THE CANCER LETTER

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Vol. 38 No. 20
May 18, 2012

Biomarkers

Experts Claim Errors in Breast Cancer Study, Demand Retraction of Practice-Changing Paper

By Paul Goldberg

A group of experts in pharmacogenomics has reopened a scientific question that affects therapy for millions of breast cancer patients worldwide: is it possible to measure how a breast cancer patient metabolizes the drug tamoxifen and tailor the therapy to improve clinical outcomes?

This question first surfaced in 2005, when doctors started to investigate the role of a mutation, called CYP2D6, in the metabolism of tamoxifen. By predicting response or resistance to this inexpensive, widely used drug, doctors were hoping to be able to decide whether a patient would do better on tamoxifen or another therapy—such as aromatase inhibitors.

The ability to make this decision intelligently is of paramount importance to an estimated 150,000 newly diagnosed estrogen receptor-positive breast cancer patients a year in the U.S. alone, many of whom take such drugs for as long as five years.

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The Science Behind the Controversy

Ratain: Data that Killed CYP2D6 Testing Contradict Fundamental Law of Nature

The Cancer Letter asked Mark Ratain, an expert in pharmacogenomics at the University of Chicago, to explain his rationale for challenging a study that suggests that testing for CYP2D6 has no value in clinical practice.

The interview was conducted by Editor and Publisher Paul Goldberg.

PG: *Why would someone hypothesize that there is a relationship between variation in the CYP2D6 gene and response to tamoxifen*

MR: Tamoxifen is a prodrug, and requires activation by the hepatic P450 system to its antiestrogenic metabolites. The most potent metabolite, endoxifen, is primarily formed by CYP2D6, which is highly polymorphic.

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In Brief

ECOG, ACRIN Form Single Cooperative Group

THE ECOG-ACRIN CANCER RESEARCH GROUP was officially founded May 17, after leaders of the **Eastern Cooperative Oncology Group** and the **American College of Radiology Imaging Network** separately approved the new group's constitution.

In March 2011, the two groups signed a letter of intent announcing their plans to merge.

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CYP2D6 Test Could Guide Care For Millions of Women Worldwide

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Alas, for the past year and a half, most oncologists believed that the answer to this question was a resounding "No."

That's because in December 2010, at the San Antonio Breast Cancer Symposium, two groups of researchers presented separate analyses of tissues obtained in two large randomized clinical trials.

Both groups reached the same conclusion: metabolism of tamoxifen has no bearing on the outcome of disease in post-menopausal women. The controversy was over—or so it seemed.

By the time the data from the two trials were published in the peer-reviewed journal JNCI, very few clinicians tested women with estrogen receptor-positive tumors for CYP2D6.

"After the presentations in San Antonio in 2010, testing fell out of favor," said Joanne Mortimer, director of the Women's Cancers Program and vice chair of medical oncology at City of Hope Comprehensive Cancer Center. "I know of no one who still tests CYP2D6."

Now, this state of affairs may change because a group of six highly regarded pharmacogenomics experts has submitted the data to a simple test, called the Hardy-Weinberg Equilibrium.

Data in the in the paper by Meredith Regan, et al.—one of the two papers based on data originally presented in San Antonio and published in the journal's March 21 issue—pointed to genotyping errors, the experts declared.

The Hardy-Weinberg Equilibrium is expressed in two formulas that look like something out of an Algebra I textbook. Yet, it describes a fundamental law of nature.

To illustrate the magnitude of error, the experts calculated the p values for the observations in the Regan paper that were consistent with the equilibrium. Probabilities fell into the range from 10^{-5} to 10^{-173}, depending on the gene variant. For the most important variant, the p value was 10^{-91}.

"Thus, these data could never occur by chance," said Mark Ratain, who is the Leon O. Jacobson Professor of Medicine, director of the University of Chicago Center for Personalized Therapeutics, and associate director for clinical sciences at the university's comprehensive cancer center.

In a letter to JNCI, Ratain and his colleagues demand that the Regan paper be retracted, a remarkably severe remedy. (A Q&A with Ratain appears on page 1 of this issue.)

The six experts don't claim to know what went wrong with the data. Rather, they say that there the errors in the genotyping of tumors in the Breast International Group 1-98 Trial makes the entire dataset uninterpretable.

BIG 1-98 was a phase III randomized, double-blind trial, in which investigators obtained tumor tissues and isolated DNA from 4,861 of the 8,010 postmenopausal women with HR-positive breast cancer who were randomized to receive tamoxifen and/or letrozole treatment.

The letter caused the journal to look into the matter.

Authors Stand By Their Work

One of the corresponding authors of the Regan paper, Brian Leyland-Jones, formerly of Emory University who now heads Edith Sanford Breast Cancer Research at Sanford Health of Sioux Falls, S.D. and Fargo, N.D., said that the group stands by its findings, pledging to provide an explanation of the massive equilibrium imbalance to the journal's editors.

"We stand firmly behind the quality of methodology of the BIG 1-98 study, the contribution of our results to the body of literature, and the value that the two investigations together bring to informing the care of patients with breast cancer," Leyland-Jones said in an email."

Leyland-Jones declined to discuss the controversy in greater detail with a reporter.

"The application of HWE to our study is

THE CANCER LETTER

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Editor & Publisher: Paul Goldberg
Copy Editor: Conor Hale

Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $405 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.

comprehensively addressed in our response to JNCI," he said.

"[JNCI Editor-in-Chief Barnett] Kramer and our team note that the usual process in these types of scientific debates is in the correspondence and responses in the peer reviewed journal in which the original publication appeared (as opposed to the press as the initial primary venue)."

James Rae, the author of the second JNCI paper on the subject, similarly declined to comment while the journal is conducting its review.

"This issue is being worked out in the peer review process and I do not think it is appropriate for me to discuss the letter or my response in the lay press until after they have been published," said Rae, assistant professor of internal medicine and pharmacology at the University of Michigan Medical School. "I agree completely that patient safety and well-being are of the highest priority and we are doing everything we can to resolve this issue promptly."

The Rae paper represents an analysis of tumor specimens that were obtained from a subset of postmenopausal patients with hormone receptor-positive early-stage (stages I, II, and IIIA) breast cancer, who were enrolled in the randomized double-blind Arimidex, Tamoxifen, Alone or in Combination clinical trial.

Meanwhile, breast cancer experts who have been briefed about the controversy say that they want the matter resolved—fast.

"I would probably resume CYP2D6 testing because it makes sense," said Mortimer, who is not involved in this controversy.

The data from the two large trials need to be reanalyzed, said George Sledge, the Ballve-Lantero Professor in the Division of Hematology/Oncology, co-leader of the Indiana University Simon Cancer Center's Breast Cancer Program and immediate past president of the American Society of Clinical Oncology.

"The lesson from this letter to the editor is that we simply are not sure we can trust the data on the large analyses," Sledge said. "The analysis probably needs to be redone on these large trials, and we need to see whether CYP2D6 is, in fact, important."

Altogether, 220,000 women are diagnosed with breast cancer every year in the U.S. alone, and 70 percent of them are estrogen receptor-positive, which makes them candidates for hormonal therapy.

"It would make a huge amount of difference in terms of whom we give tamoxifen to," said Sledge, who is also not involved in the controversy. "Since it's probably the most widely used hormonal therapy drug on the planet, if it was true in terms of making it a more targeted therapy.

"It's a story that we really would like some true closure to."

The letter to JNCI was written by a team that includes some of the

most prominent experts in pharmacogenomics. Including Ratain, they are:

• Yusuke Nakamura, professor of medicine and deputy director of the University of Chicago Center for Personalized Therapeutics, as well as one of the most prominent geneticists in the world (he has served as the director of the Riken Center for Genomic Medicine and as secretary-general in the Japanese government's Office of Medical Innovation).

• Nancy Cox, a statistical geneticist and chief of the University of Chicago Section of Genetic Medicine.

• Howard McLeod, the Fred Eshelman Distinguished Professor and director of the Institute for Pharmacogenomics and Individualized Therapy.

• Deanna Kroetz, director of the University of California, San Francisco, Pharmaceutical Sciences and Pharmacogenomics Graduate Program and professor in the department of Bioengineering and Therapeutic Sciences.

• David Flockhart, the Harry and Edith Gladstein Chair in Cancer Genomics, professor of medicine, medical genetics and pharmacology, and director of the Division of Clinical Pharmacology at the Indiana University School of Medicine.

CYP2D6 Testing: Clinical Implications

The prevalence of women classified as "poor metabolizers" is approximately 7-10 percent in Caucasians of northern European descent, 1.9–7.3 percent in African-Americans, and about 1 percent or less in Asian populations.

"The CYP2D6/tamoxifen issue is important for patients—many patients—as the issue of endocrine therapy affects about 70 percent of women diagnosed with breast cancer," said James Ingle, head of the Breast Cancer Research Program at the Mayo Clinic Cancer Center and the Foust Professor of Oncology at the Mayo Clinic College of Medicine.

Ingle's 2005 paper in the Journal of Clinical Oncology (with Matthew Goetz as first author) first reported the relationship between CYP2D6 and tamoxifen effectiveness.

"We are talking about over 150,000 women this year in the U.S. alone," said Ingle. "Each of these women is an individual for whom the choice of the

right therapy can be the difference between relapse of the cancer or not."

Ingle said he uses CYP2D6 in his practice at Mayo "after a thorough discussion with the patient, including the fact that controversy exists.

"Understanding that replication is essential, we have worked to accomplish this," Ingle said. "The strongest study, in my opinion, is that published in [The Journal of the American Medical Association] in 2009 in collaboration with a German group (Schroth et al.), involving over 1,300 patients that showed an association between CYP2D6 genotype and outcomes. Nothing has appeared since that time to change my position, including the Regan and Rae manuscripts, which have weaknesses that we pointed out in a letter to JCO in 2011.

"Thus, I totally disagree with the accompanying JNCI editorial [by Kathleen Pritchard, of Odette Cancer Centre at Toronto Sunnybrook Health Sciences Centre, and Catherine Kelly, of Mater Misericordiae University Hospital, Dublin,] because these two studies 'confirm' each other that 'this matter has likely been laid to rest.'

"The fact remains that the proper study has not been reported that replicates (or not) the veracity of the CYP2D6-tamoxifen efficacy relationship," Ingle said. "Because endocrine therapy alternatives exist, the best interest of the individual patient is served, in my view, by knowing their CYP2D6 genotype, while awaiting resolution of the matter."

Unlike Ingle, Sledge doesn't test for CYP2D6.

"We have always been incredibly conservative about suggesting that patients use this," he said. "We felt that we did need to wait for these large studies to come in. So we have never recommended this as part of routine testing for patients getting tamoxifen."

If analysis in the two trials is shown to be flawed, the question should be revisited, especially in the treatment of post-menopausal women, he said.

"The original analyses suggested that there might be populations of patients where you could remove the poor metabolizers and statistically might do better on tamoxifen than on aromatase inhibitors," Sledge said. "That's the challenging issue here."

Sledge said that tamoxifen would likely remain the drug of choice for patients who are pre-menopausal. "You have to give tamoxifen, because outside of ovariectomy it's the only thing we have," he said. Also, CYP2D6 isn't well studied in that population.

"If CYP2D6 really mattered and you had a patient who is post-menopausal, it's theoretically possible that CYP2D6 analysis would tell you that tamoxifen might be a better drug than an aromatase inhibitor," Sledge said.

"Similarly, since these patients have different toxicities, it might suggest that based on CYP2D6 analysis, if someone had a particular problem—a blood clot problem or rheumatoid arthritis problem—you might be better off using one drug or another based on the CYP2D6 analysis," Sledge said. "It might inform things from both from the toxicity and from the efficacy standpoint."

Some studies also suggest that women who are found to be poor metabolizers of tamoxifen should receive higher doses of the drug.

In an email, Leyland-Jones acknowledged that his paper influenced the standard of care.

It was one of two large independent studies with identical results.

"To quote from our paper, 'In order for our study to have obscured a true hazard ratio of 1.5 and observed a hazard ratio near 1.0, 75 percent of patients classified as EMs would have to have been misclassified," Leyland-Jones wrote.

"Clinicians can judge for themselves."

Methods: Google the Hardy-Weinberg Calculator

Not much work was required to evaluate the data in the Regan et al. paper.

Ratain eyeballed the data in Table 2, then searched for something called "The Hardy-Weinberg Equilibrium Calculator."

He likes the Tufts University version of the calculator best: http://www.tufts.edu/~mcourt01/Documents/Court%20lab%20-%20HW%20calculator.xls, because it allows you to use the equation in a nifty Excel file.

Then Ratain started plugging in the values from Table 2.

"This is trivial," he said. "If you know how to do genotyping, you know how to do this. The only hard part was converting the chi squared to a p-value, because the calculator simply gave zero."

Getting other experts in pharmacogenomics to co-write a letter to JNCI didn't require much work, either.

No such evaluation was possible for the Rae *et al.* paper, because it didn't include the actual genotype frequencies, Ratain said.

Now, as Ratain and colleagues eagerly await explanations of the deviations, they note that such information should have been published in the original paper.

If there was no compelling explanation of the

Table 2. *CYP2D6* genotyping and prevalence of CYP2D6 metabolism phenotype in BIG 1-98 trial participants*

CYP2D6 allele†	SNP	Assessable, No.	Polymorphic alleles, No. (%)	Genotype, %		
				Homozygous	Heterozygous	Wild-type
*CYP2D6*4*	1846G>A (rs2892097)	3828	1444 (18.9)	8.6	20.5	70.9
*CYP2D6*2*, **4*, **10*, **41*	4180G>C (rs1135840)	0	—	—	—	—
*CYP2D6*10*,**4*	100C>T (rs1065852)	0	—	—	—	—
*CYP2D6*41*	2988G>A (rs28371725)	3842	643 (8.4)	4.2	8.4	87.4
*CYP2D6*3*	2549delA (rs35742686)	3012	80 (1.3)	0.4	1.9	97.7
*CYP2D6*6*	1707delT (rs5030655)	2707	101 (1.9)	0.2	3.3	96.5
*CYP2D6*7*	2935A>C (rs5030867)	2767	0	0.0	0.0	100.0
*CYP2D6*17*	1023C>T (rs28371706)	0	—	—	—	—
	2850C>T (rs16947)	2285	1550 (33.9)	16.2	35.4	48.4
CYP2D6 metabolism phenotype‡, No. (%)						
Patients classified	—	4393 (100.0)	—	—	—	—
Poor metabolizer	—	365 (8.3)	—	—	—	—
Intermediate metabolizer	—	1294 (29.5)	—	—	—	—
Extensive metabolizer	—	2734 (62.2)	—	—	—	—

* BIG = Breast International Group; *CYP2D6* = Cytochrome P450 2D6; SNP = single-nucleotide polymorphism; — = not applicable.

† *CYP2D6*4* (1846G>A; rs2892097) and *CYP2D6*41* (2988G>A; rs28371725) were genotyped in all 4861 patient DNA samples; other alleles were genotyped in 3691 patient DNA samples. One hundred seventy-nine patient DNA samples failed *CYP2D6* genotyping. Genotyping was done using polymerase chain reaction–based methods.

‡ Patients were categorized into predicted metabolism phenotypes as follows: poor metabolizer (PM) phenotypes were homozygous or compound heterozygous for *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*6* or *CYP2D6*7* alleles (PM alleles); intermediate metabolizer (IM) phenotypes carried either homozygous *CYP2D6*41* alleles (IM alleles) or a *CYP2D6*41* allele in combination with a PM allele (ie, IM/IM or IM/PM alleles, respectively; n = 215 patients; 5%), or were heterozygous carriers of one PM or IM allele with an extensive metabolizer (EM) allele (heterozygous for EM allele or hetEM; n = 1079 patients; 24.5%); EM phenotypes were characterized by the absence of PM and IM alleles.

The critics' case at a glance: Ratain took the numbers from this table in the Regen, et al., paper and plugged them into the Hardy-Weinberg Equilibrium calculator.

deviation, the paper should have been rejected. If there was an explanation, it should have been included. As it stands, the Regan et al. paper has no references to the Hardy-Weinberg Equilibrium. The Rae et al. paper states that such an analysis had been performed.

The journals' peer review process needs to evolve to reflect the need for technical evaluation of data, whether such evaluation requires thousands of hours of hard work or a few minutes of geeky amusement.

"You need to consider the average reviewer of one of these papers: if it's someone like me, a clinical breast cancer doctor who is used to reviewing large phase III trial datasets, most of us are not competent to analyze these datasets from the genomic standpoint," Sledge said.

"That requires specialized expertise in bioinformatics that an average reviewer lacks. And you always wonder when you see these papers coming out: have they actually been reviewed by someone who has a deeper understanding of genetics and bioinformatics than an average reviewer has?

"I don't think it's a JNCI problem," Sledge said. "I think it's a much more global problem for major medical journals."

Ingle, too, questions the adequacy of peer review. "The fact that these weaknesses were not identified by the peer review process, including editorialists, raises concern regarding their understanding of basic pharmacogenomic principles," he said.

Ironically, JNCI is one of the more rigorously reviewed journals, and its editor-in-chief, Kramer, is a skeptic who is particularly insistent on thoughtful examination of biomarkers.

In an interview, Kramer, director of the NCI Division of Cancer Prevention, said his journal has sent Ratain's letter to the authors of the papers in question and is awaiting their responses. The journal will publish the letter and the response online as soon as possible.

"I can't speak to the substance of the arguments until I see all of the responses come in," he said.

Both the Rae and Regan articles are being discussed because they came to the same conclusion, Kramer said.

Kramer said he has gone over the original review of the two papers. "All the reviews were quite positive, and the authors addressed the requests for edits and changes, as always happens," he said. "The associate editor was very comfortable with their response, as was the in-house senior editor."

The peer reviewers were chosen by an associate

editor.

"I don't know whether the expertise of the reviewers will satisfy the criteria of the critics of the articles, but I am not sure whether this is going to be a critical issue now, because the issue has been raised and it will be either successfully rebutted or not," Kramer said. "It's always best not to go after the qualifications of people who did the review, but to go after the science."

The review process is imperfect, and "errors are made in either direction," Kramer readily acknowledges. "I don't think any editor is going to tell you that peer review is perfect, but I can tell you that in this case the usual process was followed."

Kramer said he is aware of the questions related from the Hardy-Weinberg Equilibrium.

"Mark Ratain has raised it as a direct issue, and it will be addressed," he said. "The authors have the opportunity to either admit error or address that particular criticism head-on, and it's my understanding that they intend to address it head-on.

The Science Behind the Controversy

Genotyping Errors in Study May Render Results Uninterpretable

(Continued from page 1)

MR: In fact, some individuals (about 7 percent of Americans) do not even have any active CYP2D6 protein. The first study demonstrating the importance of CYP2D6 polymorphisms in the context of tamoxifen was published by Goetz and colleagues (from the Mayo Clinic) in JCO in 2005, demonstrating that women who are genetically poor CYP2D6 metabolizers have a shorter disease-free survival with tamoxifen, suggesting that this subset of women has little or no benefit from the drug.

PG: *Why is there a controversy?*

MR: All important findings require replication. Although many investigators have replicated the seminal study of Goetz and colleagues, others have not. There have been a variety of designs utilized to evaluate this hypothesis, generally retrospectively.

Since concomitant medications, particularly many SSRI antidepressants, can inhibit CYP2D6, retrospective studies cannot provide a definitive answer, as medication histories may be lacking.

In addition, some studies have utilized DNA extracted from tumor, while others have utilized DNA extracted from blood or buccal smears.

PG: *Has the FDA ever considered this issue?*

MR: This issue was considered by the FDA and its Clinical Pharmacology Subcommittee in 2006, in the context of a possible label revision. There was a lack of consensus (by the subcommittee) at that time as to how the label might be revised, and no label revision was made.

PG: *Why did you and your colleagues decide to request retraction of the BIG 1-98 paper by Regan and colleagues?*

MR: This study, as well as the ATAC study (by Rae and colleagues), was presented at the San Antonio Breast Cancer Symposium in December 2010.

Neither study could replicate earlier studies showing a relationship between CYP2D6 genotype and tamoxifen's efficacy. Given the size of these studies and the visibility of the meeting, most oncologists came to the conclusion that there was no basis for testing CYP2D6 genotype before prescribing tamoxifen.

In reading the full papers in print, it was quickly obvious that the genotyping in the BIG 1-98 paper was flawed. Since this has been such a controversial area, retraction is necessary to prevent these data from being utilized in future meta-analyses.

PG: *What is the basis for your allegation that the genotyping data in the Regan paper are flawed?*

MR: There is a fundamental law of genetics, the Hardy-Weinberg Equilibrium, which ensures that the ratio of the genotype frequencies for any biallelic genotype meet certain mathematical relationships.

Therefore, testing for deviation from HWE is a standard approach used to screen for genotyping errors, particularly in larger data sets. The probability that the data are not in HWE are expressed as a p value, and if the p value is low, one must be concerned that the data are invalid.

Although a p value less than 0.05 for a single polymorphism does not imply genotyping error, the data in the BIG 1-98 paper showed consistent evidence of deviation from HWE, with p values ranging from 10^{-5} to 10^{-173} (for the five variants of potential interest). For the most important variant, corresponding to the *4 allele, the p value was 10^{-91}.

Thus, these data could never occur by chance (the combined probability is approximately 10^{-345}).

PG: *Are you suggesting that this was a scientific error?*

MR: I believe strongly that this was legitimate scientific error, due to the use of DNA extracted from the tumor itself.

Although other authors have used DNA extracted

from surgical specimens, most investigators have tried to avoid genotyping tumor DNA.

This is particularly important for studies of CYP2D6, which is located on chromosome 22q13, an area commonly deleted in breast cancer. In women who are heterozygotes, deletion of this region would result in misclassification of such patients as homozygotes (if tumor DNA is used for genotyping).

The data of Regan and colleagues are consistent with this theory, with an estimated misclassification rate of about one-third of the true heterozygotes. (This is consistent with prior studies of the 22q13 deletion.)

PG: *If this is an error, why was it not picked up in the review process?*

MR: We have asked ourselves the same question. Unfortunately, pharmacogenomic studies often get lumped with other biomarker studies, and do not always get scrutinized by individuals with true expertise in genotyping and statistical genetics.

Thus, if the paper was reviewed by experts in breast cancer, this would not have been obvious.

PG: *Do you recommend the use of CYP2D6 genotyping prior to tamoxifen use?*

MR: Unequivocally yes. I believe that the preponderance of the evidence supports the notion that CYP2D6 poor metabolizers have decreased benefit from tamoxifen (at standard doses).

Such patients should be treated with alternative options, or potentially a higher dose of tamoxifen, as suggested by the study from North Carolina (by Irvin and colleagues) published in JCO last year.

PG: *What if you are the one who is mistaken? Can you think of a satisfactory scientific explanation for these deviations from HWE, or does it absolutely have to be a genotyping error?*

MR: CYP2D6 is a notoriously difficult gene to study (see attached), because there are nearby pseudogenes (CYP2D7P and CYP2D8P) and occasional deletion of the gene (*5 allele). However, if one genotypes appropriately (i.e., using germline DNA) and accurately (i.e., using well-designed primers) for any single nucleotide polymorphism, then the results should be in HWE.

Yes; there can be random deviation from HWE, but not to the magnitude seen in Regan et al. Therefore, there is no satisfactory scientific explanation.

PG: *You are out on a limb, no? How does it feel?*

MR: I do not feel I am out on a limb.

There are many poor quality genetic studies in the literature, and this has been reviewed extensively. There has been insufficient attention to quality of pharmacogenomic studies in general, and certainly not in the oncology literature.

Hopefully this will raise the bar for publishing pharmacogenomic studies, at least in high-impact journals such as JNCI.

Mark Ratain is the Leon O. Jacobson Professor of Medicine, director of the University of Chicago Center for Personalized Therapeutics, and associate director for clinical sciences at the university's comprehensive cancer center.

In Brief

ECOG, ACRIN Complete Merger, Form Single Cooperative Group

(Continued from page 1)

The new constitution integrates the governance, administrative and scientific components of ECOG and ACRIN.

The constitution adopts a hybrid membership structure that embraces both the ACRIN model of institutional participation in the scientific program on a study-by-study basis and the ECOG model of multiyear institutional memberships.

ECOG-ACRIN's co-chairs, **Robert Comis** and **Mitchell Schnall**, issued a joint statement: "Building the most attractive scientific program is the motivation for all our efforts. With this constitution as the framework, ECOG-ACRIN establishes for the public and private sectors one organizational structure capable of studying the entire cancer care pathway—prevention and screening, surveillance, early detection, staging, diagnosis, treatment, follow-up, and survivorship.

"We are driven by a genuine belief that together ECOG and ACRIN will contribute more to oncology than either organization could individually. For example, our core pathology and imaging scientists, and their associated laboratories and extensive IT infrastructures, make it entirely possible for the Group to integrate large data sets required for biomarker-driven science.

"Thus, future ECOG-ACRIN studies will be

informed more by process than the classic definition of disease, to allow our patients throughout North America and the world the best, most advanced clinical research opportunities."

Comis is president and chairman of the Coalition of Cancer Cooperative Groups and professor of medicine and director at the Drexel University Clinical Trials Research Center. Schnall is the Matthew J. Wilson Professor of Radiology and the associate chair for research in the radiology department at the University of Pennsylvania.

The constitution establishes co-statistical leadership to oversee study design, data management, results analysis, and reporting of all group studies.

The co-statisticians of ECOG-ACRIN are Robert Gray and Constantine Gatsonis. Gray is professor of biostatistics in the Department of Biostatistics at Harvard University and professor of biostatistics in the Department of Biostatistics and Computational Biology at the Dana-Farber Cancer Institute. Gatsonis is the Henry Ledyard Goddard University Professor of Biostatistics and chair of the Department of Biostatistics at Brown University.

The new group comprises nearly 650 institutions with legacy affiliations.

THE AMERICAN STATISTICAL ASSOCIATION elected new officers and board members. **Nathaniel Schenker** was elected president. He will take the position Jan. 1, 2014, and will serve as president-elect beginning Jan. 1, 2013.

James Rosenberger, of Penn State University, was selected to be vice president.

Mary Kwasny, of Northwestern University, will serve as the council of chapters board representative. **Richard De Veaux**, of Williams College, will serve as the council of sections board representative. **John Czajka**, was selected as chair-elect of the council of sections governing board. **John Stevens**, of Utah State University, was chosen as chair-elect of the council of chapters governing board. Their terms will begin January 1, 2013.

Schenker is the associate director for research and methodology at the National Center for Health Statistics at the Centers for Disease Control and Prevention. He is also an adjunct professor in the Joint Program in Survey Methodology at the University of Maryland. Previously he was a faculty member in the Department of Biostatistics of the UCLA School of Public Health. He has served two terms on the ASA board, most recently as a vice president.

Also elected were new officers for each of ASA's 25 sections. Complete election results can be found at: http://www.amstat.org/news/pdfs/ASA2012ElectionResults.pdf.

THE CONQUER CANCER FOUNDATION of the **American Society of Clinical Oncology** will present more than $5 million in grants and awards to more than 200 promising oncology researchers at ASCO's 48th Annual Meeting in Chicago, taking place June 1-5.

With a focus on clinical and translational research, the foundation's Grants and Awards Program has awarded more than $77 million to researchers worldwide.

The Drug Development Research Professorship, designed to provide flexible funding to outstanding researchers who have made, and continue to make significant contributions to the direction of cancer research, was awarded to:

• **Alex Adjei,** of Roswell Park Cancer Institute, for *Development of the toll-like receptor 5 agonist, CBLB502 for cancer therapy.*

The Advanced Clinical Research Award is designed to fund investigators who are committed to clinical cancer research in an area not currently funded. The ACRA supports physician-scientists in their fourth to ninth year of faculty appointment to perform original research, and provides a three-year grant totaling $450,000. This year's recipient and research project is:

• **Janette Vardy,** The University of Sydney, for *Cognitive rehabilitation for breast cancer survivors with perceived cognitive impairment*.

The foundation will distribute 105 Merit Awards to oncology fellows who submitted high-quality research for presentation at the Annual Meeting. Five of these researchers will receive Special Merit Awards. This year's Special Merit Award recipients each authored the highest-ranking abstracts in select categories:

The James B. Nachman ASCO Junior Faculty Award in Pediatric Oncology:

• **Yael Mosse,** The Children's Hospital of Philadelphia, for *Efficacy of crizotinib in children with relapsed/refractory ALK-driven tumors including anaplastic large cell lymphoma and neuroblastoma: A Children's Oncology Group phase I consortium study.*

• **Giles Robinson,** St. Jude Children's Research Hospital, for *Use of whole genome sequencing to identify novel mutations in distinct subgroups of medulloblastoma.*

The Bradley Stuart Beller Special Merit Award:

• **Tom Waddell,** Royal Marsden Hospital, for *A randomized, multicenter trial of epirubicin, oxaliplatin, and capecitabine (EOC) with or without panitumumab in previously untreated advanced esophagogastric cancer (REAL3).*

Brigid Leventhal Special Merit Award:

• **Fernanda Arnaldez,** NCI**,** for *Identification of TNK2 as a critical kinase in rhabdomyosarcoma through a loss of function shRNA screen.*

Pain and Symptom Management Research Merit Award:

• **Lisa Sprod,** University of Rochester Medical Center, for *Physical activity participation and functional limitations in geriatric cancer survivors.*

To view the full list of 2012 Merit Award recipients, please click here.

The Career Development Award provides funding to clinical investigators, who have received their initial faculty appointment, to establish an independent clinical cancer research program. This year's 11 recipients will each receive a three-year grant totaling $200,000. The 2012 recipients and their research projects are:

• **Philippe Bedard,** Princess Margaret Hospital, for *A randomized, open-label phase II trial of combined pathway blockade for PI3K and MAPK pathway mutated breast, colorectal, non-small cell lung, and ovarian cancer.*

• **Mrinal Gounder,** Memorial Sloan-Kettering Cancer Center, for *A phase III, double blind, randomized, placebo-controlled trial of sorafenib in desmoid tumors or aggressive fibromatosis (DT/DF).*

• **Michaela Higgins,** Massachusetts General Hospital, for *A phase II trial of cabozantinib in women with metastatic hormone-receptor-positive breast cancer with involvement of bone.*

• **Alan Ho,** Memorial Sloan-Kettering Cancer Center, for *Targeting the oncogenic transcription factor c-myb in adenoid cystic carcinomas.*

• **Gopakumar Iyer,** Memorial Sloan-Kettering Cancer Center, for *TSC-1: Mutational analysis and clinical impact in metastatic bladder cancer.*

• **Rom Leidner,** Case Western Reserve University, for *Molecular cytology in Barrett's esophagus.*

• **Kasiani Myers,** Cincinnati Children's Hospital Medical Center, for *Chemoprevention of leukemia in a genetically susceptible population.*

• **Geoffrey Oxnard,** Dana-Farber Cancer Institute, for *Characterizing a new familial lung cancer syndrome through the identification and study of patients with germline EGFR mutations.*

• **Paul Paik,** Memorial Sloan-Kettering Cancer Center, for *Squamous cell carcinoma of the lung mutation analysis program (SQ-MAP).*

• **William William Jr.,** The University of Texas MD Anderson Cancer Center, for *Non-coding RNAs as predictive biomarkers of benefit from epidermal growth factor receptor-targeted therapies in head and neck squamous cell carcinomas.*

• **Toni Zhong**, University Health Network, for *The use of human acellular dermal matrix in one-stage implant breast reconstruction: A multicentered, randomized controlled trial.*

The Young Investigator Awards provide funding to promising investigators to encourage and promote quality research in clinical oncology. The award funds physicians, who are within the last two years of their final subspecialty training at an academic institution, to aid their transition from a fellowship program to a faculty appointment.

This year's 42 awardees will each receive a one-year grant of $50,000 to fund their investigative studies as they begin their careers in oncology research. To view the full list of recipients, please click here.

The International Development and Education Award provides opportunities for early-career oncologists in low- and middle-income countries to further their knowledge and careers and establish strong long-term relationships with leading ASCO members who serve as scientific mentors to each recipient. This year 24 awardees are participating in the IDEA program, including four oncologists who have an interest in palliative care. This year's IDEA recipients are:

• **Yazan Abuodeh,** King Hussein Cancer Center

• **Sandhya Acharya**, National Academy of Medical Sciences, Bir Hospital

• **Adeyinka Francis Ademola,** University College Hospital

• **Nicolas Castagneris**, Oncological Institute of Cordoba

• **Kezhong Chen**, Peking University People's Hospital

• **Shi-Jiang Fei**, Guangdong Lung Cancer Institute

• **Irine Gagua**, National Cancer Center of Georgia

• **Hoover Henriquez Cooper**, Hospital General San Felipe

• **Mercy Isichei**, Abubakar Tafawa Balewa University Teaching Hospital Bauchi

• **Rahul Krishnatry**, Tata Memorial Hospital

• **Susheel Kumar**, Shaukat Khanum Memorial Cancer Hospital and Research Centre

• **Milena Mak**, Instituto do Cancer do Estado de Sao Paulo - University of Sao Paulo

• **Catherine Mwaba**, Cancer Diseases Hospital

• **Evangeline Njiru**, Moi University

• **Alexey Novik**, N.N. Petrov Research Institute of Oncology

• **Kristina Orlova**, N. N. Blokhin Russian Cancer Research Center

• **Pooja Nandwani Patel**, Gujarat Cancer and Research Institute

• **Gaurav Prakash**, All India Institute of Medical Sciences

• **Mateus Sahani**, Agir Ensemble

• **Emadeldin Shash**, NCI, Cairo University

2012 International Development and Education Award in Palliative Care was awarded to:

• **Munesh Lakhey**, B.P. Koirala Memorial Cancer Hospital

• **Monica Malik**, Nizam's Institute of Medical Sciences

• **Tonia Onyeka**, University of Nigeria Teaching Hospital Enugu, Nigeria

• **Rakesh Roy**, Cancer Centre Welfare Home and Research Institute

The Long-term International Fellowship provides early-career oncologists in developing nations the support and resources needed to advance their training through a one-year fellowship with a U.S. or Canadian colleague at the colleague's institution. When the recipients return home, they in turn apply the new knowledge and skills gained from the valuable training experience in their country. The 2012 recipients are:

• **Luiz Henriquede Lima Araujo**, Brazilian National Cancer Institute, for *Molecular profile of lung adenocarcinoma in Brazil*

• **Guochun Zhang**, Guangdong General Hospital, for *Inhibiting STAT5 in breast cancer prevention*

The Medical Student Rotation for Underrepresented Populations provides 8- to 10-week clinical or clinical research oncology rotations for U.S. medical students from populations underrepresented in medicine who are interested in pursuing oncology as a career. This year's recipients are:

• **Kathlene Babalola**, University of Pittsburgh

• **Colby Cantu**, University of Wisconsin

• **Brainerd Erhiawarien**, University of Maryland

• **Jacquelyne Gaddy**, Loyola University of Chicago

• **Giorgio Guiulfo**, University of Central Florida College of Medicine

• **Eva Hudgins**, University of Pennsylvania

• **Jaselyn Justiniano-Torres**, Albert Einstein College of Medicine of Yeshiva University

• **Teresa Martin-Carreras**, University of Central Florida College of Medicine

• **Jonathan Christopher Martinez**, Morehouse School of Medicine

• **Armando Villanueva**, University of Kansas Medical Center

The Resident Travel Award for Underrepresented Populations provides financial support for residents from underrepresented populations to attend ASCO's annual meeting. This year's awardees are:

• **Miguel Albino**, Veterans Affairs Caribbean Healthcare

• **Ibiayi Dagogo-Jack**, Brigham and Women's Hospital

• **Alejandro Garcia**, Columbia University Medical Center

• **Efe Williams Iyamu**, Meharry Medical College

• **Catherine Renee Lewis**, Morehouse School of Medicine

• **Melody Smith**, The University of Texas Southwestern Medical Center at Dallas

• **Justin Taylor**, Brigham and Women's Hospital