

# NDRI Research Brief

News from National Disease Research Interchange

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## HOT TOPICS

### CMS Ruling Encourages More Research Donations

A new ruling by the Centers for Medicare and Medicaid Services (CMS) now factors into the OPO certification process the degree to which OPO's facilitate and recover organs for research. Specifically, the new ruling, which was published in May, requires OPO's to report "the yield measure for both organs transplanted per donor and organs used for research per donor."

As justification for this change, the authors of the ruling stated, "like organs for transplantation, organs for research are a precious national resource. We believe OPO's should recover organs for research whenever possible to aid researchers looking for new therapies for debilitating and fatal diseases, many of them the same diseases that cause end-stage organ failure in patients waiting for transplants. Although recovering organs for research is not an OPO's primary mission,

*"This can only help the research cause."*

Tom Mone, CEO, OneLegacy OPO

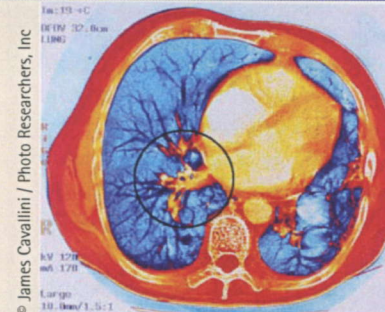
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## FEATURED RESEARCH

### Breathing New Life into Cystic Fibrosis Research

In 1989, the discovery of the gene that causes cystic fibrosis (CF) caused a flurry of excitement in families plagued by CF, a rare inherited disease that causes an excess buildup of mucus in the lungs and other organs. Now that scientists had uncovered the cause of the disease, surely a cure for it would be around the corner, many reasoned, encouraged by the optimism of the researchers. "When they announced the cloning of the gene we thought we'd all be out of business within a year," remembered Dr. David Waltz, the director of the Cystic Fibrosis Center at Children's Hospital Boston.

But seventeen years later, a cure still eludes researchers, because of complexi-



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ties in how the gene causes CF, as well as major roadblocks in the pathway to using gene therapy to treat the disorder. The discovery of the CF gene did lead to a better understanding of what goes awry with the disease. This gene encodes a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) that acts as a passageway in the cell membrane for the chloride component of salt. The correct functioning of this passageway is key to maintaining the thin layer of mucus that coats the inside of the lungs and helps guard it from

This colored CT scan of a patient's lungs (blue) shows cystic fibrosis. The heart (orange) is seen at upper right. CF causes excessive production of mucus in the airways of the lungs as evidenced by the thick orange branching in the lung at center left. The mucus clogs the airways causing them to expand, a condition called bronchiectasis.

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## DONATING TO THE CAUSE

## CF Patient Donates Tissues to Research

When Suzanne Pattee was diagnosed with cystic fibrosis (CF) as a baby in the 1960's, her doctor told her parents she had only a 50 percent chance of living to her fifth birthday. Forty-three years later, she's still very much alive, in large part due to the advances made in CF research and treatment during her lifetime.



Suzanne Pattee, vice president of regulatory and patient affairs for the Cystic Fibrosis Foundation, was recently awarded the Heroes of Hope award for serving as a role model for others with CF. She is pictured here with her parents Bill and Connie Pattee.

"My parents were always pretty aggressive about finding me experts in CF and they were very much interested in research. I began participating in clinical studies when I was only 14," Pattee recalls.

Today, Pattee is the vice president of patient and regulatory affairs for the Cystic Fibrosis Foundation, whose mission it is to promote research to find better treatments, if not a cure, for CF. But in addition to doing advocacy for CF research, Pattee has supported the research in a more personal way—she continues to participate in CF clinical trials, she donated the polyp tissue removed from her nose to researchers at Johns Hopkins University, and has stipulated in her will that her body be donated to research when she dies.

"I wanted to help the progress of research on CF," she said. "I figured that any small step forward can benefit people with CF. A lot of hope hinges on the research and that's a big part of what keeps us going."

Even though she has a relatively mild form

of the disorder, Pattee said that living with CF is no picnic. Like most CF patients she still spends a good part of her day taking oral and aerosol medicines and doing physical therapy to clear her lungs of mucus buildup. She has been lucky and experienced relatively few bouts of pneumonia, unlike many CF patients who are in and out of the hospital because of frequent lung infections. But Pattee does have the digestive complications of CF that led to diabetes 10 years ago.

Pattee noted that many CF patients do not

*"I wanted to donate my tissues so they would be used to further research, and not just sit on a shelf."*

*Suzanne Pattee,  
CF patient*

have the time and energy to join the CF Foundation's efforts to promote research because they are so busy taking care of their own health. But little time is needed to participate in one of the many clinical trials for new drugs on the horizon, any one of which could represent a real breakthrough in CF care, she stressed.

And, Pattee added, donating tissue requires little to no effort from CF patients. "It seems like the easiest thing I can do to help CF research along. I wanted to donate my tissues so they would be used to further research, and not just sit on a shelf," she said.

► *Breathing New Life into Cystic Fibrosis continued from page 1*

infections. But there are more than 1,500 known mutations of the CF gene that disrupt the production or functioning of CFTR. So a treatment that overcomes one defect in the CF gene may not work on a patient whose CF is caused by a different flaw in the gene.

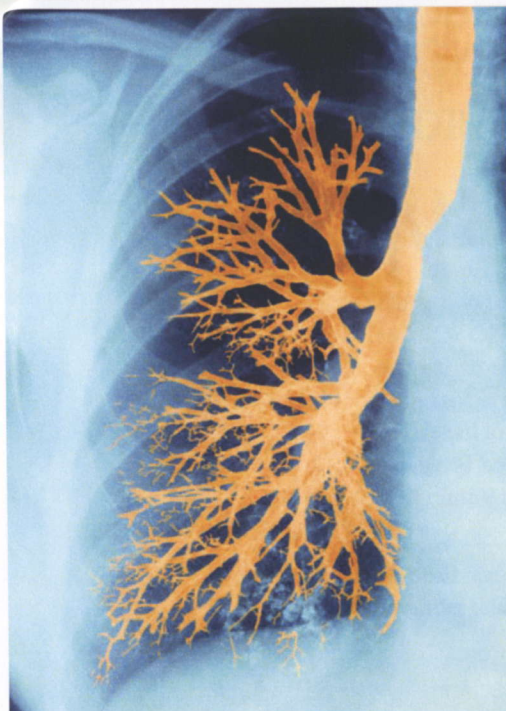
Using gene therapy to get a correct version of the CF gene into the lung cells of CF patients also has been more trying than expected. At first, researchers tried to deliver correct copies of the gene to lung cells of CF patients by putting them into the shells of a type of cold virus, which were inhaled into the lungs. But these "repair" viruses were quickly detected and destroyed by the immune systems of the patients on which they were tested. The strength of the immune response was also worrisome because of the potential risks it posed to patients.

Scientists have since developed other ways to deliver the correct CF gene into lung cells, including via microscopic fat globules that do not trigger an immune attack, or on the backs of synthetic "nanoparticles" so small they can easily slip into the and deliver the gene to their genetic machinery cells without alerting the immune system.

Usually the effectiveness of a new treatment is shown in animals before it is tested in people. But there is not a good animal model of CF on which to test new treatments. Researchers can also use established CF cell lines to test new

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This image of a normal human lung highlights the structure of the bronchioles and the alveoli.

► *Breathing New Life into Cystic Fibrosis continued from page 2*

treatments, but the artificial conditions used to maintain these cell cultures fosters changes that don't appear in CF patients. The best research specimen is lung tissue removed from CF patients. "It's very helpful for researchers to have fresh samples that haven't been grown in a lab for months to years to look at some of the basic underlying defects in CF and to test new therapies," Dr. Waltz said.

NDRI supplies donated CF lung tissue to several

researchers working on new treatments including innovative gene therapies and promising drugs targeted to repair the faulty CFTR proteins in the lung cells or to boost their production of normal CFTR. NDRI-supported researchers also use donated CF lung tissue to better understand how defective CFTR proteins cause the symptoms of CF. For example, it is still a mystery as to how the faulty transport of chloride ions in and out of cells fosters the digestive problems they experience (See sidebar "Starved for a Cure"), or why CF patients are particularly susceptible to certain bacterial infections in their lungs, but not to others.

But fine-tuning the understanding of what goes wrong in CF patients and how

best to treat it is greatly hampered by the availability of CF lung tissue.

"We're to the point where our efforts in drug discovery as well as basic research are outstripping the available primary cystic fibrosis cells," said Dr. Chris Penland, Director of Research at the Cystic Fibrosis Foundation. "We must get the word out to patients, caregivers and transplant teams that we're in need of these organ donations to facilitate research and drug discovery."

To this end, the Cystic Fibrosis Foundation recently provided NDRI with a grant to boost efforts to acquire more CF lungs and bronchi for researchers. "We looked at the field of organ procurement and NDRI seemed to be the one that's at the forefront of acquiring organs for research purposes," said Dr. Penland.

The CF Foundation grant led to a collaboration between NDRI and the CF Center at Children's Hospital Boston whereby explanted CF lungs would be placed by NDRI with CF researchers. In the past, the Center had attempted to supply such tissue to researchers in their area who notified them of their need for CF lungs. But because CF lung transplants were infrequent, by the time the CF lungs were available, the researchers were no longer doing studies that required the donated organs. "It seemed a waste to throw the CF lung tissue away after a transplant when if we made those tissues available to the researchers who needed them, that would hopefully help the search for a CF cure," Dr. Waltz said.

"The patients we've approached in the past have been very eager to help in any way they can, so this is a great thing that NDRI is doing and that the Cystic Fibrosis Foundation is trying to expand," he said. (See sidebar "Donating to the Cause")

Healthy donated lung tissue is also in demand for CF researchers trying to assess how the lung cells of CF patients operate differently from those of normal individuals. Asthma, emphysema, and severe acute respiratory syndrome (SARS virus) researchers also need donated lung tissue to gain more insight into these diseases.

To assist CF and other lung researchers, NDRI accepts CF lungs removed at the time of transplant, as well as other lungs recovered within three hours post-mortem. NDRI staff, who can be reached 24 hours a day at 800-222-6374, will coordinate and ensure payment for all the packaging and shipping logistics. Most CF researchers request donor genetic information (CF genotype) but are able to determine this themselves if it is not available at the time of donation.

*"Our efforts in drug discovery as well as basic research are outstripping the available primary cystic fibrosis cells.*

*We must get the word out that we're in need of these donations."*

*Dr. Chris Penland, Director of Research at the Cystic Fibrosis Foundation*



## NDRI Teleconference Provides CMS Rule Update

**N**DRI recently sponsored a teleconference for donor programs and procurement agencies around the nation to discuss changes in CMS rules for OPOs and research donations. More than 60 transplant professionals and representatives from OPOs participated in the call to learn more about the CMS rules and how NDRI plans to assist donor programs with compliance with the new rules.

The call featured Lee Ducat, NDRI Founder and President, Sally Strickler,

NDRI Vice President of Operations, Jeff Thomas, NDRI Director of Donor Services, John Lonsdale, Ph.D., NDRI Research Director and Paul Schwab, Executive Director of the Association of Organ Procurement Organizations (AOPO).

To learn more about this teleconference please contact Carissa Groff at 800-222-6374 ext 250.

Below are remarks made by AOPO Executive Director Paul Schwab during the teleconference

*Comments by Paul Schwab, AOPO Executive Director*



Paul Schwab, Executive Director, Association of Organ Procurement Organizations

I'd like to take an occasion to provide thanks to Lee Ducat for your continuing leadership and vision and most importantly sensitivity to the needs of all who benefit from research.

As you know that although AOPO doesn't provide individual company endorsements if you will, I certainly want to highlight our excellent relationship with NDRI which goes back many years and welcome their support and initiatives such as this call.

The call is timely given the new CMS outcome measures. As all of you are aware in a final rule as part of a yield outcome measures in the rule, CMS included one focusing on the number of organs used for research per donor. Truly of all of the provisions in the final rule, this was one that is fair to label as the surprise, the one that may have come out of left field. Given the

history and given the preliminary final rule, it was indeed a surprise.

As OPOs all know this area is very well developed for some in the community and uncharted territory for many others. When we look at the data for example that get reported by OPOs

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► *CMS Ruling Encourages Donations*  
*continued from page 1*

the organs it places with researchers may help lead to treatments or cures that will reduce the transplant waiting list as surely as organs that are used for transplantation."

To comply with recertification requirements, OPO's must meet two of three yield measures, one of which is having an organ yield for research that is not significantly below the average national rate for this measure

(at or above one standard deviation below the mean) for the three years considered for each recertification cycle. CMS will count in this measure any whole organ that an OPO sends to an individual or organization for research purposes. The CMS will also base its awarding of additional service areas to OPO's on the OPO's organ yields for transplant and research purposes, among other factors.

*"We believe OPO's should recover organs for research whenever possible to aid researchers looking for new therapies for debilitating and fatal diseases, many of them the same diseases that cause end-stage organ failure in patients waiting for transplants."*

*Statement from CMS Ruling*

"Overall, I think the ruling will have a net positive effect on increasing the number of organs donated for research," said Paul Schwab, Executive Director of the Asso-

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# Mystery

## MICROSCOPY

### Win a \$25 Amazon.com Gift Certificate

**Congratulations to Lora Shell from Transplant Resource Center of Maryland**, the winner of last issue's Mystery Microscopy contest, who correctly identified the image as rods and cones of the retina.

Be the first to identify this image and win a \$25 gift certificate to Amazon.com. Simply send an email to Jeff Thomas at [jthomas@ndri-resource.org](mailto:jthomas@ndri-resource.org) with your answer. The first person to email Jeff with the correct answer will be the winner. Here's a hint: Aids in digestion. Good luck!

**RULES:** You may only win this contest one time. Winner must be a primary recipient of this newsletter or employed by an organization affiliated with NDRI as a donor agency, tissue or eye bank or other scientific or medical organization. Please no family members or friends. By participating, you agree to allow NDRI to publish your name in a future edition of NDRI Research Brief if you win.



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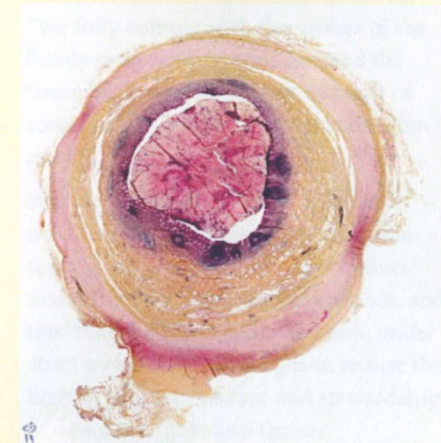
## CF Patients Starved for a Cure

*Research looks for answers to malnutrition*

**F**or most people who have some awareness of cystic fibrosis, it is first and foremost a disease that affects the lungs. However the same factors that cause mucus to build up in the lungs also affect multiple organ systems including the pancreas, intestine, liver and other digestive organs causing impaired digestion and painful stomach cramps and bloating.

Most CF patients are underweight and despite consuming high calorie and high fat meals, many suffer from malnutrition.

For many years, doctors attributed the malnutrition in CF patients to mucus



Cross-section of the appendix from a CF patient shows mucous obstruction.

Courtesy of Hospital Sainte Justine

### ► CMS Ruling Encourages More Research Donations continued from page 4

ciation of Organ Procurement Organizations. "Some OPOs may also look at this new provision as an opportunity to boost their overall ratings, particularly if they aren't doing so well in one of the other yield outcome measures."

To assist OPOs with the new CMS requirements, NDRI is providing OPO partners with monthly reports of the total number of organs offered and accepted for research. Additionally, NDRI plans to introduce new programs enabling OPO's to increase acceptance rates through dissection and preservation.

"A lot of our peers are going to have to start thinking about our role in research

in addition to the transplant piece and about trying to get research consent more often," added Tom Mone, Chief Executive Officer of OneLegacy in Los Angeles. "This can only help the research cause."

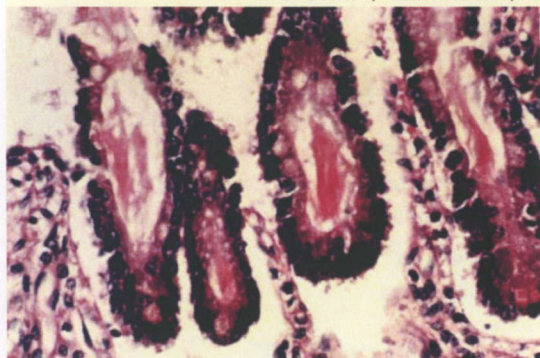
In a recent teleconference with OPO representatives around the country, NDRI discussed the CMS requirements and changes in NDRI's program policies for working with OPOs. For a transcript of the teleconference and to learn how NDRI can assist you with compliance with the new regulations, contact Jeff Thomas, Director of Donor Services, at 800-222-6374, ext. 239.

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► *CF Patients Starved for a Cure continued from page 4*

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White areas of a section of the ileum of a cystic fibrosis patient show the presence of thick mucous which impairs digestion.

*NDRI-supported researchers have found that some of the genes responsible for processing digestive fat are not as active in the intestinal tissue of CF patients.*

clogging the pancreatic ducts that convey digestive enzymes to break down fats in the small intestine. So doctors gave CF patients supplemental pancreatic enzymes as a means of relieving the malnutrition they experienced. But

these supplements, although beneficial, have not been able to solve the problem, leading researchers more recently to study what goes wrong in the digestive tracts of CF patients.

The importance of this new line of study is underlined by the growing appreciation for how malnutrition experienced by CF patients adversely affects their ability to fight frequent lung infections. Such malnutrition is linked to decline in lung function, one study found. Malnutrition also has emerged as a more important issue now that CF patients live longer due to advances in treatments.

Although studies revealed the basic genetic flaw that underlies CF is a lack of a functioning protein that affects the passage of chloride ions out of cells, how this affects digestion in CF patients is a mystery. To tackle that mystery, researchers are comparing the molecular machinery that drives digestion in CF patients to that of people without this disorder. Preliminary findings of these studies on donated human tissue may reveal why CF patients

are prone to malnutrition as well as why they are prone to lung inflammation and diabetes. Half of all CF patients develop diabetes by age 30.

NDRI-supported researchers at Case Western University have found that some of the proteins responsible for processing digestive fat are not as active in the intestinal tissue of CF patients compared to that of normal individuals. One of those genes helps make a fat component that appears in below normal levels in people with CF. Studies suggest that this fat component plays a role in suppressing inflammation and may help explain why CF patients experience heightened lung inflammation, which promotes scarring and other changes that eventually destroy lung function.

Studies in mice also suggest that the same master switch for fat metabolism that is faulty in many patients with diabetes also does not work effectively in CF patients. Some new diabetes drugs target this master switch, so if the animal findings are duplicated in human studies, these diabetes drugs may also help CF patients.

To move this promising line of research further, investigators need donated digestive tissues from both CF patients and normal individuals. Tissue donated from biopsies and other surgical procedures is especially valuable. Contact NDRI's Donor Services staff to learn more about organ and tissue needs to support research into CF and other diseases impacting the digestive organs.

## Maximizing Research Donations

*Good Stewardship and Data Key to Success*

Fulfilling the wishes of research donors and their families begins with good stewardship of the gift. This begins the moment that donation for research is broached by families and procurement coordinators. The principles of good stewardship of organs and tissues donated for research is one of the guiding principles that most influences NDRI's consent, recovery and placement protocols.

"We take the responsibility of these donations very seriously and never forget about their origins," said Sally Strickler, Vice President of Operations at NDRI. "We fully comply with the wishes of the family or individual who donated the tissue because after all, this is a part of someone's loved one, not just some commodity."

Strickler added that NDRI is the only non-profit organization providing anatomical gifts for research that receives major funding from federal agencies, and therefore the only agency to come under strict government oversight to ensure the highest standard of care and stewardship of donated organs and tissues.

NDRI must report to the National Institutes of Health (NIH) every six months

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► *Maximizing Research Donations continued from page 6*

on how it uses grant money to procure and distribute specimens for research, as well as report the research results of all the researchers to which NDRI provides tissues. Renewal of the government funding depends, in part, on how many publications these researchers produce.

"No other organization that recovers organs and tissues for research has the kind

*"I've been working with NDRI for 12 years now, and I don't think there's anybody else in the industry that has the reputation that NDRI has for doing such a good job."*

*Susan Sullivan, Vice President,  
Upstate New York  
Transplant Services*

of oversight that we have from the federal government," Strickler pointed out.

NDRI also ensures the integrity of the research for which it allocates anatomical gifts. All researchers must be affiliated with a university or research institute and must sign a contract that prohibits them from sharing specimens with investigators not affiliated with NDRI or for educational purposes.

All requests for tissues are reviewed by NDRI's research staff and approved by NDRI's scientific advisory

committee, which is comprised of leading physicians, researchers and ethicists.

"Put simply, NDRI's process of vetting researchers and research projects is the most stringent in the nation. Our approach and policies also fill a regulatory gap created with the new CMS ruling, which does not provide for oversight as to how donated organs or tissues are used for research," said Strickler.

"It's extremely important that OPO's involved in research are confident and familiar with the quality or credentials of the research investigators," said Paul Schwab, Executive Director of the Association of Organ Procurement Organizations. "Protocols need to be followed and there's no guarantee that just because a researcher is from a university, that his or her research is going to be considered legitimate."

Part of ensuring a donated tissue or organ gets put to good research use is making sure it meets the specific criteria of researchers before NDRI places it. This match making requires as much clinical information as possible.

"More and more it's not just the tissue that the researcher wants, but the data that accompanies it," said John Lonsdale, Ph.D., Director of Research at NDRI. Cancer researchers, for example, need to know the donor's treatment history and what the outcome of that treatment was in order to put their donated tissues into the proper context. "Researchers are not just interested in, but often request information going back to the original diagnosis of the disease. Anything OPO's can do to facilitate our access to clinical data that they may have at the time of offer would make it more likely that the tissue will be used," Lonsdale said.

Recognizing the challenges sometimes presented by additional information needs, NDRI recently streamlined the research offer sheets its staff uses, and specified the minimal information needed

## Required Information of Donor Referrals for Organs and Tissues

### Minimal Information

- UNOS ID or Reference ID
- Medical/Social history
- Specific organ function tests
- Medication history
- Serology results
- Consent restrictions
- Age/sex/race
- Height/weight
- Cause of death
- Reason for non-transplant
- Estimated OR time or cross clamp time
- Culture results

### Additional information required for some researchers

- Biopsy results
- Visual examination
- Kidney pump parameters
- ECHO results if preformed
- Chest x-ray interpretations
- Cold and warm ischemic times

to accept an organ or tissue for research. (See box above.)

"People frequently want to donate anything that can be used to help another person," said Susan Sullivan, vice president of Eye and Tissue Services at Upstate New York Transplant Services. "So working as individual tissue banks we cannot do as good a job at maximizing the donation as we can with the help of a national organization such as NDRI, which registers more than 500 researchers. I've been working with NDRI for 12 years now, and I don't think there's anybody else in the industry that has the reputation that NDRI has for doing such a good job."



► *Comments by Paul Schwab continued from page 4*

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*Paul Schwab,  
Executive Director, Association  
of Organ Procurement*

to the OPTN, in 2005, 50 percent of all OPOs in the country reported less than 10 organs recovered for research and less than 10 organs recovered for transplant but sent for research. That's across the industry. When we talk about 10 organs we're talking about an average of two

a week and that's from half the OPOs. In fact, among the organs recovered for research that were reported, only three OPOs out of 58 registered more than 100 organs recovered for research for the whole year of 2005. In fact, for OPOs that reported on organs recovered for transplant but sent for research, the

highest number for any OPO for the year was 66 — basically one per week. So, we are talking about a lot of uncharted territory for quite a few OPOs.

From an industry standpoint, OPOs coming into this area now really want to avoid what I would label as the "Big Four." In brief, one is having wishes of donor families not honored. Second, having adverse effects on transplantation and recipient needs. Third, incurring unnecessary costs and waste. And, last, being involved with and having illegitimate research or research entities resulting in next morning

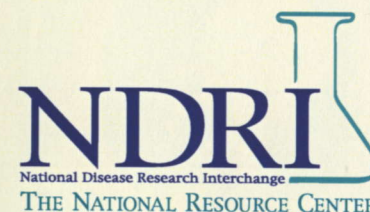
stories in the media that can undermine organ donation initiatives.

Within AOPO we have put together a research group headed up by Lori Brigham from WRTC with excellent representation from the industry, including those with a lot of experience with research and those with hardly any. The outcome measures that are involved with CMS begin with data being collected this coming January for the next three years. The CMS interpretive guidelines are being developed and we hope they'll be completed shortly. In the meantime, AOPO remains in contact with CMS regarding the rules implementation.

In sum, it's a new area for many. It's clearly an important area. We all want to perform well and do well, and having information from experts on this call is extremely helpful.

## Human Tissues and Organs for Tomorrow's Scientific Breakthroughs

NDRI is committed to providing the nation's top scientific laboratories with donated human cells, tissues and organs in order to better understand diseases and help develop new drugs and therapies for treatments and cures.



NDRI  
8 Penn Center, 8th Floor  
1628 JFK Boulevard  
Philadelphia, PA 19103

800-222-NDRI (6374)  
[www.NDRIresource.org](http://www.NDRIresource.org)

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