is a tremendous cost savings and a logistics savings when we look at additive.

So now to get into really the heart of it, which is qualification for us. So our journey. It's great we're leveraging the technology like I've just described, it's great we're getting the benefits out of the technology, but what's important and what in large part I think the FDA and many of you are interested in is the qualification process.

So really if you look at how we look at our qualification, we go from our concept of feasibility development and maturation of a technology. That's really the path that we're ultimately taking. And materials and process content become very important to us on that journey, with our deliverables being that we understand what we're doing, we characterize the materials, and we have a component stability at the end of the day.

So materials become very important, and so I'll dwell on the material portion of it just very -- well, a couple slides here.

The items that you see up here become things that we need to control and that we need to understand. So if we are looking at a fuel nozzle that has to survive a certain number of hours in the engine before overhaul or before replacement, we become very concerned about the lifing of that particular component, so we need to understand a lot of the different factors of the materials. We need to understand when we produce a component out of the machine that we're getting fully dense material. We need to understand our thermal

processes. We do go through a series of thermal treatments, which include stress relieving, HIP, and a solution heat treat on the back end. Now, this is for cobalt chromium up here, but you can get a sense of what happens to the microstructure as we go through the process of out of the machine in through the post-thermal processing and on the back end after post-thermal treatment. And we really get a very isotropic grain structure, as we see at the very end there.

So this allows us to be able to -- you know, when we get these kind of properties, it allows us then to design to a spectrum of components that if we didn't know this, if we didn't have this characterization of materials, our engineers and our designers would be very limited in what they can use the material for and the process for. So it's actually kind of an evolving issue in the industry, and that is, characterization of materials and how many different materials are truly characterized.

So within Aviation, we are working on many different materials, but because the fuel nozzle built in cobalt chromium was our first alloy, that's really the first one we have fully characterized and what we call our redbud (ph) curves assigned to. Not a cheap process and not a fast process.

So, look, if we look and if we take a broad view, a global view, of the process and we say, "Okay, what are the things that we are concerned about? What are the things we ought to be looking at as we go forward in trying to qualify, characterize, and certify the process and the parts that we're producing?" what you're going to find is that these or many of the items that we have to be feeling very comfortable about.

So you'll see that they kind of get grouped. They get grouped into your raw material, which for us would be the metal powder, they get grouped into the machine parameters, so what's your speed, what's your wattage of power, how much depth, what spot

size, et cetera. And then we have the post-thermal treatment aspect. And then after that, we then go through surface finishing, so it could be machining, it could be the surface finishing of the parts themselves to get a better surface finish to reduce that debit we see on the LCFH (ph), et cetera.

So these are big buckets, but these are a sampling of the kind of buckets that we are concerned about that we must check off and have a complete understanding of before we can march forward, taking it to MRL9 and above.

So another aspect is once the part is built, we have, of course, post-inspection. Post-inspection to us right now is quite intensive, so we're actually -- we're doing 100 percent dimensional and CT scan of every part currently. We're doing cut-ups per build per a quality plan, so that means every build that we do -- and we're doing hundreds of builds -- we're taking two of those parts out and we're doing cut-ups on them. We're doing 100 percent tensile bar testing, and you can see that we do a lot of things to the actual fuel nozzle, the production fuel nozzle, before they would go to the next steps, which would be fuel flow, airflow, and 100 percent proof of pressure.

So there are a lot of steps that we go through. This is very expensive, by the way. This is not something we plan on doing for every fuel nozzle as we make 40-some thousand fuel nozzles a year. We probably can't afford to do this, but right now we have to collect data because data doesn't exist. So we go to these extreme tests. And then finally once we feel very comfortable, we then will probably back into a sampling plan that makes more sense than having to do 100 percent for every single component.

So if we look at the qualification roadmap, it's really pretty straightforward in a lot of ways, but it's identify what kind of components do we want to go out and leverage this

technology to. That's a moving target. Technologies get faster, better, more accurate. We start to increase the number of components that can fit into that bucket.

We then mature the process, so we can mature that in a whole variety of ways. It could be in the materials, it could be in our process, it could be in the surface finishing, it could even be in the machines. We then design to the process. I mentioned before that's really very important to design specifically to the additive processes. And then we go through this long period of time in the aerospace industry of qualification, and that's to make sure that when you're flying on that plane home and you look out the window and see an engine that's zipping along at multiple thousands of RPMs, you feel very comfortable that engine is not going to have a failure.

And then we validate, of course, and certify the engines, and certifying the engines would be at the component level and engine level qualification. Very important again, not the process, but the component level and the engine level. That's where we're certifying.

That's all I had. And I didn't know if you want questions now or later.

DR. DI PRIMA: If we have time, we'll take the questions at the end, but I want everyone to get some time to eat. Perfect.

Thanks, Greg.

(Applause.)

DR. DI PRIMA: So our next speaker is going to be Bill Brodbeck of STERIS. He is going to be discussing some of the various sterilization techniques and sort of the pros and cons with various 3D printing approaches.

So, Bill?

DR. BRODBECK: Thank you. Good morning, everyone. First I would like to thank

the FDA for the ability to speak to all of you today. And secondly, in full disclosure, my experience with 3D printing devices is kind of limited, probably consisting of about 3 hours and 26 minutes right now.

(Laughter.)

DR. BRODBECK: So I apologize for that, but the point being is that being from STERIS and having some obvious interactions with the Infection Control Branch at CDRH, we have grown to learn that there are some common motifs that we see and challenges that different manufacturers of devices face when sterilizing their devices, and not only do we know those challenges, but we also know what FDA is expecting when we approach them to address these challenges.

So starting off, very simply, if you don't know this, you should, the definition of "sterilization" as well as "sterile," and obviously we're going to stick with the motif here of FDA's definitions because this is coming right out of their guidance document. And "sterile" is defined as the absolute state where all forms of life have been eliminated. Right. In the practical sense, though, absolute sterility cannot be proven, therefore, sterility is considered achieved when organisms are eliminated, inactivated, or destroyed such that they are undetectable in standard media in which they have previously been found to proliferate.

As you are going to see in the next slide, we can never guarantee 100 percent sterility of any device. Okay? We have to rely on a sterility assurance level, and I'll talk about that in a little bit. And also we'll get into maybe how you can build that into your program as well, and that is achieving that sterility assurance level.

Sterilization, of course, is an act or process which completely eliminates or destroys all forms of life particularly microorganisms.

So the sterility assurance level itself is a value indicating the probability of a survivor after a sterilization process. As we said previously, we can never guarantee 100 percent sterilization. For example, an SAL, or sterility assurance level, of 10(-6) is the probability of 1 in 1 million nonsterile units after exposure to a sterilization process. So we find that acceptable. You're going to see that in many cases we have 10(-6) SALs or in some cases there may even be a 10(-5) SAL, but the point being is that again we cannot guarantee 100 percent sterility, and there is an acceptable level of 1 out of every million devices being processed not being sterile.

One of the major things that we would also like to point out is that the goal of sterility assurance is to verify and maintain the sterility of a medical device or medical instrumentation until it is used on a patient. Okay? So not only when we talk about sterilization is the point of contact or the point of sterility or the process itself but also following that and whether it be it's within the container or a pouch, et cetera, until it's delivered to the patient.

So some challenges. Number one would be your materials consideration. Obviously I know we talked a lot about metal this morning, and I'm sure there are a lot of individuals out there or companies that are considering polymer 3D printed devices as well, but you really have to start off with considering your materials. And any metal-containing devices, obviously gamma sterilization is fine, steam sterilization is fine as well. However, the problems start getting into when we start talking about polymer-coated or polymer-containing devices because there is irradiation sensitivity, and you really can't use gamma for all polymers. Also, there is a temperature sensitivity. So steam and some other modalities are not going to work out for you either if you're using polymers.

There are also several other materials constraints that we know of. Some of the polymers out there, and even some metals in some cases, may actually neutralize the sterilant and therefore providing it ineffective for providing sterilization of your device. And really we know of certain materials that are used are actually contraindicated through their sterilization process. For example, we know that you can't use vaporized hydrogen peroxide with nylon. It's just contraindicated, it will not work, you must move on.

So those are different things concerning the materials.

Secondly, you've got to look at the design. Okay? Number one, does the design allow sufficient contact with the sterilant? This probably should be obvious, but if you're talking about a 3D printed device, does it contain enclosed or difficult-to-penetrate spaces? We're talking about steam. If steam cannot penetrate all spaces, you're not going to have contact, you're not going to be able to sterilize that device.

Can the device design withstand contact with liquid and variations of pH? There are different types of liquid sterilants out there, I should say liquid chemical sterilant processing systems even, with peracetic acid, performic acid, et cetera. If you cannot penetrate spaces with liquid, you're not going to be able to sterilize the device in that case.

Also, if your polymer cannot withstand any pH variations, then I would highly recommend not using an acidic environment.

Can the design withstand an environment under vacuum? All right. Some of the steam sterilization processes pull a vacuum in the pre-vac cycles. Also, if you are considering something like VHP, vaporized hydrogen peroxide, or hydrogen peroxide gas plasma, both of those will vacuum as well. So you need to understand whether or not the 3D printed device can expand or contract or deform due to increased or decreased pressure, obviously

eliminating your availability of sterilization methods there.

When coming into contact with a sterilant, can unintended reactions/residuals result? Obviously, if you're going to have a polymer or other chemistry and you're going to introduce additional chemistry through that sterilant, you have to be sure that you're not really creating any byproducts that could be leachable byproducts, and you would want to also make sure that you're not changing your microstructure of your device, maybe increasing where it's not going to be brittle. So there are several different considerations that you need to take into account when looking at using possible chemical sterilant processing. And obviously there are limitations of different sterilization technologies.

Going through just some of these, we group them generally into high temperature, high pressure, as well as chemical, but under your high temperature/high pressure, there is steam. We know that that's primarily used in hospitals, academia, and industry, so really steam is used everywhere. However, obviously, it cannot be used for any devices that cannot tolerate the heat or high temperature or high humidity or high pressure.

Dry heat, this is only primarily used in academia. Obviously any devices that cannot be used with that is sensitive to high temperature. And I don't know if it makes a big difference, but in a lot of cases, several manufacturers don't like long cycle times for sterilization because it cuts into the manufacturing time or other reasons. However, we know that dry heat does have very long cycle times.

Regarding chemical methods, ethylene oxide gas is probably one of the most common that's used in hospitals, academia, and industry right now. The good news is it's low temperature; however, if -- hopefully you're familiar with the ISO 10993 series. One of those standards actually specifically addresses just ethylene oxide residual. So there is a high

potential for residuals, and if you're using some type of polymer, that's to be taken under consideration. You should also know ethylene oxide is highly flammable and carcinogenic, and as well as there are very long cycle times associated with ethylene oxide, specifically associated with the degassing phase. So there are different methods that can be used to increase the efficiency of degassing and reduce those cycle times, and we would be happy to discuss that.

Vaporized hydrogen peroxide, this is actually my specialty at STERIS right now. It's primarily used in hospitals mainly for reprocessable endoscopes as well as several other materials, but it is something to consider. It is very low temperature. Okay. You're looking at 55 degrees at most. And the problem with it, it is high vacuum. And also the other problem could be it is hydrogen peroxide, can actually cause some chemical reactions on the surface of your device. So a few other things to consider there.

Some additional chemicals, peracetic acid, primarily used in hospitals. Performic acid, also used in hospitals in Europe. Hydrogen peroxide gas plasma, very consistent with the vaporized hydrogen peroxide; that's also used in hospitals. Gaseous chlorine dioxide. Vaporized peracetic acid, usually used in hospitals in Europe. Ozone, mainly used in industry right now. And formaldehyde steam, also used in European hospitals.

No matter what modality you're looking at here, there is always a potential for material compatibility issue as well as generating residuals whenever you're talking about interactions with chemical sterilants.

Thirdly, we could consider radiation. Radiation is primarily used in industry. Obviously, there is gamma radiation, but we know that it could have some negative effects on polymers if processed through gamma. Electron beaming also has some potential damaging effects, especially if you're talking about microstructures. And there is also infrared radiation.

One thing we have to note, too, is if you are planning on using any radioactive or radiation sterilization, there is some special licensing required to handle those radioisotopes.

Okay, so there we have the challenges of trying to define the appropriate sterilization modality with your 3D printed device. Once you think you have it, then you have to move into establishing your sterility assurance level and attempting to identify how you are going to do that, so you have to develop a method.

And I'm just putting out here some of the common methods that we see being used throughout the industry today, and usually that starts with direct or indirect inoculation in which you actually use your most resistant organism, which could be another challenge because every modality out there, every sterilization modality, does have a most resistant organism, whether it be steam or VHP -- for those two, it's geobacillus stearothermophilus -- and you have to identify that for whatever modality you're about to use. But anyway, in order to verify your inoculation method, you're going to inoculate with that most resistant organism a known number of microorganisms.

And the next challenge you are going to have is verifying your recovery rate. You're going to have to validate your recovery rate. I think 80 percent is somewhat acceptable. You would like to have 100 percent demonstration of recovery, but whatever you inoculate -- and you're going to inoculate your most resistant organism in your most resistant site in the device, okay, and demonstrate that you can recover at least 80 percent of that. Then you are going to go ahead and use your modality and see what recovery rates you get. Okay.

So there are a lot of challenges here because porous materials, you're not going to have a very easy time recovering, and therefore unless you are using complete submersion, which is something you may consider, not obviously ideal, you're going to have some

challenges with that as well.

Secondly, after -- well, many steps down the path here -- once you identify what your most resistant site is, your most resistant organism, your recovery rate, and you're able to demonstrate that you are able to get at least 100 percent kill or at least your recovery validation of the microorganisms, you don't have to do that for every device that you process; correct? So you would like to have some way of comparing that.

And there are several different sterility assurance level products out there, basically biological indicators and chemical indicators right now. What you would want to do in this case is you would compare the results of your validated method of recovery and your inoculation to a known resistance or available biological indicator that is on the market. And there are several different biological indicators for several different sterilization modalities. If you can make that comparison in a validated method, then you would be able to use that biological indicator moving forward.

In some cases -- I don't believe that we're there yet with FDA, but there are other cases in which you can add chemical indicators. FDA recognizes three classes of chemical indicators right now for several different sterilization techniques. What we would probably recommend in order to further verify that you're hitting the right conditions of sterilization is the emulating type of indicators, which ANSI, AAMI, and ISO identify as Class 6 indicators.

So, again, identify a method and be able to compare that method with something that's either currently available or something that you're willing to help develop, whether it be a biological indicator or a process challenge device and even possibly a chemical indicator.

Once you have your modality, once you have your potential sterility assurance

device or level product set up, then you have to move into your sterilization validation and provide that information as well. Several different steps are taken. I only listed a few of them here. In the interest of time, I am not going to go through each one of these, just know that there are several facilities out there and several ways that you can identify what the appropriate sterilization validation is. Again, ideally you want to have to verify every single device and you would have a method of validation available.

So in summary, the challenges that we see here, although we have limited experience with 3D printed devices at this point, our experience throughout a number of different devices and the sterilization challenges that they are finding is you have to identify whether the process is compatible with the device material. So the materials of construction is going to be of primary concern.

Is the process compatible with the device design itself? Obviously the more crevices or cracks or channels or porosity that you have, the more difficult it's going to be to sterilize. And in that same effect, will the sterilant penetrate those porous surfaces? Once the potential process is identified, you need to be able to verify that method through direct inoculation or indirect inoculation, and you need to be able to compare that with the appropriate SAL products, so make sure that they're available or you have the ability to design one.

And last but not least, can that method be validated?

That's all I have. Thank you very much for your attention.

(Applause.)

DR. DI PRIMA: Again, in the interest of time, we'll hold any questions until our last speaker. And with that, we have Dr. Boland from the University of Texas at El Paso, and he

is going to be talking a little bit more on the cellular side of things. So this should be a little bit different and hopefully really interesting for everyone.

So with that, Dr. Boland, thank you so much for coming.

DR. BOLAND: Thank you so much. I am delighted to be at this interesting panel, so many different people from very, very different areas.

So what we do is we talk about actually 3D printing tissues, not really devices, but cells and tissues. And it's going to be an academic talk because I'm primarily in academia. But I did, full disclosure, found or co-found a company called TeVido Biodevices, which is trying to commercialize some of these early attempts, and this is my one slide from the company. And what the company does or wants to do is tissue print a nipple, an areola complex, for women that had a mastectomy, so cancer survivors. There are really no good options for reconstruction of the nipple, and it's a small enough device that I think 3D printing can really make a difference there, and it's sort of a low entry to this market, which apparently is huge according to this market research. Within 10 years, 650 million, 10 billion by 2030, and I think the FDA will probably see some of those bioprinted submissions coming your way. So that's my one market slide.

So I was asked to talk about post-processing. So really -- let's see. Okay. We don't have a -- do we have a pointer? Okay. Really, I -- hmm. I am talking about this part here, biofabrication, what are the materials and certain cells that they use in the processes? And really after that, how are we going to actually characterize that and what's going to happen after the processing? Right?

So there are a number of people that have been using tissue printing, cell printing, and these are some of the tools here that have been used, and they are summarized in

a summarized bulletin here Ringeisen, et al. And I'm not going to go through all of these. We do mostly inkjet printing, but whether you use inkjet or some of these other techniques, really there is transfer of power from that cause something to solidify or become liquid and then solidify on a substrate. So whether or not you are using heat or piezo or laser, it's very similar to the other additive manufacturing. You need to have some kind of power source. And so there are things you have to worry about when you're dealing with tissues; right?

So we use inkjets, and these are the reasons why. It's very fast, it's very quantitative, programmable, transportable, very small devices really, and as somebody has already mentioned, inkjets come with different inks and different colors, so we can really mesh different serotypes using inkjet printer.

So we use thermal inkjets, and for those of you who don't know, here is a little schematic. There is a heating element that heats an air bubble that's trapped. Okay, I'm going to go back and look. Oh, hold on. Can I go back? Okay, so I'm not sure. It's going forward. Oh, here we are. Okay.

So we have a heating element, air that's trapped, and it shoots out the bubble. Okay. We can use this with cells, but we need to have some support for the cells, so typically we have polymers, naturally occurring polymers have been used quite a lot, alginates, for example, so these gel or crosslink with calcium, which is one particular process you might have to worry about because when you are running it out of calcium, they decrosslink. Others that we use is fibrinogen and thrombin, so which form fibrin and here this is a (inaudible) action, so as long as there is thrombin there, this will go on for a long time. Right? So it's a different mechanism and both of these mechanisms you have to worry about different things -- right? -- once you print them out.

Dealing with cells, so we have cells in our ink. There's a number of concerns, obviously. Size concerns of the cells, are they small enough to fit through a nozzle? How can we enumerate these cells? Are these cells alive, at least alive after they're printed? How do we print support and things like that? All right, so let me go through some of these.

If I can get that little schematic again.

Again, so let's say size. For cells, they're really not -- they're very unsimilar, like the powders, for example, that we use. They can be squished to a certain extent, as you see in the holding pipette there, but typically you try not to squish them too much, too long; right? So we typically pick orifice diameters of our devices that are about a little bit more than the size of the cell but a little bit less in diameter than two cells sizes, so we can typically fit about one cell in a drop, and we typically use the HP devices, which they already manufacture and seem to work quite well for most cells. It depends on the kind of cell you want, they come in different sizes as well, these cells.

And then you can establish a relationship between how many cells are ejected and how many cells you actually put in your ink, and there is a linear relationship until you get to a crowding effect where at really high concentrations suddenly your cell count drops. So probably the cell is blocking the nozzle or some things like that. So you can place yourself in a regime where there is less than one or less than one cell per drop being ejected.

Then you're looking at, okay, once the cells are ejected, are they alive? So we did this with neurons because neurons are very difficult to keep alive in general, and so if they are printed and stay alive, then it's a good process; right? So we see some of these neurons after 2 weeks, or 9 days and 2 weeks, extending the axons, we can image them, we can stain them, make sure that they are behaving like neurons on these stains.

And we can measure all kinds of properties, electrophysiology, on neurons; right? And so typically what we do is we compare cells that are printed out of our devices and then we compare this to a standard sort of pipetting normal biological technique, or cell culture technique, and we have a bunch of parameters, we can look at any variations, and typically they are not -- or if they are not, as shown here, then we have a pretty decent process; right?

Now, this is what happens after about 2 weeks in culture, so you print and have these cells grow for 2 weeks, and when you look and see what happens immediately after just sort of post-processing, sort of like, you know, seconds or minutes after the printing, and it turns out that these printed cells, at least with our process, have pores, and this can be visualized by adding a dye, in this case, propidium iodide, and you can see on the right that these cells are pretty much all red, so the dye actually entered the cells after they were printed, and this was done just printing and adding the dye, so basically immediately afterwards.

You can do this with different dyes, with different molecular weight dyes. So here we have dextrans that are red labeled and they have different sizes and molecular weights -- 3,000, 10,000, 40,000 -- and again they go into the cells pretty much after printing, but a dye of 70,000 molecular weight is excluded. Okay? So that tells us the size of the pores that we're forming as we print them.

And we can -- I'm sorry for this slide, it didn't come out so nice from the PC transition, I guess -- we can do these kind of experiments like immediately after printing, we can wait an hour, incubate cells, and do this experiment, so we can wait an hour and a half, or we can wait 2 hours; right? And every time we wait a little longer, we can see that the smaller dyes are excluded, so by the time we wait 2 hours, basically none of those dyes can enter the cells. So the pores that were created initially after 2 hours have been closed.

So it's important I think to understand these kind of processes when you want to design a sort of more commercial process -- right? -- and to use these printers, where if something happens to these cells and you've got to keep them, at least in this case, 2 hours before you do something else with them; right?

So we also measured apoptosis, which is basically cell death, after this, and we really have never seen an increase in apoptosis ratios compared to normal pipetted cells, so that's encouraging as well.

Then what else we do, we do microscope characterizations, for example. So here we print these channels and we line them with cells and we do light microscope, we do parfocal microscope and we can actually see how these cells grow and fill out these channels, for example. So, again, this is similar data.

We can look at unfinished printed vasculature or finished ones like in the bottom panels. And again we would have to sort of wait probably 14 days for this to happen. So this is post-printing. So you print and you wait, incubate, and then get a result after 2 weeks or so.

More in terms of post-printing, what we have to do, we have to certainly find out, is our printed structures -- how do they behave? Is this really skin in this case or tissue or is it just a bunch of cells; right? So we have to use animal models before we can actually test them on humans; right? So we put these -- we print a piece of skin, you can sort of see the printing pattern there on this blowup, and then we implant them onto animals, as shown here, and we look at a number of clinical indications like wound contraction, for example, and again we compare to controls.

And this time we have a printable skin, which is the blue one, but then we compare to commercial skin, a skin graft, that's available commercially, or doing nothing, which

is wounds contract by themselves in these mice even if you do nothing. But in this case, the contractions is less with our printed skin, which is a good thing, less contraction, because it means there is actually some skin that is remaining left onto the mouse, it's not its entire skin just contracting over the wound.

We can look at histology seeing what kind of inflammatory responses there are. When we do nothing, we basically just get a scar. Commercial grafts and printed grafts look fairly similar except for the printed grafts, you also see vasculature shown by these small arrows, I don't know if you can see that, but we can see actually with the dermis, it's much more like the more natural dermis compared to the commercial graft.

We also want to find out, do these cells integrate into the skin of the animal? And when we use animals, it's nice to do because we can use human cells and put them on the animal and we can find we can stain for human cells. Are there any human cells left? And it looks like the vascular cells, in Panel B there, are human, and so they integrated actually into these animals.

We can do the same thing with our fat implants, our nipple areola constructs. Again, we characterize them just by microscopy and then we obviously make them, implant them into the animals, explant them, and then looking at biocompatibility, for example, and compare this to maybe an injected material, which is sort of the same material, but injected or molded. We can mold these kind of materials as well, and we can print them as well, and it looks like we get a little bit less of an inflammatory response when we use printed vasculature and when we inject it, which was terrible, and when we mold it, it's still quite inflammatory.

We can look again as vascular infusion, which we've done here. So we see some vascular infusions. And if we're looking at the origin of the cells, first of all, here we see

vascular cells, so the green ones, and we're looking at blood vessels or blood vessel formation throughout the fat tissue that we implanted that we see when we print them, but we don't see that when it's molded. And then again we can look at the source of the cells, so we see human cells making up most of the vasculature in these tissues.

Again, so this was a sort of very quick rundown of the various kind of characterizations we do when we print out a 3D structure that is alive, and it's quite different, of course, from probably what most of you are doing here.

But just to summarize again, we use different tools that people have used to do this bioprinting, we just do mostly inkjet, but whatever technique is favored by various investigators, the kind of post-printing analyses that I've just shown I think would need to be done to make sure that the kind of tissues that are coming out of the bioprinters are actually going to be useful for treating humans.

Acknowledgements of the funding sources. And I'll be happy to answer questions I guess after the break.

DR. DI PRIMA: Yes. Given that we're running a little bit more than 15 minutes behind time, we will save any questions for these speakers for the breakout sessions.

(Applause.)

DR. DI PRIMA: And speaking of breakout sessions, we do have two breakout sessions this afternoon, both are going to be in Room 2, to address these topics. And this is a link for the docket. This is going to be sent out to everyone, but for the people online, this is going to be the best way for you to communicate your thoughts right now.

Clinical Perspectives on 3D Printing

DR. DI PRIMA: And with that, I would like to introduce Dr. Irada, and she is going

to -- and Vorvolakos, Kat Vorvolakos, and Irada, they are going to be moderating the clinical speaking -- or the clinical session. Thank you.

DR. ISAYEVA: Thank you, Matthew. Thank you all for coming. I would like to welcome you to the last presentation session of today, and it's going to be on Clinical Perspectives on 3D Printing. We're delighted to have today three distinguished clinical researchers who have been at the forefront of applying the novel tools of 3D printing to create medical products that will be used to meet specific and sometimes urgent clinical needs.

At this point, I would like to introduce Dr. James Yoo from Wake Forest Institute for Regenerative Medicine, who will talk about novel and versatile approaches, bioprinting approaches, to building 3D complex tissue constructs using 3D printing technology.

Dr. Yoo is a surgeon and a researcher who is currently Professor and Associate Director and Chief Scientific Officer at Wake Forest University Institute for Regenerative Medicine, and a Professor at the Department of Physiology, Pharmacology, and Biomedical Engineering. Dr. Yoo has been a leading scientist in bioprinting program at Wake Forest and has been instrumental in developing skin bioprinting and integrated organ printing systems for preclinical and clinical applications.

Welcome.

(Applause.)

DR. YOO: Thank you for the nice introduction. And I would like to thank the organizers for the opportunity to be here.

What I would like to share with you is -- my talk will be a very nice transition from Dr. Boland's talk in printing tissues and organs for clinical applications. And I would like to explain to you why we got into 3D bioprinting area, because over the past 25 years we have

been trying to build tissues for clinical applications, and among the many strategies, our strategy that we have shown to be working involves the use of cells and scaffolds. And we sometimes use cells alone, in that case, we are trying to get the cells to enhance cellular function in the body. We sometimes use scaffolds composed of biomaterials, and in this case, we are trying to bridge small tissue defects. And also these biomaterials do stimulate a body's ability to regenerate.

However, when the defect is large, obviously cells alone or biomaterials alone will not work. In these cases, we combine the use of cells in our scaffolds to build a tissue construct that gets implanted in vivo to eventually achieve a functional tissue structure.

So this is an approach that we have used for bladders. When you have a patient with bladder defect, we would take a small tissue biopsy from the bladder and we would isolate those bladder cells and grow them in large quantities outside the body and then those cells do get eventually placed back onto a bladder-shaped scaffold composed of biodegradable polymers, and then the cell-seeded scaffold gets eventually implanted back into the patients where the cells came from so that you don't have to deal with rejections.

So using this approach, using the cells, patients' cells, and scaffolds, we have developed several technologies which we eventually brought that to patients. However, there are many more applications we are currently developing, and as you see, the tissue engineering approach has had initial successes in building a certain number of tissues clinically. However, the challenges still exist in developing more complex tissue systems that require either systemic or coordinated function.

So what are these challenges? There are a million and five different challenges that we face, but one main challenge that I would like to discuss today is the engineering

challenge. If we are trying to build a tissue in our body, we would need to replicate its microstructures, and body's tissue is very complicated and complex. So such as our vascular network that we have in our body, they are very complex, and it is impossible to build and fabricate a tissue scaffolding system that would mimic the microarchitecture, as you see here, outside.

So scientists have looked into various different ways to achieve that, and one approach is to actually take a donor organ and remove all the cellular components from a donor tissue or organ and use that as a scaffold. In that case, the organ without cells would retain all the ultrastructure structural architecture that we have in our body. That's one approach.

And the other approach is actually bioprinting technology. And we were looking at a way to achieve a better tissue, and so over 10 years ago we looked into bioprinting technology as a potential means to build a great -- good tissue, and bioprinting has many advantages as that it can deliver multiple cell types, cell biomaterials, and other macromolecules that would assist in regeneration.

So this is the initial prototype that we have used. And we actually got into this area because of Dr. Boland's postdoc came to our lab, and we initially used an inkjet printer, modified an inkjet printer, where we have put in a Z axis so that when you print cells over and over again and as we print each layer, the elevator platform, which is a Z axis, would depress one cell layer deep. And using that, we were able to build and print different types of tissue structures.

But what's more interesting is that we were able to demonstrate that we can actually print multiple cell types within a confined small construct system, as you see here. In

this case, we have printed muscle cells, stem cells, and vascular cells, all in a pie configuration, and when you implant it in vivo, these constructs would form tissue with those specific cell characteristics.

So this is one of the areas that we have worked on. And soon after that we have had an opportunity to work for the DOD to build a bioprinter that can deliver skin cells to repair. And back then, soldiers deployed in Afghanistan and Iraq had many burn injuries, and these injuries are very extensive, and we wanted to come up with a delivery system that would deliver skin cells and cover the burn wound immediately. So our proposed solution for that is to build a tissue that can deliver right directly onto the skin.

So this is a schematic of the printer. And what's unique about this printer is that it has a built-in scanner system that could identify the extent of wound, including the depth, and from that, we can deliver different cell types in layers to repair the wound. And this is the prototype that we have built and we have tested in a preclinical model, in a pig model, where we create a 10-by-10 centimeter full thickness wound and have tested different types of therapies. And what's more interesting is that when you use cells from each autologous source, it would heal better with minimal contracture, as you see here.

So encouraged by these results, we then built a next prototype which could potentially be used clinically, and this is the actual printer that we have built. And we have used all of the medical grade materials for this printer.

So to validate this, we went back to the pig model, created 10-by-10 centimeter full thickness wounds, and then delivered these cells onto the wound to repair the wounds. So the printing process with the skin printer is that we created a wound defect and then the wound is scanned, and then as a result of scanning, we were able to get a digital image of the

defect, and from that digital image, it was processed to figure out the nozzle path and that eventually led to the printer to execute and deliver different cell types in layers, and this is the treated wounds.

So from that experiment we were able to show reepithelialization of the wound defect within 2 weeks whereas other test groups failed to do that in that amount of time.

Now, either skin printer or inkjet printer, it is able to deliver different cell types and gels and macromolecules or drugs, however, if we wanted to build tissue that can be actually implanted by a surgeon, it has a lot of limitations because when you deliver gel, no matter how well you crosslink it, it is unable to use it for surgical repair because it is very difficult to suture it.

So we have developed a printer that would allow us to generate a 3D freeform-shaped construct but at the same time can deliver not only gel biomaterials, but polymeric materials, which would provide the durability. And this has a resolution of anything greater than 50 micron nozzle for cell printing. Now, considering the size of each cell is about 10 microns and then we're able to print anything greater than 2 microns using biomaterials.

So this is like any other printers, it has nozzles that deliver specific materials and this just shows how it works.

Okay. But more importantly, when you deliver cells, obviously the cells have to be placed in the right location within a tissue construct. So we have labeled these cells with different colors, green and red, and delivered and created a tissue construct, and I have demonstrated that the cells can be distributed uniformly throughout the 3-dimensional scaffolds, but more importantly, when you deliver cells, you want the cells to be viable. Those cells delivered through a nozzle is able to not only survive, but they are able to proliferate

within 3-dimensional structures, as you see here.

So using this, we are able to build and print those microstructures like liver, bladder tissue, heart, testes, and kidney structures in very fine detail. Of course, they are not identical to tissues that you find, but they are very similar and they do mimic. And as you print these, you end up with larger tissue structures that can be implanted in vivo.

So these are some of the examples of the utility of the printer. So when you have a boney defect, you would take a medical image like CT or MR, and from that image you are able to generate digital images that can eventually be used to print a tissue structure or tissue defect which can be repaired surgically. This is the printed bone with bone cells. And this is the printed muscle construct where you can actually use it to surgically repair muscle defects. And when you look at closely all the screen colors are the cells that are labeled with fluorescent proteins, and because you are able to place them in a precise manner, these individual cells fuse to form fibers in a certain orientation, and when you implant this in vivo, these fibers further mature into thicker fibers in unidirectional orientation. But what's more important is in order for muscle to function, they have to be not only vascularized but innervated, and we were able to show that these muscle tissue is functional with identification of neuromuscular junctures, which means that it gets integrated with the host nerve and connected so that the muscle tissue would function normally.

This is a printed ear. The ear is a very complex structure, and you can use the other ear if you are missing an ear as a template and use it to print a ear structure, as you see here. And this is a ear structure that was printed with polymeric material, gel material, and cartilage cells, and when you culture them, mature them, in vitro, you do see cartilage tissue characteristics, and when you implant that in vivo, you do see a fully mature cartilage tissue in

vivo.

So this is printing of the ear. So it's delivering polymers as well as muscles.

Now, this is an example of a composite tissue system like muscle-tendon junction, which has a very nice gradient where we would print the muscular portion with muscle cells and the tendon portion with the fibroblasts or tenocytes and we are able to show a nice interface between two different cell types, and if you look at closely, you are able to see muscle cells, which is labeled in red, and this green is the collagen that was generated by fibroblasts, and these blue stained are individual cells that are placed within that same construct. So we are very excited about these developments.

And so where are we going with this technology? We do envision when a patient comes into a clinic with the abnormalities they have, they would take CT or MRI to get the medical data, and from that medical data, we can reverse engineer them to come up with a digital image which can be used for the printer to execute and deliver and print an implantable organ or tissue systems that can be delivered to the operating room so that the surgeon can take that tissue construct and use it to repair any tissue abnormalities. That's where we would like to go.

So in conclusion, bioprinting technology is a fascinating tool to generate 3-dimensional tissue construct with precision, and cells are delivered with the materials and they can be placed where you want them to be. And we think that this tool can be used to build complex tissues that require a body's coordination. So we would really like to use printer to print organs that can be used for tissue repairs. However, there are so many challenges, not only technological or scientific challenges, but we do have to figure out the regulatory pathway, and if we wanted to distribute it widely very quickly, we do need to have a sound

commercialization strategy so that those can be distributed.

Lastly, I would like to acknowledge our institute members. We have over 300 individuals who are concentrating on developing new tissues for clinical applications, and we currently are developing over 30 different tissues and organ types for clinical applications.

Lastly, I would like to thank our sponsors, who share the same vision as we do.

Thank you.

(Applause.)

DR. VORVOLAKOS: Unfortunately, we don't have time for questions. If you would like to speak with Dr. Yoo, please approach him individually.

So our next innovator, or per Bryan's admonition, our next free-thinking experimentalist, is Dr. Laura Olivieri. She is a pediatric cardiologist who focuses on imaging techniques. She is currently at the Sheikh Zayed Institute. She will speak on the research she and her team, which includes Dr. Axel Krieger -- hello, Axel -- to develop high-fidelity 3D printed models of hearts with congenital defects.

DR. OLIVIERI: Thank you for that kind introduction.

So good afternoon, everyone. I am a pediatric cardiologist. I'm a clinician. My talk is going to be along slightly different lines than the other talks that we've heard about in the clinical session. What I would like to do here very briefly is review some literature in 3D cardiac printing, describe the 3D printing workflow that we use at Children's, and then discuss clinical applications, as requested.

So I'm sure most of us are aware, within medicine anyway, about these literature reports of combining 3D printing and structural heart disease that have appeared in the literature basically since 2006, and in technical journals and in more prominent medical journals

since 2007/2008. Certainly the lay press has picked up on these kind of academic achievements and has publicized them widely. In addition, there are government directives supporting this type of technology as well.

So I would like to discuss kind of the scope of the clinical problem as we see it from our work, which is different than the other clinical problems presented today.

So congenital heart defects are the most common human birth defects. If something is going to go wrong in organogenesis, chances are it's going to be the heart. They affect between 1 and 2 percent of the population depending on how various malformations are characterized, either as defects or normal variants.

There is a wide variety of defects. There are dozens to hundreds of ways that the heart can form improperly, and within each of those defects, there is a wide range of severity and a wide range of clinical presentation.

Clinical decisions for patient care are made largely based on the appearance of the heart on imaging. In this way, the diseases that we see, congenital heart diseases that we see, can really be managed, certainly not solely but largely on how the heart appears when we look at it with whatever imaging technology we use.

And the care of patients with more complex congenital heart defects requires a lot of things. It requires really high-resolution, high-fidelity imaging, and it's ideal if it's 3D in nature. Frequently these patients require procedures, either surgeries or interventional procedures to repair a defect or to palliate a defect. And then after these procedures are performed, these patients require expert postoperative care.

So basically the scope of this clinical problem is that it's common, and it's a common problem comprised of many heterogeneous groups where structural information is

absolutely critical to guiding the management of individualized specialized care. So in short, congenital heart disease and 3D printing are kind of a natural tandem -- natural marriage, if you will.

So let's talk about rapid cardiac prototyping now currently in 2014. As we all know, 3D printers are more accurate and they're more affordable than ever. 3D segmentation software -- so this is the software of which there are many options that allows people to basically take a medical image and translate it into a 3D digital model -- are fairly user friendly and they allow for complex segmentation shapes. And then kind of more my area is the 3D cardiac imaging we use and push the limits of ultrasound CT and MRI every day to create these really precise and really beautiful images of heart defects to inform the segmentation process.

This is just an example of a -- this is actually a 3D -- it's a contrast-enhanced CT of a specific type of cardiac defect. You can think of this medical image, this cardiac CT is a block of data, a volume of imaging data, and these three images that you see are the data sliced in the sagittal, coronal, and axial projections, and then one can pan in and out of the dataset in whatever projection is kind of optimal to look at the defect.

You'll notice the blood pool in this is bright. Cardiac CTs are typically performed with contrast agent, blood pool contrast agent.

This is an example of a cardiac MRI. It looks very similar to cardiac CT. Again a blood pool contrast agent is typically used, and the same thing, think of it as a volume of data that can be panned through in any way.

So I would like to just take a moment and say a little bit about the segmentation process. Segmentation is basically a process of selecting -- a 2D image is made of pixels, a 3D dataset is made of voxels, so segmentation is selection of voxels to be included in a 3D digital

model, if you will. So, again, the top panels and the bottom left panel represent the imaging data, the clinically acquired imaging data, and the bottom right panel represents kind of the 3D model that was built based on this by using the 3D imaging panel as a guide, and the pink in the upper right panel represents those voxels that were included using the image as kind of a roadmap.

And then this is kind of our main area of interest. This is a 3D echocardiogram. This is displaying a prosthetic valve in the aortic position, and this is kind of a cone. Rather than a block of data, this is a cone of imaging data acquired by ultrasound but in a similar fashion, it can be looked at through a sagittal, coronal, and axial display, and the segmentation process can take place in similar type of segmentation software. Ultrasound does not involve any IV contrast and typically doesn't require sedation either.

So just the overview of the process. In the upper left-hand corner, clinical images are obtained as clinically indicated. The right top panels indicate the segmentation that's performed based on the images. And then the 3D result or the result of the segmentation is sent to the printer and a heart model is printed.

So what are those models used for? Well, unlike many of the other speakers, these models don't really touch the patient, they don't come anywhere near the patient. What they're used to do is inform medical decision making.

So I have a couple of cases that illustrate how we use these models. I think something to keep in mind as we go through the cases are that the models are only as good as the imaging they're derived from, so when we think about this process of creating models to inform medical decision making, it is really important to think about the process of how the images were acquired as well as the segmentation process.

So we'll go through these cases I have.

So this is an adult actually who was born with a pretty significant heart defect, had a surgery as an infant and then had a known late complication of that surgery where there was a narrowing between two chambers of the heart that should have had freely flowing blood between the two. So in an attempt to kind of relieve this narrowing in the cardiac catheterization lab, the operator asked us to print out the heart, so a CTA was performed. We created a model, printed it, and you can see the kind of highly complex nature of the stenosis, as indicated by the arrows here on the printed model, really helped inform decision making, procedural planning, for this particular individual.

And you can see in Panel C here, actually a trial's relief of the stenosis was performed before the patient even showed up at the hospital, which helped the procedure go fairly smoothly. With the lights up, you're probably not going to be able to see this. This is actually a fluoroscopy image just showing perfect placement of the stent in this patient's heart. And these are just echo images that demonstrate relief of the stenosis. This is a pre-procedural image here and a post-procedural image here, and basically the stenosis was cured.

Another case, also an adult who suffered a -- unfortunately had a myocardial infarction that weakened the wall between the bottom two chambers of the heart, the ventricular septum, actually weakened it to the point where it developed an aneurysm and a hole at the end of the aneurysm causing severe congestive heart failure. It was going to be attempted to close this VSD again in the cardiac cath lab. And so imaging was obtained in preparation for this kind of unusual type of procedure. A segmentation was created derived from the imaging, and the bottom right panel here represents the digital form of the 3D model. Arrows are indicating the area of aneurysm with the defect, the hole, at the end of the

aneurysm.

This is just the printed model. Again an arrow indicates the area of aneurysm. That should be a straight line instead of a pouch, and there is a defect at the end of there. So the patient was brought to the lab. This angiogram demonstrates the hole, blood flowing between the two chambers of the heart that should not be in communication. And the angiogram on the right demonstrates successful placement of a closure device.

And then a third case is a child who was born with a pretty severe congenital heart defect, had a surgery, and unfortunately had maybe a midterm -- a known complication of the surgery that required operative revision of their surgical procedure. So in this case, this printed model was derived from cardiac MR data which demonstrates, really quite beautifully I think, right where the arrow is pointing where there is a blood vessel of a certain caliber, and the caliber greatly diminishes at the point of that arrow. So this was again, in conjunction with the images that are standardly obtained and used to prepare for surgery, this was also used in preparation for his procedure, which went well.

And then this is an unusual case that we did at Children's. It was a large group effort, which was a separation surgery for conjoined twins who shared a liver, a portion of the chest, a portion of the abdomen. Surgical feedback indicated that these, both digital and printed models, were really helpful in informing preoperative care as well as planning of the operative procedure to successfully separate the twins.

And I just want to say a word on education, although certainly not super pertinent to the FDA. These models clearly have enormous educational impact, which I think is also important, and the education of clinicians does indirectly affect patient care. At our institution, we are also looking at patient-specific education, so education of care teams who

are about to go in and take care of a patient with a specific type of defect as well as lesion-specific education for our doctors in training, et cetera.

So I hope I have provided you a little bit of a different perspective on 3D printing today. I would like to acknowledge the fantastic group of people that I get to work with, surgeons, cardiologists, and engineers.

Thank you.

(Applause.)

DR. VORVOLAKOS: Thank you, Dr. Olivieri. I should also mention that the last portion which you said, is not super pertinent to the FDA, it actually is because a lot of adverse events, we find some -- I shouldn't say a lot or some -- there is a certain number of adverse events that are due to physician error and sometimes it happens because instructions for use are not clear. So physician education on how to use devices, whether they contact the patient or not, is very critical. Thank you.

Our next speaker is Dr. Peter Liacouras. He is the Director of Services for the 3D Medical Applications Center at Walter Reed National Military Medical Center. He has applied additive manufacturing techniques to medical applications and implant designs. He routinely designs and creates custom implants, surgical guides, and prosthetic attachments for the Department of Defense. He will speak on the clinical considerations for 3D printing and implantable device.

Thank you, Dr. Liacouras.

DR. LIACOURAS: Okay. So I am from Walter Reed 3D Medical Applications Center. We're a relatively small service under the Department of Radiology, which works great for us because everything starts with the scans. We only have six people in our department: a

chief, two CT technicians that now work on segmentation, a metallurgist, and myself, I'm a biomedical engineer, and then we have one administrative staff.

This is just the disclaimer I'm obligated to show.

(Laughter.)

DR. LIACOURAS: So this is why we're all here. We're comparing additive manufacturing to the subtractive manufacturing: different techniques, different ways things are built, different pros and cons to each manufacturing technique.

Like I said, everything starts with scans, and that's either a CT, an MRI, or a cone beam CT. Cone beam is relative new, but they're not going away. We see more and more of these. And when you go to segmented cone beam, it's slightly more difficult.

There are other methods of scanning, too. Laser scanning, white light scanning, contact scanning, and 3-dimensional photogrammetry. You saw in some previous presentations the photogrammetry laid over the CT scan, which is something we can look at, too, but I won't be discussing that. But it's here, and we don't really use it for the implant design, but you can use it to simulate surgical outcomes.

So like I said, primarily here we're dealing with CT. And we like to get the medical grade CTs. What we found works best is scans of 1.25 millimeter slices or thinner, and standard or soft tissue protocol with no gantry.

So there are numerous software packages available. You've seen some examples. I am not going to go into them all, but they convert the radiology images to the STL file. Eventually we might move to this additive manufacturing file, which allows you to put units, color, texture into the file, but right now we're still on the STL, and that's primarily what you feed the additive manufacturing machines.

So the steps in creating a model, because before you have to create the implant, you have to create the model, so you have to acquire the CT and then import your CT. You apply a threshold, you remove extraneous data, export the STL, you edit, manipulate, design, and then you build using commercially available software and equipment.

Here is just a workflow of that. You can see you import the DICOM, you threshold, eliminate unwanted artifacts, and you export your STL. A lot of this has been mentioned, so I'm moving relatively fast.

The software is more powerful than just that, too. You can do mirror imaging, you can add geometry, you can separate all the bones, do some morphology operations, overlay MRI with the STL. You can back-import your implant after it's been designed to make sure there is no overlap between your implant and your CT scan.

For our department, what happens is we bring in the CT scans. We have direct access to packs. Then the engineer or technician gets that CT scan and creates a 3D model. From there, you'll work on creating the implants. Where I am going to focus today is in the maxillofacial arena, the neurosurgery arena, and the dentistry arena. These are where we're focusing mainly right now. You've seen some presentation on orthopaedics. Loading-bearing implants for us is another complication that we're not ready to deal with yet, but we are doing a lot of research in that area.

So the purpose of these models: you enhance patient consent, you design custom pre-bent models, time reduction in surgery, and hopefully they are better fitting and easier for the surgeon to implant.

When deciding what technology to choose, sometimes it comes down to what you have available. But here are just some of the aspects you can pick from. You can look at

the speed, the material, the capabilities of the machine and the materials that run in the machine, the biocompatibility of that material, and then if you're going to do any investment casting or indirect manufacturing, you look at that, too, but a lot of institutions look at the overlying reasons or costs.

So when I was doing this presentation, I decided to break it out into different subjects here. So I have direct versus indirect manufacturing, temporary versus permanent implants, and load-bearing versus non-load-bearing implants. Like I said before, I am going to focus on non-load-bearing implants today, so I tried to give three example cases.

Here is an example case of a custom mandibular spacer. This was used to just maintain the mandibular space within the soft tissue because the mandible was diseased, had to be removed, half of it, on one side. And when they remove half, if they don't put something in that, the tissue will close and basically adhere to itself so they won't have the space to put in the final implant. This was a relatively fast turnaround project, too; they needed it within a couple days.

This was manufactured on a stereolithography machine out of a Class 6 material sterilized by ethylene oxide. You can see also in the bottom picture right there it was covered with foil before they put the PMMA. That's antibiotic-impregnated PMMA they used. And they created that mold of a half a mandible. They then finished that up and implanted it. You can see they took out the diseased mandible right there, finished it off with a hand piece, implanted it, and then in the radiograph down there you can see the PMMA right behind the drain tube right there.

So then after a few weeks or a month, they'll go back and put the final implant in, but they have to make sure this patient is clear of the infection.

My next example here is a custom dental mesh. This is a temporary implant with direct manufacturing. Here what we do is we'll create this dental mesh, and the purpose is to hold bone filler and growth factors in place to allow for bone regeneration. So once that bone regeneration occurs, they'll remove this and put an implant in. The reason that they need this is there is not enough bone there to put the dental implant in, so if they put one in, it won't be sturdy enough, it will probably loosen up, and over time have to come back out.

You can see some different design steps here. Originally I got this. This was from a cone beam you can see, so the model isn't as crisp as a medical grade CT. You have to spend a little more time segmenting those cone beams. But here my first instinct was to design it across that whole back section of that maxilla right there. Then you meet with the surgeon, they come in, they say, "No, we really don't need it that long," so we reduce it down to the section they need and where they are going to put the implant. Then you can discuss with the surgeon the hole size they might want, the fixation locations, if they want holes to pack the bone filler and growth factor. Once that's all decided, you'll send them a picture or they'll approve the design, and you will go ahead and manufacture this.

This was manufactured on Arcam A1 Titanium 64. You can see it's a relatively small implant. This one does not have fill holes, but you see the larger three holes are for 1-1/2 millimeter screws to fix that down. So they put the bone and the growth factors on that and then flipped it over and put it on the mandible in the patient. I have a picture of that here. And this will stay in for I believe 3 to 6 months until that bone regenerates. Once that bone regenerates there, they will remove this mesh and they'll place their dental implants.

Like I said, there are some new design changes, we go back and forth, but these are totally surgeon-specific. They pick where they want the fixation screws, where they want

the packing for the bone access. And you can see on the radiograph this particular patient had two placed.

So my last example here is custom cranial plates. This is where a lot of the press comes in, big press item here. But these are custom titanium plates made on an Arcam machine. The purpose is to close the cranial vault. This is kind of funny because we once had five neurosurgeons in a room. We asked, "What do you want out of the cranial implant?" They gave one answer, "Close the cranial vault." We were like, "Well, we have this machine. We can do mesh. We can do solid. We can do holes here, here." "Close the cranial vault," was the answer.

Here the way you do this is you basically start with your model again. If it's a side implant, you can use mirror imaging. Front implants are a little more complicated, you have to hand-sculpt those or maybe, if you're lucky, the patient had an existing CT scan prior to the injury, and you can use that, overlay that, or you ask for pre-injury pictures because you don't know if the person had a sloping forehead or a tall forehead, and you really want to give the patient back the forehead he had, give him that aesthetic look that he once had.

The injury was not this big. The injury was probably a lot smaller, but what happens is the brain swells and the pressure has to be relieved, so they go in and remove that larger section of bone.

I'm not the surgeon, so everything I have here is secondhand. I'm an engineer, just to clear that up.

(Laughter.)

DR. LIACOURAS: So once you do the mirroring, the cutting, or the designing, if it's a frontal implant, you can go ahead and create smooth transitions. There are numerous

softwares that will do this. This was done here in FreeForm Modeling Plus. So you create those smooth transitions. You are going to add your fixations, your clearance. Some surgeons request holes for temporalis suturing. That's the muscle that lies right over the cheekbone under that zygomatic arch. You'll get the surgeon approval and move on to print. Like I said, every surgeon is different. They'll request their fixations in different places. Some request their implant to go down under the zygomatic arch. If the implant has to go down, some want it cut short.

But here is an example of a titanium implant. You can add these fixations. And this is a cost savings to the institution. Each of these fixations save the institution several hundred dollars.

Another case for an example here is tumor cases. You can not only design an implant, but you can also design a cutting guide or a marking guide. Again, it's surgeon's preference. Some will put down this titanium marking guide, they'll come in, we'll discuss the case, they'll tell me, "I want a 1 centimeter border around the tumor." You can make this cutting guide to lay on that bone. Hopefully you can find a few landmarks that that cutting guide will lay on. The best landmarks are the sutures of the skull because they can see those during the operation. So they'll lay that down. They'll either mark that out or some cut directly with the titanium cutting guide on, remove that section, and then they can place their implant, which is sized directly exactly to the size of the cutting guide. So in some previous cases this was done in a two-part procedure, they would remove that, then the implant would be designed, and place it, but now we can do it all at once.

So you see here I also brought back the PMMA here because this was how we still manufacture them in PMMA, but we've gone mostly towards titanium. The PMMA is an

indirect manufacturing technique, but it still uses additive manufacturing. You're making the prototype, and then from that prototype, they mold that, fill that mold with the PMMA, and create that implant that way. Again, this is surgical preference. Different surgeons request different materials.

So just in conclusion, we see that the printing is being manufactured. They are patient-specific. A lot of times additional machining is required. And what I do want to hit upon here is implant variations can be made easily and manufactured easily.

We've had a few cases where the surgeons say, "Well, make the implant this way, and then if I don't like it, I'll cut it in the OR," and I kind of give the surgeon a weird look, like, "Really? You're going to cut a titanium implant in the OR? Why don't I just make you two implants and if the one doesn't work, you can implant the second one?" because you can print them both at the same time. That's one of the beauties of additive manufacturing, you can print them both and have them both ready for them.

So that's what I had for you today. I hope you enjoyed it. And any questions.

(Applause.)

DR. LIACOURAS: Did I get us back on time?

DR. ISAYEVA: Yes. Thank you very much for your interesting presentation.

Unfortunately, we do not have time for questions. We hope that we will have time during breakout sessions for questions and for in-depth discussions on the topics that were discussed today during the presentations.

And now we are joined for lunch and we are looking forward to see you back at 1:30.

Thank you.

Dr. Di Prima: So real quick comment as people are breaking for lunch. We're going to need to clear this room so the event staff can set up for the breakout sessions, so at 1:30, if you have a red lanyard, you are supposed to be in this room. If you have a blue lanyard, you are going to be in that room. And again we need to start promptly at 1:30 for the webcasting. So the food should be here if you preordered lunch. If not, you should still be able to buy some. And we'll see you all in 45 minutes.

Thank you.

(Whereupon, at 12:16 p.m., the opening presentations of the Food and Drug Administration (FDA) Public Workshop -- Additive Manufacturing of Medical Devices: An Interactive Discussion on Medical Considerations of 3D Printing was adjourned.)

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was recorded by me and thereafter reduced to typewriting under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

MICHAEL FARKAS

Notary Public in and for the

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My commission expires: 8/31/2019

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I, Debbie Arbogast, do hereby certify that this transcript was prepared from audio to the best of my ability.

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Date Debbie Arbogast

Transcriptionist