THE CANCER LETTER

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

Vol. 38 No. 18
May 4, 2012

Grant Funding

NCI Pulls Back Curtain on "Zone of Uncertainty" Funding Patterns Released With Little Comment

By Paul Goldberg

NCI earlier this week published a series of graphs and a table that offer an at-a-glance picture of the patterns in funding of investigator-initiated research.

A visual aid of this sort is useful because last year, Director Harold Varmus changed the procedures used to award grants.

In the past, proposals that received scores that fit under a cutoff called the payline were funded automatically. Now, only grants that are scored by study sections in the top 7 percent receive funding automatically.

The rest are bounced back into the general application pool, which Varmus has dubbed the "zone of uncertainty," where they are subjected to another level of review. This review involves the institute's top scientific leadership, all the way up to the director.

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Breast Cancer Screening

Studies Seek to Identify High-Risk Groups To Justify Mammography Screening at 40

Younger women at increased risk for breast cancer may benefit from mammography screening every two years beginning at age 40, according to two studies published in the Annals of Internal Medicine.

In the first study, researchers evaluated data from 66 published articles and from the Breast Cancer Surveillance Consortium to determine the factors associated with an increased risk for breast cancer in women aged 40 to 49.

Of the 13 possible risk factors examined, the data showed that having extremely dense breast tissue and a first-degree relative with breast cancer doubled a woman's breast cancer risk. The risk was even higher for a woman with more than one first-degree relative with breast cancer or first-degree relatives with a diagnosis before age 50.

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In Brief

Lippman Named UCSD Cancer Center Director

SCOTT LIPPMAN is the new director of **Moores Cancer Center** at the **University of California, San Diego**.

Lippman leaves the job of chair of Thoracic/Head and Neck Medical Oncology at MD Anderson Cancer Center.

Lippman's fields of research include translational/molecular studies of

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Charts Show Patterns in Awards Of Investigator-Initiated Grants

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The materials released by the Institute, in effect, offer a glimpse at this zone of uncertainty.

One of the graphs shows the range of scores received by grant proposals for R01 grants, demonstrating that a proposal originally scored in the 8th percentile may lose the competition to a proposal scored in the 24th percentile.

The newly released materials show trends in funding R01 and R21 grants that emerged in 2011, and which can guide scientists as they vie for NCI funds this year and beyond. Yet, the manner in which these documents were released was almost as interesting as the trends they map out.

The seven graphs and a table appeared without fanfare—and largely with no explanation—on one of the institute's websites Tuesday, May 1.

Institute officials declined requests for interviews, in essence allowing the graphs and tables speak for themselves (or leaving it to observers interpret the documents at their own peril).

In some instances over the past two years as NCI director, Varmus has chosen to have the institute remain silent, and for reasons not publicly known, in this instance he appears to have opted to avoid any exegesis.

The data released by NCI show that "early stage" investigators applying for R01 grants have a higher success rate than established investigators.

THE CANCER LETTER

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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.

The success rate for established investigators was 16 percent, compared to 17 percent for early stage investigators. Early stage investigators are defined as scientists who are within 10 years of completing training and have not had a previous grant.

This bit of data appears to preempt potential criticism that the review system Varmus has adopted to replace the pay line system may favor established investigators doing the same old thing.

In the documents, NCI acknowledges that newer investigators now receive "preferential consideration" in awarding of R01s.

The silent rollout of these materials is also interesting, because the materials, while clearly useful, don't seem to be especially controversial. Though unprecedented at NCI, such data are published routinely by several other NIH institutes.

Most importantly, the tables show that even with abandonment of reliance on the payline, the success rates for R01 grants remained roughly where the payline has hovered over recent years, at 15 percent.

This shows that while the grant awards procedures have changed, an investigator's chances of getting an R01 grant funded have remained roughly the same.

For R21 grants, the competition was more intense and the overall success rate was at 10 percent.

Overall, people who track NCI funding saw no surprises in patterns of funding R01s, but said they had no prior information on R21s.

The R01 awards have no dollar limit and are awarded for one to five years. The R21s are intended to encourage exploratory and developmental research by providing support for the early and conceptual stages of project development. The grants can continue for up to two years and the combined budget for direct costs for the two-year project period may not exceed $275,000. NCI uses the R21 mechanism only when specified by PAs or RFAs.

Within the Research Project Grants, NCI spent $424 million on new investigator-initiated grants and grants requiring competitive renewal in 2011. Of these funds, $392 million was spent on investigator-initiated grants. Within these investigator-initiated grants, $261 million was spent on new and competitively renewed R01s and $48 million on R21s. (These numbers, contained in Congressional justifications for the 2013 budget, are posted at http://obf.cancer.gov/financial/attachments/2013cj.pdf.)

In spare language that accompanied the materials released this week, NCI reports that new investigators applying for R01 grants receive preferential

consideration. No such preferential consideration is given to applicants for R21 grants.

This results in a difference in success rates that NCI officials describe as "striking." New investigators applying for R01s had the success rate of 13 percent while their counterparts applying for R21s had the success rate of 8 percent.

Other highlights of the newly released data include:

• Altogether, 48 percent of R01 grants funded had rankings greater than the 7th percentile.

• The number of grants funded decreased in direct proportion to the percentile ranking.

• For established investigators, the success rate is consistent with the overall pattern. If R01 applications only from new and early stage investigators are considered, there is a broad spread in the percentile rankings of applications, extending to higher percentiles that were selected for funding. This distribution of scores suggests that NCI is making sure that the overall success rate for new investigators approximates that for established investigators.

• The funding patterns for R21s are different from those of the R01. The institute receives a disproportionate number of applications relative to the number of R21 grants. Only 30 percent of the grants funded had rankings beyond the 7th percentile.

• Success rates for R21s from new and early stage investigators are significantly lower than for established investigators (8 percent versus 14 percent success rates).

The new materials are reproduced below, and are posted at: http://bit.ly/KzZDS9.

NCI FY2011 Competing R01 Applications and Awards

Figure 1: All Investigators: Experienced, New and Early Stage

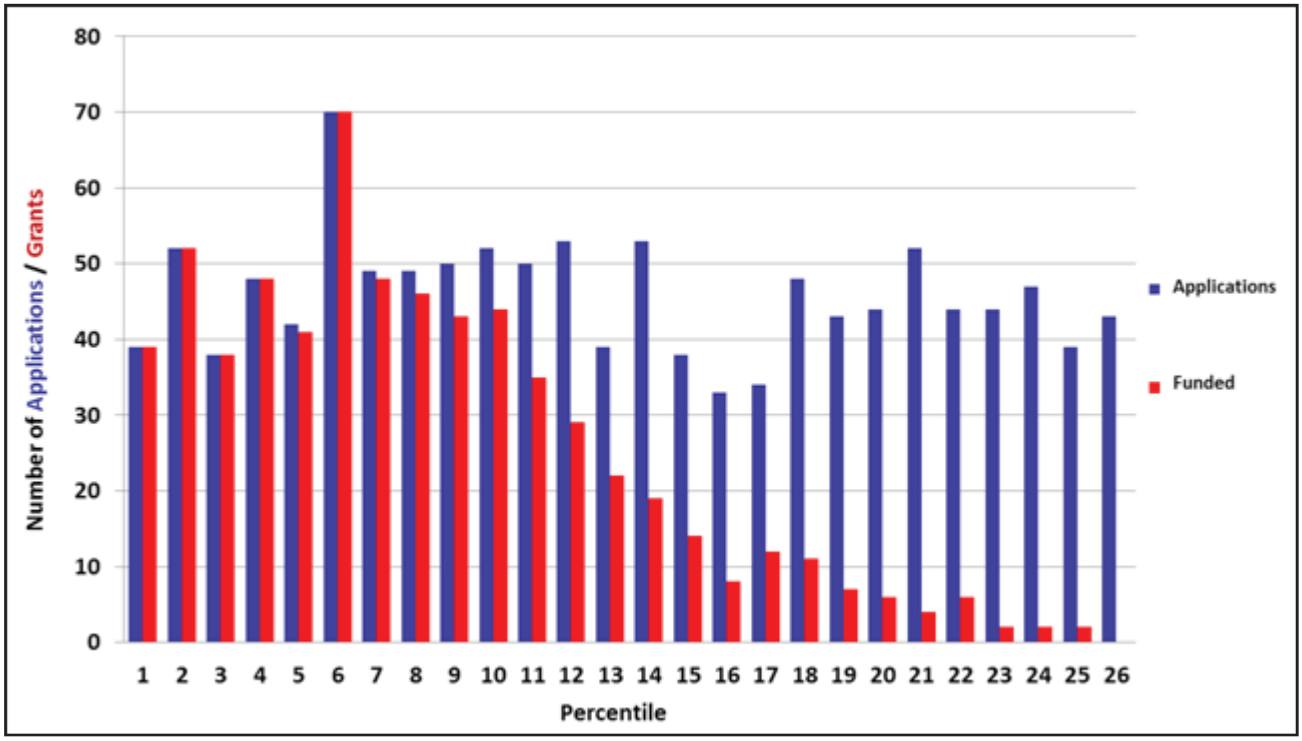
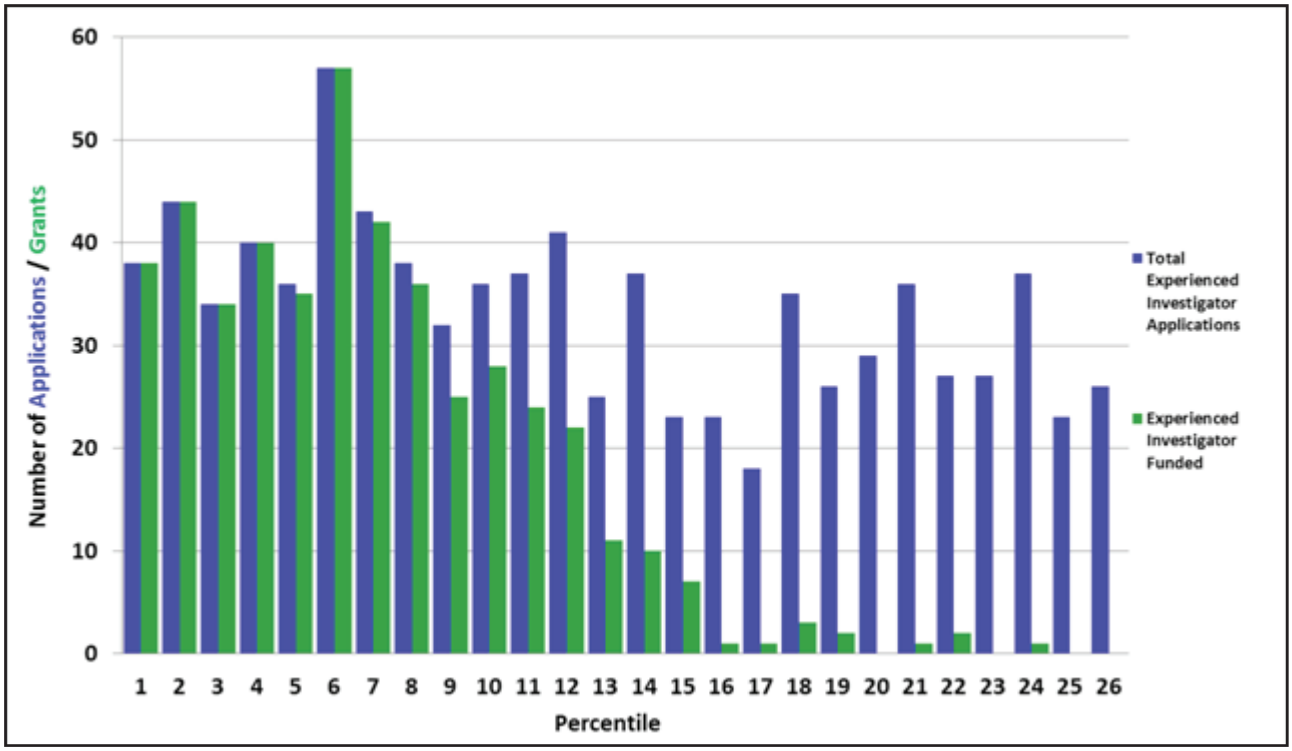


Figure 1 includes data from all categories of investigators: experienced investigators who have had NIH grants in the past, new investigators who previously have not had a substantial independent NIH award, and early stage investigators who are within 10 years of completing their training and have not had a previous grant. If applications from only experienced investigators are considered, the same pattern of funding success is observed (Figure 2).

Figure 2: Experienced Investigators



In striking contrast, if R01 applications only from new investigators (Figure 3) or only from early stage investigators (Figure 4) are considered, there is a much broader spread in the percentile rankings of applications, extending to higher percentiles, that were selected for funding. This distribution, across a wide range of scores, reflects NCI's commitment to ensuring that the overall success rate for new investigators approximates that for established investigators.

Figure 3: New Investigators

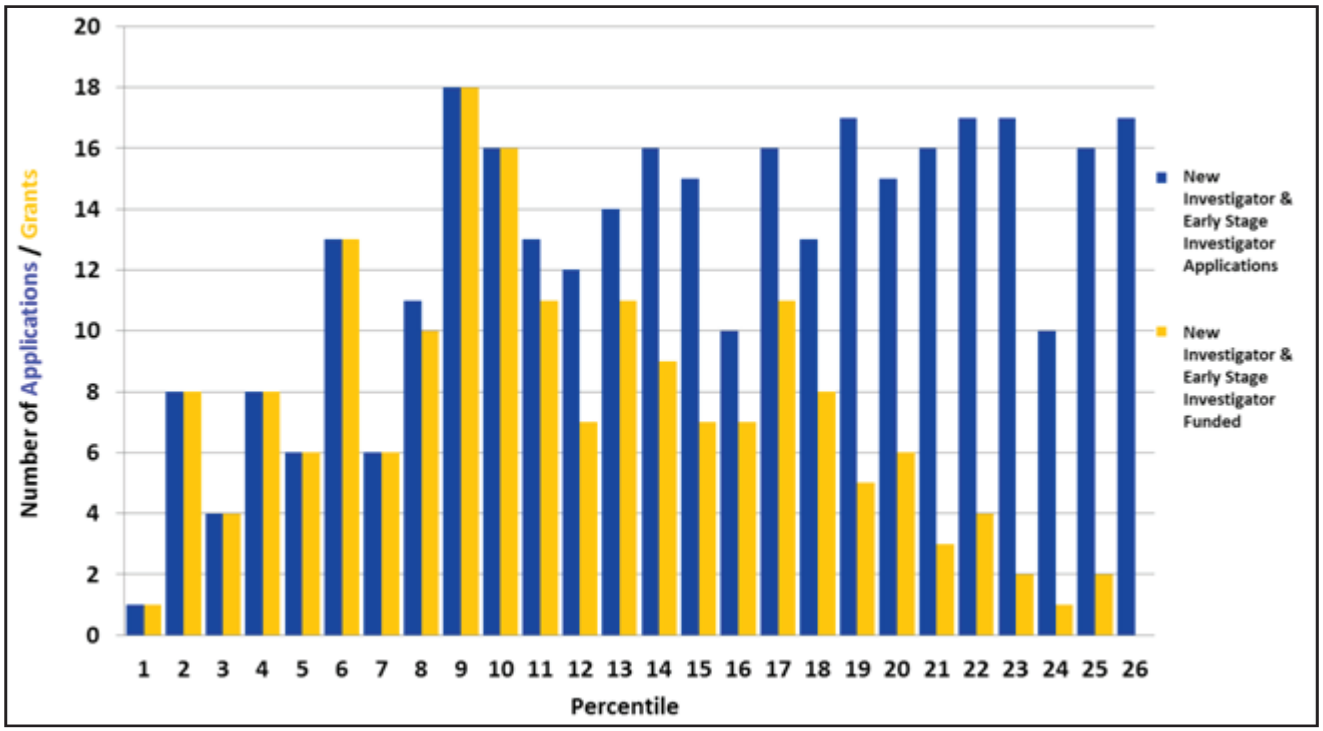
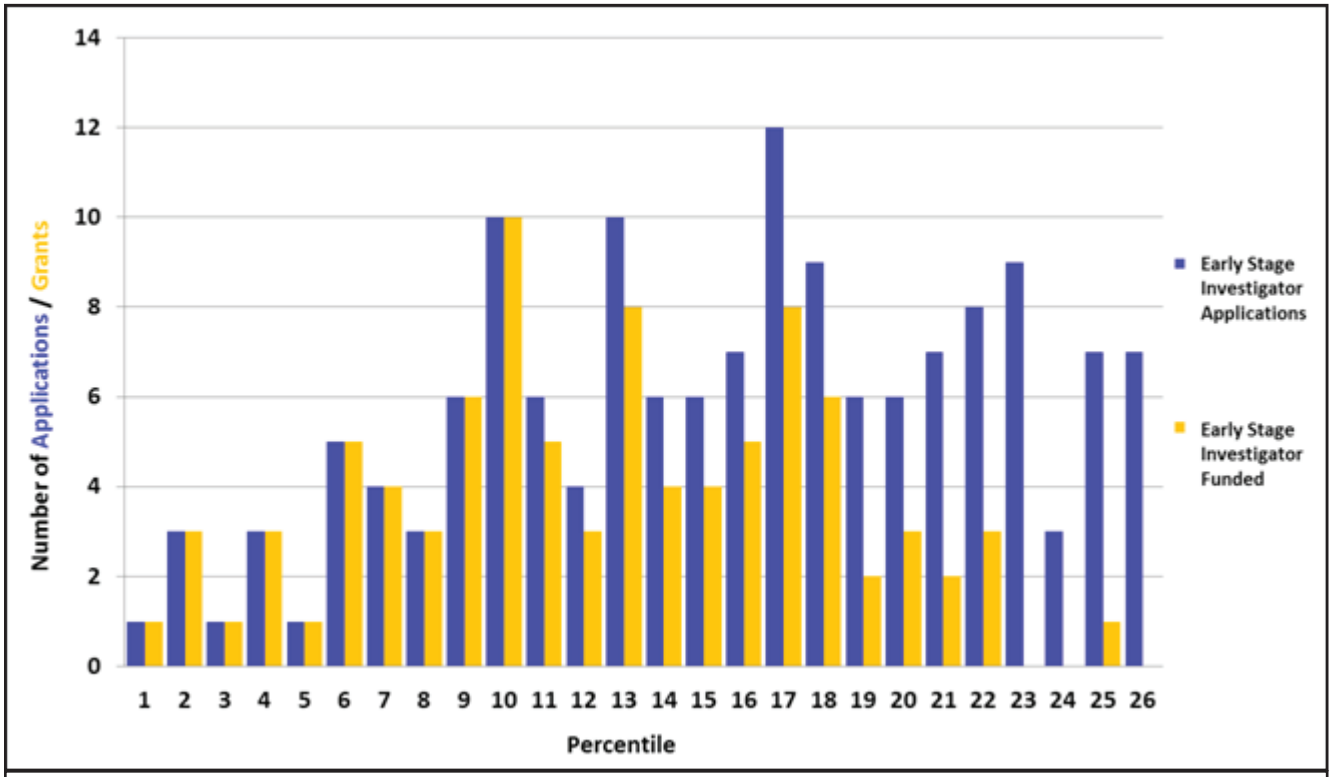


Figure 4: Early Stage Investigators



Figures 1-4: Excludes applications that did not receive a percentile ranking. When an amended application is considered in the same fiscal year as the original, only the one with the better ranking is counted.

NCI FY2011 Competing R21 Applications and Awards

Funding patterns for R21 grant applications:

The funding patterns for R21 grant applications differ markedly from those of the R01. This difference is explained by the fact that NCI receives a disproportionate number of applications relative to the number of R21 grants that can be funded (see Table 1). Thus, the cut-off for funding of R21 grant applications is more stringent than that for R01 applications for all investigators (Figure 5-7). Thirty percent of the grants funded had rankings beyond the 7th percentile.

Figure 5: All Investigators: Experienced and New

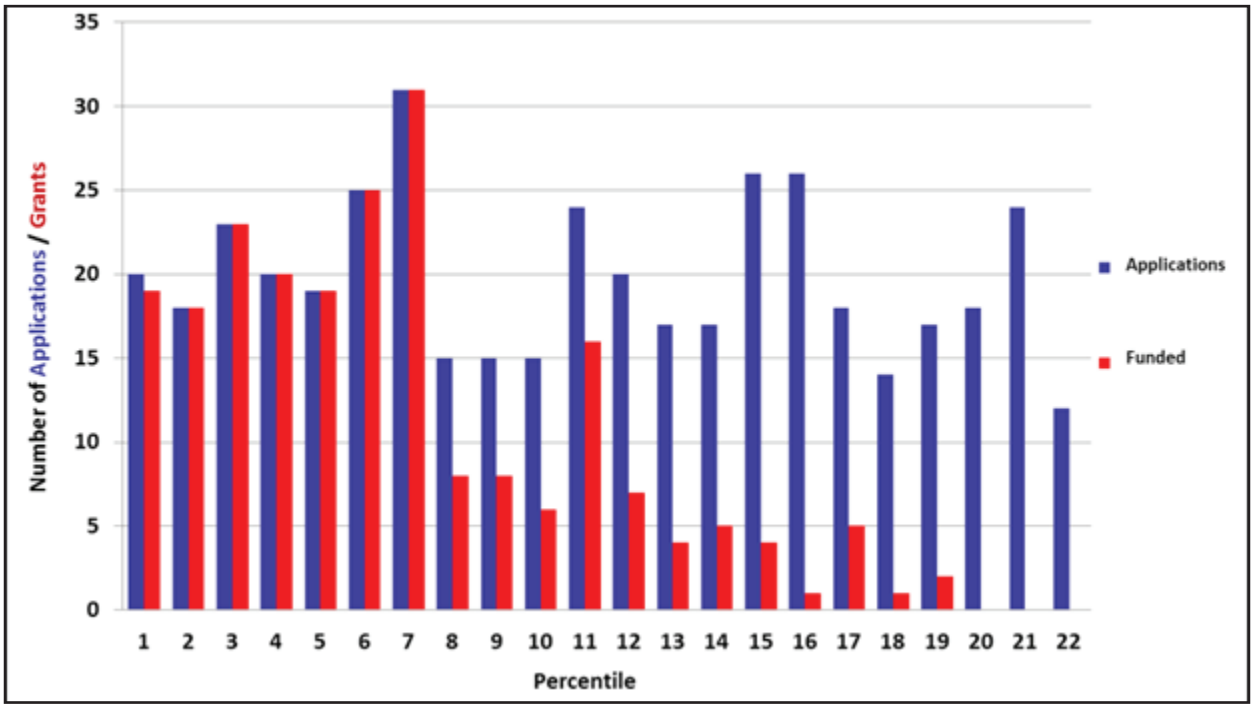


Figure 6: Experienced Investigators

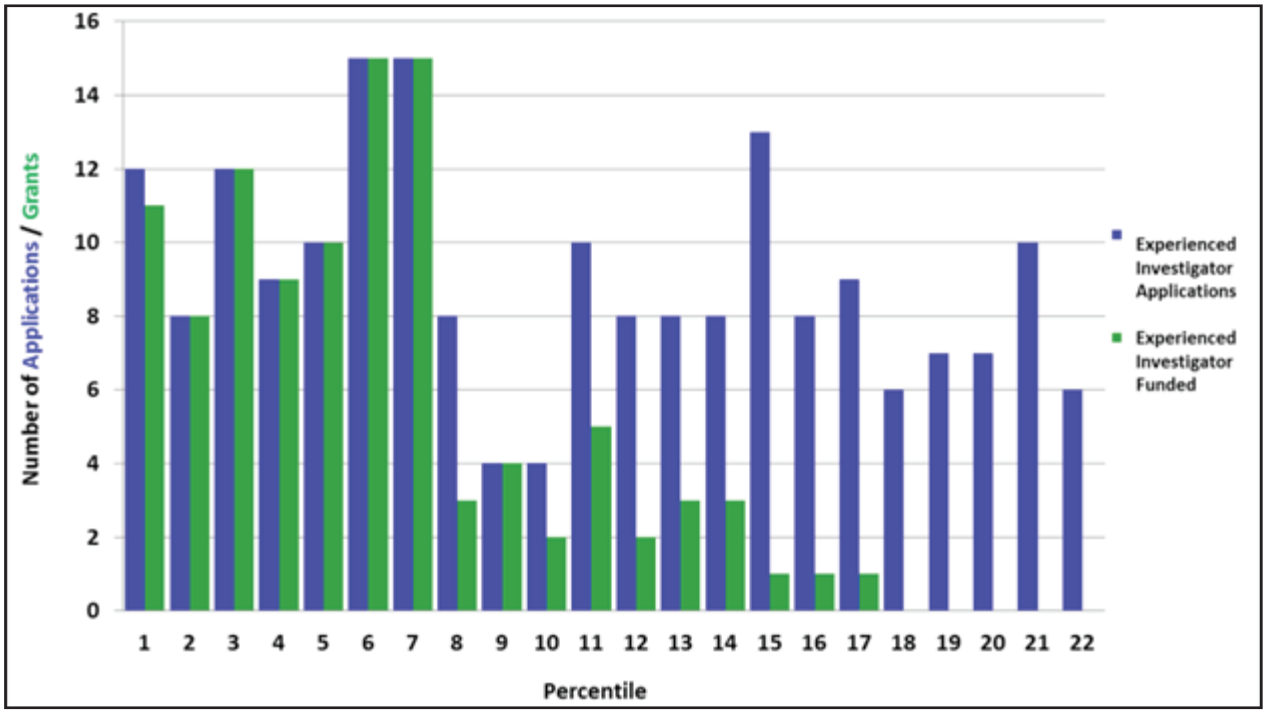
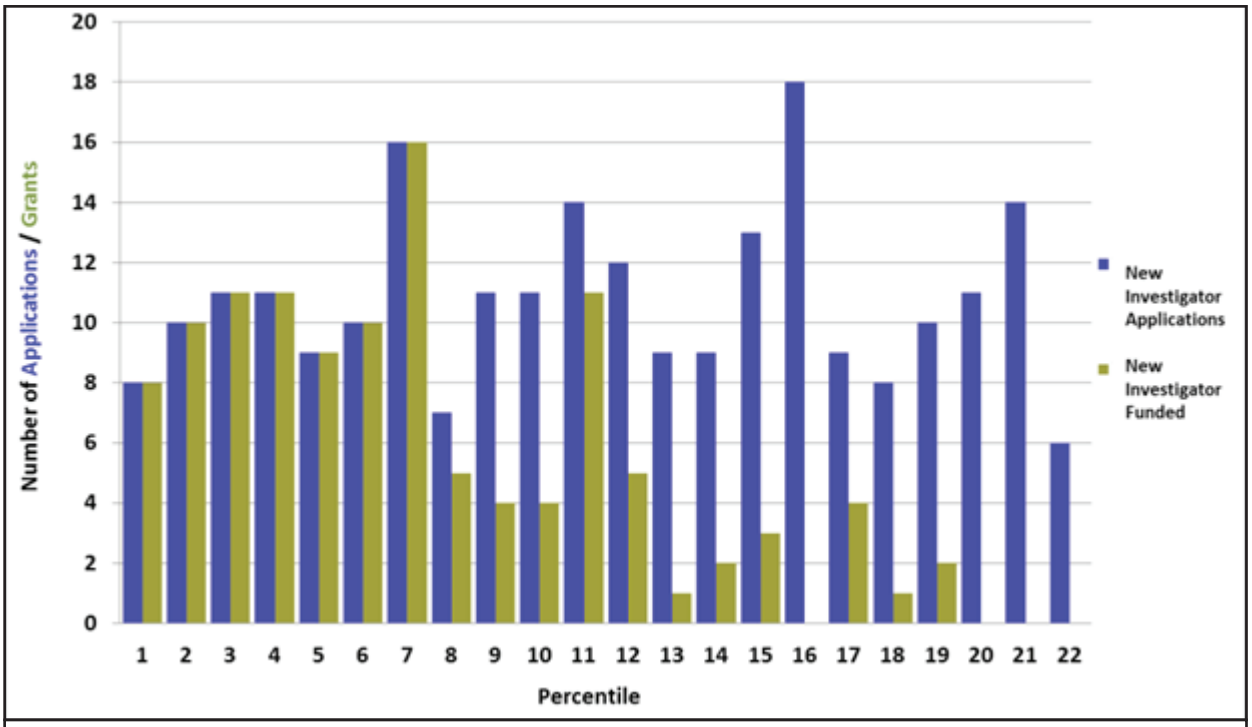


Figure 7: New Investigators



Figures 5-7: Excludes applications that did not receive a percentile ranking. When an amended application is considered in the same fiscal year as the original, only the one with the better ranking is counted.

In contrast to the case with the R01 funding patterns, success rates for R21 funding of applications from new and early stage investigators[3] are significantly lower than for established investigators (8% versus 14% success rates, respectively) (Table 1). The difference in success rates for R21 compared to R01 applications from new investigators is striking: 8% compared with 13%. This disparity results from the fact that R01, but not R21 applications, from new investigators are given preferential consideration.

Table 1: Fiscal Year 2011 R01 and R21 All Investigators Success Rates

	Total Applications	Number with Percentiles of 25 or better	Number with Percentiles of 10 or better	Funded	Success Rate
R01 - All Investigators	**4,477**	**1,145**	**487**	**652**	**15%**
Experienced Investigator - Total	3,005	837	396	468	16%
Type 1	2,440	586	265	314	13%
Type 2	565	251	131	154	27%
*New Investigator	1,472	308	91	184	13%
**Early Stage Investigator	545	143	37	91	17%
R21 - All Investigators	**2,242**	**484**	**201**	**223**	**10%**
Experienced Investigator	780	222	97	106	14%
New Investigator	1,462	262	104	117	8%

Total applications include all new and competing renewals that received a percentile, those with just an impact score as well as triaged or not recommended for funding. When an amended application is considered in the same fiscal year as the original, only the one with the better percentile is counted.

* Includes Early Stage Investigators **Included in New Investigators

Breast Cancer Screening

Women at Twice Average Risk Can Start Biennial Screening at 40

(Continued from page 1)

Having a prior breast biopsy, second-degree relatives with breast cancer, or heterogeneously dense breasts increased a woman's risk by 1.5- to 2-fold; and current use of oral contraceptives, never giving birth to a child, or giving birth to a first child after age 30 increased a woman's risk by 1.0- to 1.5-fold.

Quantifying risk associated with known risk factors may be useful to women and their doctors as they decide when to start mammography screening.

In the second study, researchers used four independent models to examine what level of risk tips the balance of benefits and harms to favor screening mammography for women aged 40 to 49.

The researchers compared mammography screening starting at age 40 versus age 50 using either digital or film mammography. The researchers also compared annual and biennial screening intervals to determine which approach yielded the most benefits, such as life-years gained, breast cancer deaths averted, and the least harms, such as false-positives.

The researchers found that for women aged 40 to 49 with a two-fold increased risk for breast cancer, the harm-benefit ratio of biennial screening with film mammography was similar to that of biennial screening of average-risk women aged 50 to 74.

"The evidence suggests that for women at twice the average risk for breast cancer, biennial screening beginning at age 40 has more benefits than harms," said study lead author Nicolien van Ravesteyn, of the Department of Public Health at Erasmus Medical Center in The Netherlands. "These results provide important information toward developing more individualized, risk-based screening guidelines."

According to Otis Brawley, chief medical and scientific officer of the American Cancer Society and author of an accompanying editorial, the public needs to be educated about the benefits and risks of mammography so that individual risk factors and patient preferences can be considered when making screening decisions. Brawley wrote that the public perceives mammography as a better technology than it actually is—and that it is important to carefully weigh the harm-benefit ratio for a specific woman before advising use of the test.

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FDA News

Xgeva Doesn't Meet The Bar In Controversial Indication

The efficacy of the Amgen drug Xgeva (denosumab) doesn't justify its risks in the controversial proposed indication of non-metastatic, castration-resistant prostate cancer.

FDA's complete response letter, issued April 26, follows the Feb. 8 vote of the agency's Oncologic Drugs Advisory Committee, which recommended against Xgeva's approval in a 12-1 vote (The Cancer Letter, Feb. 17).

Amgen sought to use Xgeva in men with castration-resistance prostate cancer, claiming that the drug improved "bone metastases-free survival." Xgeva increases the risk of osteonecrosis of the jaw.

The agency's letter requests data from an adequate and well-controlled trial or trials demonstrating a favorable risk-benefit profile for Xgeva that is generalizable to the U.S. population, the company said.

"We are reviewing the complete response letter and will work with FDA to determine any next steps," said Sean Harper, Amgen executive vice president of research and development. "The FDA's action today does not impact the approved indication of Xgeva in the prevention of skeletal-related events in men with bone metastases from prostate cancer, which was acknowledged by the FDA and the advisory committee members who discussed the application."

Xgeva, a RANK Ligand inhibitor, is approved by FDA for the prevention of skeletal-related events in patients with bone metastases from solid tumors, including prostate cancer.

ODAC's recommendation at the Feb. 8 meeting was consistent with the views it expressed about the proposed indication at a meeting last September (The Cancer Letter, Sept. 23, 2011).

This indication reflects a cascade of medical services which begin when men are found to have prostate cancer after screening with the prostate-specific antigen. After this, the patients receive surgery.

After the PSA begins to rise, the patients receive hormonal treatments. When the PSA level starts to climb despite these treatments, even in the absence of clinical signs of disease, the patients can be classified as castrate-resistant and non-metastatic.

This proposed indication was ushered into existence by the use of PSA testing, which isn't approved for population-wide screening, and by the widespread use of androgen-deprivation therapy to treat disease early in its course. (Hormones are approved for end-stage disease.)

The agency's decisions on Xgeva can affect a class of drugs that are now in the development pipeline. Also, the Amgen application raised questions about the trial designs for therapies that would be used for "maintenance."

The agency routinely approves applications based on placebo-controlled trials in the maintenance setting. However, an alternative trial design would be to compare the use of the drug in the maintenance phase, compared to starting the drug at the time of documented progression, agency officials say.

Amgen focused the trial's population of men with no bone or other distant metastases (excluding previous untreated local-regional disease and metastatic nodal disease), who had received hormonal treatments and whose PSA level was above 8 ng/mL or had doubled in less than 10 months.

Patients were randomized into two arms, receiving either 120 mg of denosumab every four weeks, or placebo. The primary endpoint—bone-metastasis-free survival—was chosen because of the prophylactic nature of the trial. Overall survival was a secondary endpoint. Patients were taken off therapy following first bone metastases or high toxicity. Patients underwent a bone scan every 16 weeks, with skeletal metastases confirmed by X-ray, CT or MRI.

In the treatment arm, denosumab increased time to bone metastases by 4.2 months (HR=0.85 [95% CI: 0.73, 0.98]).

Overall survival was similar compared to placebo, with a hazard ratio of 1.01 (95% CI: 0.85, 1.20; p=0.91), with median survival 43.9 months (40.1 NE) on denosumab, and 44.9 (40.0 NE) on placebo. Median progression-free survival was 21.7 months on denosumab, and 19.3 on placebo.

IOM Recommends Consolidating Each Drug's Lifetime History

The Institute of Medicine recommended that FDA create a risk and benefit assessment and management plan for each drug, made available as a single, comprehensive, public document.

IOM underscored the need for a more systematic and transparent process to collect, assess, and act on data about a medication's risk/benefit profile throughout its entire life cycle, from approval until it is no longer marketed.

The institute's report, "Ethical and Scientific Issues in Studying the Safety of Approved Drugs," said that the document should include a description of any safety questions that exist when a drug is approved or that emerge over the course of the product's use, as well as benefit and risk assessments specific to these questions. And that it should also include details on regulatory actions taken on the medication, such as restrictions on its use or the decision to require further research, as well as the results of these actions.

Much of this information is already being gathered by FDA, but it is currently scattered across multiple records. The institute's report was sponsored by FDA.

The committee concluded that there are too many individual factors involved in each case and too great a variety of drugs to provide a single universal set of criteria for determining what should trigger a postmarket study. However, the committee identified some circumstances in which a product's benefits or risks are particularly uncertain, including "first in class" drugs that have been approved based on surrogate endpoints used previously for other drug classes, and drugs for which several endpoints provide conflicting evidence about risk, such as an anti-hypertensive drug that lowers blood pressure but increases weight.

In such cases, the committee recommended that FDA require safety research after approval or provide a public rationale for why it is not necessary. Early initiation of such studies could limit the harm done by drugs with risks that are later found to be unacceptable and avoid crises in which the agency is faced with few good options, the committee said.

The committee said FDA should only require postmarket research if a regulatory decision cannot be made based on existing safety evidence; the research can sufficiently reduce uncertainties about the benefit-risk balance to help inform a regulatory decision; the results will be used to make a decision in a timely fashion; and the rights and interests of the research participants can be adequately protected.

"It is not possible to know what the full range of a drug's benefits and risks will be until it is used by many different kinds of patients over time, so it is critical that FDA continue to monitor and learn about the effects of drugs after they are marketed," said committee co-chair Ruth Faden, Philip Franklin Wagley Professor of Biomedical Ethics and executive director of the Berman Institute of Bioethics at Johns Hopkins University. "Our report focuses on how the agency can be proactive so that situations in which a drug's benefit-risk profile becomes problematic can be detected earlier, and it details how FDA can get the additional information on a drug's safety in the most ethical and scientifically sound ways when questions arise."

In Brief

Lippman Made New Director Of UCSD Moores Cancer Center

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cancer risk, molecular-targeted drug development and personalized therapy. His record of funding from the NCI in these research areas include, recently, the role as a principal investigator of two program project grants and a Specialized Program of Research Excellence.

He was also leader of the Lung Cancer Program of the MD Anderson Cancer Center Support Grant and is co-investigator on the American Association for Cancer Research Stand Up to Cancer project involving molecular studies of lung cancer. He is a member of the NCI Clinical Trials/Translational Research Advisory Committee.

"As the new director, Lippman will implement strong initiatives for ramping up the research-driven cancer therapy and prevention programs and clinical trials of the Moores Cancer Center," said David Brenner, vice chancellor for health sciences and dean of the School of Medicine at UC San Diego. "His ultimate goal, and ours, is to facilitate the translation of novel discoveries from our world-class laboratories into personalized therapies."

Lippman started the new job May 1.

THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA trade group announced that its 28 member companies invested $49.5 billion research and development in 2011.

PhRMA released its 2012 Industry Profile as well as an updated version of its informational chart pack resource, "Biopharmaceuticals in Perspective." Both sets of materials are available for public use and are intended to provide timely, relevant information about the biopharmaceutical research sector.

According to a recent report by the National Science Board of the National Science Foundation, the U.S. biopharmaceutical sector accounts for the single largest share of all U.S. business research and development, representing nearly 20 percent of all domestic R&D funded by U.S. businesses. In the U.S., R&D expenditures among PhRMA members represented 21.1 percent of domestic sales.

Last year, 35 new molecular entities received FDA approval—one of the highest totals in the last decade. This includes two personalized medicines for cancer, 11 new medicines for patients with rare diseases, the first new medicine for lupus since 1955, and two medicines that are the first in a new class to treat Hepatitis C.

According to a survey conducted by the Tufts University Center for the Study of Drug Development, 94 percent of polled companies are currently investing in the field of personalized medicine. Today, there are more than 3,200 medicines in clinical trials or undergoing FDA review in the U.S., up from 2,400 in 2005.

A list of PhRMA's 28 full members can be found here: http://www.phrma.org/about/member-companies.

INDIANA UNIVERSITY School of Medicine and **IU Health** unveiled a $150 million research collaboration, the Strategic Research Initiative, that will enhance the institutions' joint capabilities in fundamental scientific investigation, translational research and clinical trials.

IU Health will invest $75 million in the initiative, and IU School of Medicine will match that with an additional $75 million in resources. The initial focus will be on projects in the fields of neuroscience, cancer and cardiovascular disease.

In cancer, one of the initiative's primary goals is to enable the university's Melvin and Bren Simon Cancer Center to attain the NCI "comprehensive" designation. To support that goal, the initiative will provide funds to recruit leading cancer researchers and expand cancer clinical trials in Indiana.

In neuroscience, the research program will tackle a broad range of brain injuries, neurodegenerative disorders and neurodevelopmental disorders.

The cardiovascular research initiative will develop a program for the study and treatment of heart failure, from newborns to older adults. A top priority is developing a cardiovascular genetics program and recruiting a top scientist in that field.

JOANNE HAMBLETON was promoted to the newly created position of senior vice president for patient services at **Fox Chase Cancer Center.**

Hambleton was previously vice president of nursing services.

She began her career at Fox Chase in 1989 as assistant director of nursing. She received the nursing department's lifetime achievement award in 2010.

ANNE JADWIN was promoted to vice president of nursing services and chief nursing officer at Fox Chase.

She had been assistant vice president of nursing and patient services since 2008. Her new role includes responsibility for inpatient and ambulatory care nursing services, including ambulatory care clinics and the infusion room/clinical research unit.

She had served as the center's director of nursing services from 2000 to 2008.

Clarification

How FDA Monitors Shortages

A news analysis by Rena Conti in the April 27 issue of The Cancer Letter stated that FDA monitors the inventories of generic drugs.

Currently, the FDA uses syndicated data to compare average historical usage rates of selected drugs with information provided by manufacturers about existing inventories and remaining production. This analysis allows the FDA Center for Drug Evaluation and Research to estimate when and if a shortage may occur.

Under the Accelerated Recovery Initiative proposed by the Generic Pharmaceutical Association, the "trusted third party" would perform a systematic and ongoing evaluation of historical and projected demand for all drugs and evaluate supply by individual manufacturers and the market as a whole.

The supply data would likely be provided by participating manufacturers.

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