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."

> *"This can only help the research cause."*
>
> *Tom Mone, CEO, OneLegacy OPO*

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,

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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 complexities 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

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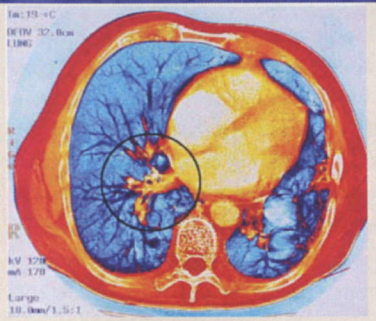

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This colored CT scan of a patient's lungs (blue) shows cystic fibrosis. The heart (orange) is seen at upper right. CF causes excessive production of mucus in the airways of the lungs as evidenced by the thick orange branching in the lung at center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

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 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.

> *"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*

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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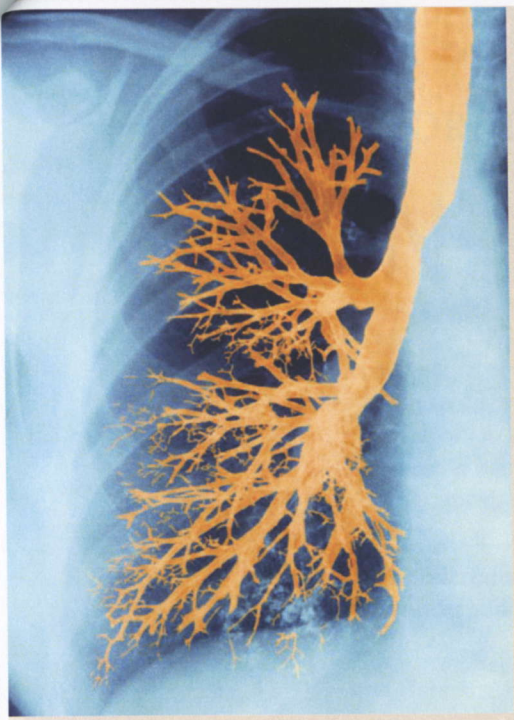

This image of a normal human lung highlights the structure of the bronchioles and the alveoli.

► *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.

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