Inside the Institute

DANA-FARBER CANCER INSTITUTE

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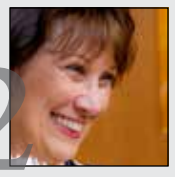

DFCI prepares for Magnet site visit in early June p.3

Wen chairs clinical trial endpoints committee p.4

Researchers led by Wayne Marasco (pictured) are involved in the scientific battle against the Middle East Respiratory Syndrome (MERS) virus. MERS was first reported in Saudi Arabia in 2012, where more than 400 cases and 115 deaths have been reported.

Antibody discovery may help combat deadly emerging disease

A recent surge in infections with the Middle East Respiratory Syndrome (MERS) virus – and the first case of MERS diagnosed in the United States – have added urgency to developing treatments and preventive measures. Scientists at Dana-Farber are part of the effort.

MERS was first reported in Saudi Arabia in 2012, where more than 400 cases and 115 deaths have been reported – a mortality rate of more than 30 percent. Infected travelers have carried the virus, called MERS-CoV, to more than a dozen other countries, raising concerns that the disease could spread globally. A Saudi health worker who was diagnosed with MERS April 28 in Indiana while on a visit is the first recorded U.S. case; he is expected to recover fully.

At Dana-Farber, researchers headed by Wayne Marasco, MD, PhD, of Dana-Farber's Department of Cancer Immunology and AIDS, are involved in the scientific battle against MERS. The Marasco team has identified natural human antibodies that can block the virus from infecting human cells and potentially could be developed into a treatment for infected health care workers and others. They reported in the *Proceedings*

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PMC team fuels research of rare pediatric cancer

Atypical teratoid rhabdoid tumor (AT/RT) is a rare and fast-growing tumor of the central nervous system that mostly affects young children. At Dana-Farber, a team of physician-scientists is making strides toward improving this devastating diagnosis – thanks largely to supporters who are aiding their progress by pedaling.

Team Lick Cancer, one of many teams that ride each August in the Pan-Mass Challenge (PMC), has raised funds for research and patient care at DFCI since its formation nine years ago. Most of those funds support the clinical efforts of pediatric oncologists Mark Kieran, MD, PhD, and Susan Chi, MD, as well as research into AT/RT here by Charles Roberts, MD, PhD, and his lab.

Roberts has studied the disease for 15 years, not only because of its dismal prognosis, but because the gene complex mutated in AT/RT is also mutated in 20 percent of adult cancers – including subtypes of lung, stomach, colon, ovarian, and brain cancers. As a result, discoveries made in AT/RT may have broad applicability to these other diseases.

"What we've discovered is that while these mutations cause cancers to grow, they also result in specific vulnerabilities that we can target," Roberts told Team Lick Cancer riders at a recent fundraising event. "We're

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Scientists find link between Down syndrome and leukemia

Although doctors have long known that people with Down syndrome have a heightened risk of developing acute lymphoblastic leukemia (ALL) during childhood, they haven't been able to explain why. Now, a team of Dana-Farber investigators has uncovered a connection between the two conditions.

In a study published by *Nature Genetics*, the researchers tracked the genetic chain of events that links a chromosomal abnormality in Down syndrome to the cellular havoc that occurs in ALL. The culprit turned out to be a gene present in too many copies. Their findings are relevant not only to people with Down syndrome, but also to many others who develop ALL.

"For 80 years, it hasn't been clear why children with Down syndrome face a sharply elevated risk of ALL," says Dana-Farber's Andrew Lane, MD, PhD, who led the study with David Weinstock, MD, of Dana-Farber and the Broad Institute of Harvard and MIT. "Advances in technology – which make it possible to study blood cells and leukemias that model Down syndrome in the laboratory – have enabled us to make that link."

Down syndrome is a genetic disorder caused by an extra copy or portion of a single chromosome, known as chromosome 21. Affected individuals have an increased risk for health problems including heart defects, respiratory and hearing difficulties, and thyroid conditions. Their risk for childhood ALL is

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Ligibel named new director of Zakim Center

Jennifer Ligibel is the new director of the Zakim Center for Integrative Therapies.

Already recognized as one of the country's leading oncology programs of its kind, the Zakim Center for Integrative Therapies at Dana-Farber will welcome new leadership as it expands the use of acupuncture, massage, nutrition and exercise, Reiki, and other complementary treatments to more DFCI patients and families.

Jennifer Ligibel, MD, is the new director of the Zakim Center. Ligibel, who has practiced in the Breast Oncology Program in the Susan F. Smith Center for Women's Cancers at Dana-Farber since 2001, has research interests in the effects of diet and exercise on quality of life and

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News of Note

Guinan appointed full professor at Harvard Medical School


Eva Guinan

Eva Guinan, MD, director of translational research in Radiation Oncology at Dana-Farber and former director of the Stem Cell Transplant Program at Dana-Farber/Boston Children's Cancer and Blood Disorders Center, was promoted to full professor of radiation oncology at Harvard Medical School.

Guinan earned her medical degree at Harvard Medical School before completing fellowships in hematology and oncology at Boston Children's Hospital and Dana-Farber. She joined Dana-Farber in 1985 and became director of translational research in 2011. Guinan is a recipient of the Harvard Medical School Excellence in Tutoring Award, Dana-Farber Stephen E. Sallan Leadership Award, and the Claire W. and Richard P. Morse Research Award for outstanding achievement in advancing cancer research.

Guinan, a native of Sweden and longtime Pan-Mass Challenge rider, lives in Newton with her family. SEW

Chong edits primary care manual


Curtis Chong

Along with a stethoscope, blood pressure cuff, and tongue depressor, a new book co-edited by clinical fellow **Curtis Chong, MD, PhD,** is becoming standard equipment for many primary care providers in the United States and abroad. *Pocket Primary Care*, published in March, is a concise point of reference for physicians, nurse practitioners, physician assistants, and other professionals working in outpatient settings. Its 187 chapters cover the major conditions and issues that primary care providers are likely to encounter in their practices.

One of the features that makes the book unique is that it is written entirely by medical trainees – hospital residents under the supervision of faculty members. The section on hematology/oncology was written in part by former fellows at Dana-Farber.

"During our residency, [co-editor] Meghan Kiefer [MD] and I noticed that while there are pocket guides for providers in inpatient settings, there weren't as many for the outpatient setting," says Chong, a member of the lab of Pasi Jänne, MD, PhD, director of the Lowe Center for Thoracic Oncology. "We found that because trainees are so focused on learning, they're able to write concisely and get directly to the information that providers need."

The book has been well-received, Chong relates. The first printing is on sale throughout the English-speaking world, and a Spanish-language version will be released this summer. ITI

Weinstock named to National Biodefense Science Board


David Weinstock

The U.S. Department of Health and Human Services (HHS) has appointed **David Weinstock, MD,** to serve on the National Biodefense Science Board (NBSB), an advisory group that provides recommendations on federal disaster preparedness.

Weinstock is a medical oncologist and laboratory investigator in the Dana-Farber/Brigham and Women's Cancer Center Division of Hematologic Neoplasia, as well as an assistant professor of medicine at Harvard Medical School. His research focuses on the relationship between DNA repair and the development of hematologic neoplasms.

"I'm excited to join the NBSB and bring a different perspective to preparedness planning by the Department of Health and Human Services," says Weinstock. "Through innovative research and support for cancer centers, there are tremendous resources that can be applied to better prepare the nation for chemical, radiological, and biological threats."

Weinstock is one of 13 voting members on the NBSB who will give guidance to the HHS secretary and assistant secretary on how to prevent, prepare for, and respond to public health emergencies. His three-year term on the board began April 30. MG

Correction: In the April 15 issue ("New microscope brings increased precision to study of cancer cells"), we inadvertently omitted Lisa Cameron's professional degree. Her correct title is Lisa Cameron, PhD, director of the Confocal and Light Microscopy Core Facility. We regret the error.

Wang receives grant for pediatric cancer research


Xiaofeng Wang

Xiaofeng Wang, PhD, a pediatric research fellow at Dana-Farber/Boston Children's Cancer and Blood Disorders Center, has been awarded a $50,000 grant from the Rally Foundation for Childhood Cancer Research for research on a lethal cancer of early childhood.

"I am honored to receive this grant from the Rally Foundation," says Wang, a member of the laboratory of Charles Roberts, MD, PhD. "This funding will help us better understand the nature of highly aggressive pediatric cancers, like malignant rhabdoid tumors."

The Roberts lab studies a group of proteins, the chromatin remodeling complex, that are mutated in nearly all rhabdoid tumors and have been implicated in 20 percent of all human cancers.

The foundation and its medical advisory board, consisting of leading childhood cancer researchers from across the nation, award grants through a competitive peer review process. All grants are made in honor or memory of a Rally Kid, a child who has fought or is currently fighting cancer. RS

Werger selected for quarterly DAISY Award


Annette Werger

Annette Werger, MSN, PNP, of Dana-Farber/Boston Children's Cancer and Blood Disorders Center, has been recognized with a DAISY Award, a quarterly honor given to an extraordinary member of the Nursing Department. Werger received the award during a surprise ceremony on April 29 in the Jimmy Fund Clinic.

Valerie Franks, a parent of a pediatric patient, nominated Werger for the award. In her nomination, Franks commends Werger's compassionate care and her connection with Franks' daughter, Nora.

"Annette is one of the few nurses who was able to get through to Nora," Franks wrote. "Even before Nora was a candidate for the outpatient clinic, Annette visited her hospital room every night and took the time to get to know her. She has made such a difference in our lives."

Dana-Farber is one of approximately 1,500 hospitals that participate in the DAISY Award program. The DAISY Foundation (Diseases Attacking the Immune System) established the award in memory of J. Patrick Barnes, whose parents created the foundation in his memory after experiencing firsthand the skills, care, and compassion of nurses. MG

Register for the Boston Marathon® Jimmy Fund Walk: Sunday, Sept. 21

Join your colleagues at the 2014 Boston Marathon® Jimmy Fund Walk presented by Hyundai on Sunday, Sept. 21. Register to walk* or volunteer at **www.JimmyFundWalk.org**.

Learn more. All past and present participants, and anyone interested in learning more, are invited to attend the next information session on Thursday, May 22, from 2-3 p.m. in the Yawkey Conference Center, room 306. Refreshments will be served.

For more information, contact Sarah Holroyd at **sarah_holroyd@dfci.harvard.edu** or **617-582-7427**.

*Use discount code "DFCI" when you register to walk for $10 off the registration fee.

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Story ideas are welcome and can be sent to Naomi Funkhouser at 450 Brookline Ave., OS301, Boston, MA 02215. You can also call 617-632-5560, fax to 617-632-5520, or email *Naomi_Funkhouser@dfci.harvard.edu*. Visit the Dana-Farber website at ***www.dana-farber.org*** or the intranet at ***www.dfcionline.org.***

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of the National Academy of Sciences that these "neutralizing" antibodies prevented a key part of the virus from attaching to protein receptors that allow the virus to infect human cells.

"This panel of neutralizing antibodies offers the possibility of developing human monoclonal antibody-based immunotherapy, especially for health care workers," note the authors, who are from Dana-Farber and the University of North Carolina at Chapel Hill.

People infected with MERS-CoV typically have cough, fever, and shortness of breath, and patients may develop pneumonia and kidney failure. Scientists recently confirmed that the virus is carried by camels, but its mode of transmission is unclear, and many people have been infected through contact with other MERS-infected individuals.

Reports of MERS in Greece, England, France, Italy, Malaysia, and other countries have raised concerns about potential global spread of the disease by infected people traveling by airplane before they develop symptoms. The virus is similar to the Severe Acute Respiratory Syndrome virus (SARS-CoV) that caused hundreds of deaths in China in 2002 and 2003. SARS was less lethal, with a death rate of about 10 percent.

Marasco and colleagues found the MERS antibodies using a "library" of some 27 billion human antibodies that they have created and maintain in a freezer at Dana-Farber; it is one of the largest such libraries in the world. Marasco is the scientific director of the Center for Human Antibody Therapies at Dana-Farber.

The body's immune system makes a huge variety of antibodies – proteins that recognize foreign viruses and bacteria. A neutralizing antibody is one that not only recognizes a specific virus but also prevents it from infecting host cells, so eventually the infection is "cleared" from the individual. The research team plucked seven MERS-specific neutralizing antibodies from the library after using samples of the virus to screen for them.

The researchers selected one of the antibodies, labeled 3B11, as a "lead" candidate for further research. Marasco said the antibody has been produced in sufficient quantities to begin testing in non-human primates and mice to determine if it protects against the virus. His research on the virus is funded in part by the Defense Advanced Research Projects Agency (DARPA) and the National Institutes of Health. He was contacted by DARPA soon after MERS was first reported in 2012 and asked to study the virus and suggest biological defenses against it.

Other Dana-Farber authors are Xian-Chun Tang, PhD; Yongjun Jiao, PhD; Jeremy Stanhope; Eric Peterson; Yuval Avnir; and Quan Zhu, PhD. RS

Dana-Farber prepares for Magnet site visit in June

Dana-Farber is preparing for a Magnet site visit from the American Nurses Credentialing Center. During the visit, which will take place June 2-4, three appraisers will validate information that DFCI's Nursing Department submitted in documentation last fall.

"The appraisers are very familiar with Dana-Farber and are looking forward to meeting our staff, patients, and families," says Colleen West, RN, MBA, director of Nursing Quality and Magnet Programs. "The site visit is a chance for staff to showcase the people and practices behind the stories they've already read about."

Initially designated in 2005 and again in 2009, Dana-Farber is one of fewer than 7 percent of health care organizations nationwide to earn Magnet – the highest accreditation for nursing and health care delivery excellence.

What questions might Magnet appraisers ask?

- Staff may be asked why they work at Dana-Farber and about their impressions of the care here.
- Patients may be asked about their experience at Dana-Farber, and specifically about their nursing care.

To learn more about Magnet, visit www.dana-farber.org/magnet. Join the Magnet team for an ice cream social on Wednesday, May 28, from 1-3 p.m. in Yawkey 306. ITI

Ligibel, *continued from page 1*

disease outcomes for individuals with cancer. She is committed to the field of mind-body medicine, and although she will continue to see adult patients in the Breast Oncology Center, strengthening the Zakim Center's mission and developing new strategies for the center will become her focus.

"For the past decade, my research has centered on physical activity and nutrition and their role both in cancer survivorship and in helping to ameliorate symptoms during cancer therapy," says Ligibel. "We have had great success over the years helping people change their lives after diagnosis, and we want to take that foundation and expand it more broadly across the Institute."

Ligibel succeeds David Rosenthal, MD, who helped establish the Zakim Center in 1999 as one of the first centers for integrative oncology and has served as its medical director ever since. Rosenthal will continue to see patients and provide integrative oncology consultations at the center.

As a wider body of research has shown the value of integrative therapies in oncology care, says Ligibel, the field has become more mainstream. A recent issue of the *Journal of Clinical Oncology* featured two articles on the value of yoga in cancer survival, and the American Society of Clinical Oncology launched an initiative focused on the relationship between obesity and cancer.

"Moving forward, we plan to become more integrated with the disease centers, so clinicians are more aware of the integrative therapies that are available for their patients," says Ligibel. "I want a practitioner to be able to say, 'I have a patient who has these side effects, and I've tried to give him medical therapies, but his quality of life is still diminished. The next step is the Zakim Center.'" SW

Why We Work Here

"The people here made a stressful, difficult time bearable. I can't say enough about everyone we have dealt with. Extremely well-run hospital. Thank you again."

– Heather and Dave K.

PMC, *continued from page 1*

getting closer and closer to what we hope is a definitive treatment, and ultimately a cure."

Study of the genetic vulnerabilities, which Roberts calls the "Achilles' heels" of AT/RT, have led to the first targeted treatment for the disease. In a clinical trial launched in 2013 at Dana-Farber and other sites around the world, children with AT/RT are receiving targeted therapies for the first time.

"There is a great partnership between Charlie's lab and our clinic, which has enabled us to take the lead on this trial," says Chi, director of the Pediatric Brain Tumor Clinical Trials Program at Dana-Farber. "We have almost 20 children enrolled from the United States, France, and the United Kingdom, and hope to learn much more about how to stop AT/RT and other cancers."

Roberts and Chi both say that they rely on the support of PMC riders. Because so few children in the United States are diagnosed with AT/RT each year, the disease receives far less government funding than more common cancers. It is cyclists like Team Lick Cancer captain Dave Christmas who raise the funds for research by the Roberts lab and clinical trials led by Chi and Kieran.

"It's great to see how we're making a difference," says Christmas, an 18-year PMC participant. "We're planning on our biggest team ever this year – maybe as many as 90 riders."

Will O'Shea is pictured with the gene dedicated by his family in his twin sister Charlotte's memory in Dana-Farber's Gene Display, located in the Robert J. Tomsich Family Gallery.

Among them will be Janet O'Shea, whose daughter, Charlotte, was treated for AT/RT at DFCI for several years before passing away at age 6 in 2010. Charlotte was a "Pedal Partner" for Team Lick Cancer, and is still on the minds of riders.

"This is my fourth PMC, and now my son, James, does the ride too," says O'Shea. "It's very emotional, of course, but the team is like a family. And while we're out there on the roads, the doctors from the hospital and the lab are pedaling right along with us." SW

A clearer path to approval for new brain tumor drugs

One of the most basic questions in designing a clinical trial of a new drug is, what will success look like? What criteria should investigators use to determine whether the medication is working?

Patrick Wen is chairing a committee of brain tumor experts tasked with defining clinical trial endpoints.

In brain tumor research, the answer hasn't always been clear, potentially discouraging pharmaceutical companies from investing in the development and testing of new drugs. In response, the National Brain Tumor Society has organized a steering committee of brain tumor experts to define clinical trial endpoints – standards for gauging the effectiveness of novel therapies. Its chair is Patrick Wen, MD, director of the Center for Neuro-Oncology at Dana-Farber/Brigham and Women's Cancer Center.

"Pharmaceutical firms face a number of challenges in developing better drugs for brain tumor patients," says Wen. "First is the complexity of the disease: There hasn't been as much improvement in treatment as in many other types of cancer in recent years. Second is the uncertainty that has surrounded some clinical endpoints, which can act as a disincentive to enter the field."

To illustrate the shortcomings of some traditional endpoints, Wen cites studies of Avastin, a drug that stops tumors from growing their own network of blood vessels. Because Avastin can cause blood vessels to be less leaky, two-dimensional MRI scans may seem to show tumor shrinkage when, in fact, the "improvement" is simply the result of less dye seeping out of blood vessels.

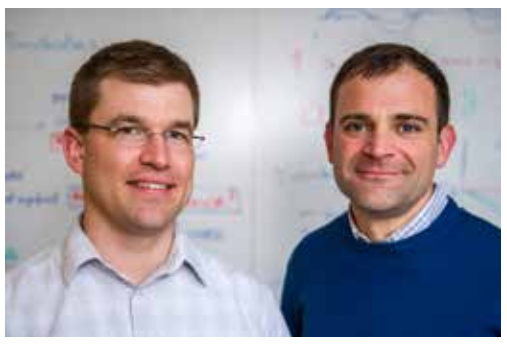
In January, the endpoints committee, in collaboration with the Food and Drug Administration, held a workshop in Washington to address such issues. The attendees, including researchers, government regulators, and representatives of the pharmaceutical industry and patient groups, agreed to develop better-defined imaging endpoints and to standardize brain-imaging techniques and measures across the country. A second workshop, slated for later this year, will focus on improving quality-of-life endpoints in clinical trials.

"The hope is that clearer and more consistent endpoints will generate more interest among pharmaceutical companies in working on brain tumor treatments and enable clinical trials to proceed more expeditiously," Wen observes. "If we have a drug that significantly shrinks tumors in early tests, the Food and Drug Administration is open to the idea that it could be eligible for accelerated approval before undergoing larger-scale, definitive testing. That would speed the development and delivery of new drugs to patients, which is our ultimate goal." RL

Link, *continued from page 1*

20 times that of the general population.

To trace the link between Down syndrome and ALL – specifically, the most common form of the disease known as B cell ALL, or B-ALL – Lane and his colleagues studied a strain of mice that carry an extra copy of 31 genes found on chromosome 21 in humans.



Andrew Lane (left) and David Weinstock published a study tracking the genetic chain of events that link Down syndrome and acute lymphoblastic leukemia.

"B-ALL occurs when the body produces too many immature B cells, which are a type of white blood cell that normally fights infections," Lane explained. "When we tested the mice's B cells in the laboratory, we found they were abnormal and grew uncontrollably – just as B cells from B-ALL patients do."

The researchers scanned the mice's B cells to learn their "molecular signature" – the pattern of gene activity that distinguished them from normal B cells in mice. The chief difference was that in the abnormal cells, a group of proteins called PRC2 was not functioning. Somehow, the loss of PRC2 was spurring the B cells to divide and proliferate before they were fully mature.

Using two sets of B-ALL cell samples – one from patients with Down syndrome, the other from patients without the syndrome – the researchers measured the activity of thousands of genes, looking for differences between the two sets. About 100 genes turned out to be much more active in the Down syndrome group, and all of them were under control of PRC2. When PRC2 is silenced – as in the B cells of Down syndrome patients – those 100 genes respond with a burst of activity, driving cell growth and division.

The question then was, what gene or group of genes was stifling PRC2 in Down syndrome patients' B cells? Using cells from the mice with an extra copy of 31 genes, the investigators systematically switched off each of those genes to see its effect on the cells. When they turned off the gene *HMGN1*, the cells stopped growing and died.

"We concluded that the extra copy of *HMGN1* is important for turning off PRC2, and that, in turn, increases the cell proliferation," Lane remarks. "This provides the long-sought after molecular link between Down syndrome and the development of B cell ALL."

Although there are currently no drugs that target *HMGN1*, the researchers suggest that drugs that switch on PRC2 could have an anti-leukemic effect in some people with Down syndrome. Work is underway to improve these drugs, known as histone demethylase inhibitors, so they can be tested in cell samples and animal models. RL

Save the date

Please join the Disabilities Awareness Committee for a presentation by Ross Lilley, executive director/founder of AccesSportAmerica.

Tuesday, May 13, noon to 1 p.m., Yawkey 307

Ross will speak about his organization, which is devoted to inspiring higher function and fitness for children and adults of all disabilities through high-challenge sports and training.

A common language for explaining research risks

For every new clinical research proposal involving human subjects, investigators must list potential risks of the treatment being studied in a consent document that is reviewed and approved by members of the Institutional Review Board (IRB). The risk language must be presented so that prospective research subjects understand the risks of the proposed research.

Until recently, investigators had no guidelines or "boilerplate" risk language to rely on, and had to more or less reinvent the wheel for each new protocol, says Michele Russell-Einhorn, JD, senior director of Dana-Farber's Office for Human Research Studies (OHRS).

"We have seven IRBs reviewing protocols for institutions of Dana-Farber/Harvard Cancer Center (DF/HCC)," she notes. "In one protocol, the risks would be described one way, in another, the language would be different. And the language has to be not only participant-friendly, but also meet the requirements of the IRB."

Michele Russell-Einhorn (left) and Emily Eldh are standardizing research risk descriptions in informed consent documents.

In a bid for consistency and accuracy, Russell-Einhorn and OHRS staff began standardizing research risk descriptions. Initially, the staff began keeping a spreadsheet of all the descriptions they saw in protocols submitted for approval that the IRB liked. Then they began crafting new risk language based on other reliable sources. Eventually, they joined forces with the MD Anderson Cancer Center and the National Comprehensive Cancer Network (NCCN) to create a single database.

The database currently contains more than 2,200 definitions that are regularly updated as relevant information becomes available. It is accessible to anyone in the DF/HCC research community. The database includes standard language for risks, such as allergic reactions, gastrointestinal issues, dermatological symptoms, infections, and many others.

"We are hoping it shortens the review time and the turnaround time from submission to approval by the IRB," says Emily Eldh, the office's assistant director for Clinical Research and manager of the project. "Investigators want us to turn these protocols around quickly."

Eldh gave a poster presentation on the database at the annual NCCN conference, where she reported that the database has more than 2,000 unique users representing 90 countries. She also presented at an annual meeting of the Association for Accreditation of Human Research Protection Programs.

Meanwhile, those involved with the database are pondering next steps. The plan, Eldh says, is to include standardized language on the risks of imaging scans and medical procedures.

"It's a big step forward," says Russell-Einhorn. "It's very exciting. We are hoping that pharmaceutical companies will use the database when they develop their own informed consent forms for research and then hopefully the IRB review process will be further streamlined." RS