THE CANCER LETTER

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FDA News

ODAC Votes to Nix Amgen's Drug Xgeva For Proposed Prostate Cancer Indication

By Conor Hale

The FDA Oncologic Drugs Advisory Committee voted 12-1 against approval of the Amgen Inc. drug Xgeva (denosumab) for the treatment of men with castrate-resistant prostate cancer who are at high risk of developing bone metastases.

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

The committee's recommendation on this Supplemental Biologics License Application also appears to constitute clinical advice on the validity of the indication of "castrate-resistant non-metastatic prostate cancer."

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Appropriations

Obama Proposes Flat Funding for NIH; And Realignment of Institutes' Budgets

President Barack Obama presented his budget request to Congress for the 2013 fiscal year Feb. 13.

The proposal freezes the funding level for NIH—with no change from the 2012 appropriations of $30.86 billion.

It does however suggest realigning funding within NIH. If approved, the Office of the Director would take a $28 million cut, down to $1.429 billion; and the National Institute of General Medical Sciences would take a $48 million cut, down to $2.379 billion.

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In Brief

Nevins Reverses Position, Claims Potti Manipulated Data At Foundation of Trials

In a dramatic reversal, Duke University genomic scientist Joseph Nevins said his former protégé Anil Potti had manipulated data that laid the foundation for three clinical trials that enrolled 112 patients.

Nevins announced his change of position in a 60 Minutes interview Feb. 12. The story, "Deception at Duke," can be found here: http://www.cbsnews.com/video/watch/?id=7398478n.

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ODAC Recommendation Echoes Discussion at September Meeting

(Continued from page 1)

This indication reflects a cascade of medical services which begins 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, 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 committee's decisions on Xgeva can affect a class of drugs that are now in the development pipeline.

Also, the application raises 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.

While discussion of the validity of this indication dominated the committee's meeting last September, the Feb. 8 ODAC meeting focused exclusively on the data Amgen provided in support of the application.

Approval, which at this point appears unlikely, would have moved the use of Xgeva, a RANK ligand inhibitor, to an earlier point in the disease. Xgeva is approved for the prevention of skeletal-related events in patients with solid tumors metastatic to bone, including prostate cancer. It is also approved under the name Prolia, for postmenopausal women with osteoporosis at high risk for fracture, and as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer.

Amgen wanted to deliver Xgeva in a preventive, prophylactic setting, and the committee had to decide whether an earlier exposure was better than using the drug in its currently approved indications, the prevention of skeleton-related events in metastatic patients.

Moreover, the committee had to grapple with the question of the magnitude of benefit demonstrated in the application. If approved for this indication, Amgen could have won a trifecta: extending from the initiation of denosumab (as Prolia) to prevent bone loss from ADT, through the prevention of bone metastases in patients who are castrate-resistant, and continuing in the indication to prevent skeletal-related events in men with known bone metastases. The use of the drug could last for many years, starting with the initiation of ADT therapy through death.

Amgen's Case for Approval

The company 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

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denosumab, and 44.9 (40.0 NE) on placebo.

Median progression-free survival was 21.7 months on denosumab, and 19.3 on placebo.

With this information, FDA sought the committee's advice on one question: "Has denosumab demonstrated a favorable risk/benefit evaluation for the treatment of castrate resistant prostate cancer at high risk for metastases?"

Echoes of ODAC Past

In September 2011, ODAC discussed what sort of magnitudes of improvement would be needed in this indication. No vote was taken, but the committee members said a delay of six months to a year or more would be compelling.

Denosumab's 4.2-month benefit in time to bone metastasis was disappointing, said several committee members at the Feb. 8 meeting.

"In the prophylactic setting, you are taking men who are asymptomatic and only have rising PSA and giving them a therapy to try and delay something down the road," said Howard Sandler, a temporary voting member of ODAC and chairman of the Department of Radiation Oncology at Cedars-Sinai Medical Center. "I think there is an extra burden that we as physicians carry in minimizing potential toxicity from prophylactic therapy."

Wyndham Wilson, committee chair and chief of the Lymphoma Therapeutics Section in NCI's Center for Cancer Research, agreed.

"I think the committee recognizes that when your endpoints are surrogates for clinical benefit, they felt that you really need to have longer times of that surrogate showing something," Wilson said. "In fact, the numbers thrown out were six to 12 months, not four months.

"And I think that the more I was looking at something being a surrogate, the more I would want it to be even longer. So I was one of the ones that said that 12 months—because it is not a direct benefit—it is a surrogate."

Matthew Smith, chair of the Genitourinary Malignancies Program at Massachusetts General Hospital MGH Cancer Center, who was the principal investigator on the Xgeva pivotal trial, disagreed.

"Clinical trial endpoints, if they matter, would be an indication of the reasons and purposes that we are here for," Smith said. "And I do believe that bone metastases are important and that the time without the burden of metastases is clinically relevant. That is a view that was shared by many of the members of the September ODAC."

Wilson conceded the point, at least in part. "Well, actually I think you're right, the committee did say that," he said. "However, the committee was trying to discuss guidelines."

The 4.2 month benefit was only slightly more than interval between bone scans on trial—one visit, every 16 weeks—a scanning frequency that members said would never be sustained in regular clinical practice, several committee members noted.

Discussion of the significance of benefit claimed by Amgen follows:

WILSON: "We are looking at a radiographic benefit here. We saw four months, which is one scan apart in improvement. In real life, you wouldn't be scanning people every four months. So this is a completely artificial endpoint.

"I am not saying that doing it every four months was the wrong way to do this trial. What I am saying is that it is relative to the magnitude of benefit within this context. If we saw significantly over six months, then I think I would feel quite comfortable.

"Maybe the sponsor could comment on that. Because, again, it's one scan improvement of a scanning frequency that would never be used in real life, with no hard endpoint that was positive. I'm just wondering where the benefit lies, other than hoping that it's going to be beneficial."

SMITH: "This was the primary, pre-specified endpoint that was, as I understand it, agreed to by the agency. I don't at all perceive that as an arbitrary endpoint.

"Separately, I believe that it's a clinically meaningful endpoint. There is clinical benefit to delaying time without the burden of bone metastases—certainly an approach I agree with, and my patients would agree with.

"To suggest otherwise, in my opinion, is a dangerous precedent for prostate cancer. I think it will have a chilling effect on drug development in the field. And that's a big problem.

"Separate from that, I think the risk/benefit should be a separate consideration. That should be discussed in a separate manner, but to say that the endpoint is arbitrary and clinically irrelevant I think is inconsistent with discussions that have gone on for a long time, including with the agency, at the time the study was designed."

WILSON: "Actually I don't think I said that.

"I think I said that this is not—scanning every four months is not something that would be done in a normal regular practice. And it has relevance to the magnitude

of the delay that is critical here.

"Lots of people seem to think that if there is a P value on a surrogate endpoint agreed to by the agency then that translates into this drug is clinically beneficial. And, again and again, this committee has dealt with the fact that when you are using a surrogate endpoint, the magnitude of benefit has to be looked at.

"And the point that I've been trying to make is that the magnitude of benefit is one scan apart, of a scanning frequency that wouldn't be done in normal practice, and therefore it just brings up this question of whether this is clinically meaningful, that's all. Nobody's denying anything else.

SMITH: "Thank you for clarifying your comment. I hope, I sincerely hope, that there is general agreement by the committee and that there will be future guidance forthcoming on whether this endpoint is clinically meaningful. Certainly that was the suggestion from the development of this clinical trial, during discussions with ODAC in September.

"Regarding the frequency of imaging, that was done to rigorously assess the endpoint. And I accept entirely what you are saying, that that would not be done in clinical practice."

Richard Pazdur, director of FDA's Office of Hematology Oncology Products, added: "When we are agreeing to the design of the trial, we are agreeing to the design of the trial, we don't know what the results of the trial are.

"And that's the issue here. If we saw an effect on the endpoint of one year that was suggested by some other people—we probably wouldn't even be here at this time.

"There is a difference in agreeing to a conceptual design of a trial, and then seeing the results of the trial."

A risk: Osteonecrosis of the Jaw

Compared to placebo, denosumab in a non-metastatic setting carried a 5.4 percent increase in osteonecrosis of the jaw.

The risk increased cumulatively with exposure, at about 1 percent per year.

Committee members said prolonged exposure that the proposed indication, combined with the approved indications, could boost the incidence of ONJ.

Denosumab is available to men receiving ADT through the Prolia label, at much smaller doses—60 mg every six months, compared to Xgeva's 120 mg every four weeks. It can be administered while the patient has clinically localized prostate cancer.

"If this drug was approved for this setting, it would be approved for the population that went into this clinical trial, almost certainly—and it will probably be a large number of folks that may be on this trial for years and years and years. Five, 10 years, etc.," said Wilson. "I think that we have to recognize that what we seem to see now is that incidence of osteonecrosis is cumulative and increases year over year, so I think we can reasonably expect that it will go up."

"No one is denying that this is a very effective drug for preventing skeletal-related events. The question is: is giving it in the prophylactic setting a benefit, over giving it at the time of actually finding a disease in the bone."

SMITH: "If I could just briefly comment, this is not maintenance therapy—these patients have progressive, high-risk disease. The median survival after development of bone metastases fell to 19 months."

"So the idea that patients on-label, so to speak, for this study population could be on treatment for five or 10 years is just inconsistent with the data. These are high-risk patients. They'll be dead a long time before 10 years, unfortunately."

Galson's "Return"

"Dr. Wilson, if I could just make a correction, with all due respect to something that you said, there are plenty of examples of FDA labeling drugs for populations that didn't exactly reflect the population the study did in the trial," said Steven Galson of Amgen Regulatory Affairs, former acting surgeon general of the U.S., and former director of the FDA's Center for Drug Evaluation and Research.

"There is a lot of flexibility that the agency has around labeling to actually be more restrictive. And I'm not suggesting that, but it is a possibility. If this were approved it doesn't mean that it has to be labeled for the same population in the study."

PAZDUR: "I don't think we want to go in that direction at all. With all due respect to you Steve and your former position here, I do not want to go into that direction.

"I think we are talking about a clinical situation and the labeling issues are really the purview of the FDA—with discussions with the sponsors after this committee—but we're looking at a clinical situation here," continued Pazdur.

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"We are not asking whether the drug should be approved or not. If you notice how we're asking the question, it's a clinical estimation [of risk-benefit].

"And as Howard Sandler pointed out, this is a different type of situation. There's a higher bar here that we're talking about. This is not a population of patients with end-stage refractory disease and there's no other option."

WILSON: "You can call it prophylactic, you can call it maintenance—I don't care what you call it. But that's what's being done here and we're seeing drugs with known effectiveness being brought up earlier, and that's very legitimate thing to do, but the bar is generally higher. Especially if there's a toxicity signal."

The only vote to recommend approval was cast by the patient representative on the committee. "I run a support group, and we have a group of men who have been on Zometa for quite a long time," said James Kiefert, the patient representative. "And if they knew they had an opportunity to have delayed onset of bone metastases… I can tell you that when we talk about the impact of osteonecrosis of the jaw, the guys in my group say 'Isn't that something, 95 percent of us aren't going to get it.'

"So we look at the side effects and we say are you willing to take that risk, knowing that there was this possibility that you'd have osteonecrosis of the jaw—people were lining up to get it. It was worth the risk."

Statistical Significance, not Clinical Significance

"There was a comment about if you ask patients do you want to delay your bone metastases the answer would be 'yes, of course. That's a no-brainer.' The answer would easily be yes," said Maha Hussain, temporary voting member and associate chief for clinical research at the University of Michigan.

"But I would say it's not just bone metastases, it's all metastases, which is an important part and that's the missing piece in this case. The other part to point out is that it's all about risk and benefit."

"Do you ask your patient and say 'Do you want to delay your disease for five minutes? But I'm going to give you a treatment that can cause you toxicities.' Then the patient is going to pause," said Hussain. "So I don't think we should think about it as benefit with no risk, there is a risk and there is a benefit and I would argue that I would love to see a significant delay, substantial not modest.

"If you look at the pure numbers and the absolute risk and potential benefits, you really have to treat a lot of patients and subject them to unnecessarily no benefit and potential risk to get a benefit in a smaller percentage, however that benefit is not quantified."

"So we have a 5 to 6 percent risk of osteonecrosis of the jaw, versus a four month delay, median, in time to bone metastases, most of them being symptomatic," said Sandler.

"And obviously the sponsor believes that the risk-benefit ratio favors the agent, but it's up to us to give our advice to FDA. At some point even the sponsor would say the benefit is too small.

"What if it was two months benefit in delay to next metastasis—or maybe if there was a 10 percent risk of ONJ—you would say the risk-benefit ratio is not favorable?

"And it's not necessarily a fair question, but I was wondering if the sponsor could speculate on when they feel the risk-benefit ratio could be unfavorable for their product."

"The question of how much benefit is enough benefit is a really legitimate question and it's very much a judgment call," said Roger Dansey, vice president and regional medical director at Amgen.

"I think that at one point that we were trying to make and let me emphasize it again, is that you can dial down the number needed to treat. You can make sure that there's more benefit by limiting the use of the drug or requiring even higher risk people than we let into the study based on the PSA doubling time.

"So you can try to adjust this use of the drug if you feel like the benefit risk is where you want to see it. Now I don't think it's possible to come up with a number."

"At times get focused on the wrong thing. We have to look at the patient as a whole," said temporary voting member Aman Buzdar, vice president of clinical research at MD Anderson Cancer Center.

"Are we making the biology of the patient's disease any different? The answer is no. Symptom-free duration is very similar between the two subgroups.

"I think we need to have robust data. Data that shows: yes, we are making an impact on the patient's quality of life, quantity of life and symptom-free interval. But the answer is no, no, no."

Explaining his vote, Wilson said: "At the end of the day, this continues to be a surrogate endpoint, because the clinical effect of a radiographic finding of bone metastasis is further behind.

"I think it would have been better to use SRE, but I would have been quite pleased with using this, but the magnitude of the benefit would have to have been considerably longer. And that's something that we simply did not see here."

"If we were dealing with breast cancer—and we were discussing radiation to the chest wall in women at high risk of local recurrence on the chest—a four month duration of control would be considered a huge failure," said temporary voting member Ronald Richardson, a consultant for the Mayo Clinic.

"A 6 percent incidence of ONJ in this group, particularly in view of the fact that these were asymptomatic patients, I think is a very distressing issue," said Richardson. "Sixty percent of these patients have persisting ONJ, and conceivably will have this until it's either subject to more surgery or they will have it until they die."

"You need to consider an early vs. late intervention scenario, and the fact is that you can't compare those using bone-metastasis-free survival," said committee member Brent Logan, professor of biostatistics at the Medical College of Wisconsin.

"So approval based on that endpoint would require a very high bar to be met."

Effort To Salvage a Failed Trial

On Feb. 9, ODAC voted 10-3 with one abstention against approval of Dacogen (decitabine) for the treatment of acute myelogenous leukemia in adults age 65 or over who are not considered candidates for induction therapy.

Dacogen is currently approved in the U.S. for the treatment of myelodysplastic syndrome.

The new drug application was based on a randomized, controlled, open-label trial, comparing decitabine to either low-dose cytarabine or best supportive care as first-line therapy. The trial's primary endpoint was overall survival.

The trial failed to meet its primary endpoint, and therefore was a failed trial. Conclusions based on analysis of secondary endpoints were, therefore, not valid.

Median overall survival was 7.7 months for the decitabine arm, and 5.0 months for the control arm (HR=0.85 [95% CI 0.69-1.04, p=0.11).

The sponsor performed an unplanned analysis a year after the planned analysis, with the p value falling below the p value falling below the 0.05 threshold.

In the FDA briefing document delivered to ODAC, the agency noted: "The study failed to demonstrate benefit based on statistical interpretation. Given that overall survival is the gold standard, we ask the Oncologic Drugs Advisory Committee to discuss the risks and benefits of Dacogen for the treatment of newly diagnosed AML in patients 65 and older."

Part of the debate focused on whether a p value should be defined as a cutoff.

"I think the agency has brought this to us because they don't have a concrete feeling about this, they recognize that there are grey areas," said Wyndham Wilson, ODAC chair. "And that this is what comes to us—grey areas."

"We're not a slave to a p value here, with .05, okay?" said Richard Pazdur, director of FDA's Office of Hematology Oncology Products. "It's not that it has to be .05, and forget everything else. Obviously .05 is a conventional level of statistical significance as it's properly defined—but there are the things that come to bear here."

The committee voted against recommending approval to FDA, with many members who voted 'no' stating that the trial did not satisfactorily meet its primary endpoint.

In explaining his vote supporting approval for decitabine, Wilson said: "I actually feel that the totality of the data did favor making this drug available. I see this as an extremely rare setting. I just couldn't get stuck on the fact that the primary endpoint p value was .11.

"Given that there is so little out there—but that this drug is out there, and that we know its safety profile—I really felt that I wanted to err on the side of choice. I felt that the data was sufficiently robust to approve this drug and have that choice available to physicians and patients."

Mikkael Sekeres, a committee member and associate professor of medicine at the Cleveland Clinic Taussig Cancer Institute, voted against approval.

"Elderly leukemia patients are desperate for new drugs. New drugs that could prolong their survival and make them feel better. And unfortunately, decitabine is not that drug," said Sekeres. "It didn't do any better than what has been tried and true and used for decades, and we need to encourage companies like Eisai to continue looking for better drugs that will improve the survival and the quality of life of our elderly leukemia patients."

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Appropriations

Budget Proposes $3 Million Increase to NCI Funding Level

(Continued from page 1)

This would allow for a $3 million increase in NCI's budget, to $5.069 billion; a $64 million increase for the National Center for Advancing Translational Sciences, to $639 million; and other relatively small budget adjustments. There is no proposed change for the NIH Common Fund of $545 million.

According to the proposal, NIH estimates that it will be able to support 35,888 research project grants, including 9,145 new and competing grants. RPGs will represent 53.3 percent of the NIH budget.

NIH estimates that this will be 672 more new-and-competing RPGs compared to 2012. The NIH-wide estimated cost for a new RPG is $431,000. There will, however, be a drop in the number of non-competing grants—to 24,837, down 777 compared to last year.

An HHS breakdown of funding level by institute can be found on page 8.

"We appreciate the recognition of the importance of basic research at NIH in the budget narrative, but the proposed funding level for the agency is substantially below that necessary to sustain the current research effort," said Joseph LaManna, president of the Federation of American Societies for Experimental Biology.

"Without an increase in funding, however, NIH will have to sacrifice valuable lines of research in order to keep up with rising costs and new mandates."

In a statement, the American Association for Cancer Research estimated that—due to the rise in biomedical inflation—the NIH has lost approximately $5.5 billion in purchasing power since 2003.

"The potential for continued flat funding could not come at a worse time because the opportunities for turning our growing scientific knowledge into effective strategies for the treatment and prevention of cancer have never been greater," said Judy Garber, president of AACR and director of the Center for Cancer Genetics and Prevention at Dana-Farber Cancer Institute and professor of medicine at Harvard Medical School.

Margaret Foti, CEO of AACR, said: "If we are going to continue to make significant progress, it will require a renewed commitment on the parts of President Obama and Congress to provide the NIH and National Cancer Institute with sustained funding increases."

AACR said it plans to call on Congress to increase NIH funding by $2 billion, up to $33 billion.

In Brief

In Earlier Appearance, Nevins Blamed "Data Corruption"

(Continued from page 1)

"There was no explanation other than there was a manipulation," Nevins said in a 60 Minutes interview. "A manipulation of the data, a manipulation of somebody's credentials and a manipulation of a lot of people's trust… It simply couldn't be random. It simply couldn't be inadvertent. It had to have been based on a desire to make something work."

This conclusion differs from the version of events Nevins presented to a committee of the Institute of Medicine March 29, 2011, where he said that "data corruption" had produced incorrect results, leading to a wave of retractions in the world's premier scientific journals.

Errors occurred when data used to develop a model for predicting patient response to therapy were commingled with data used to validate the predictor, Nevins said to the IOM Committee on the Review of Omics-Based Tests to Predict Patient Outcomes in Clinical Trials less than one year ago.

"Data corruption of the form that I just described is not something that one generally anticipates," said Nevins said at the time (The Cancer Letter, April 1, 2011).

The CBS News report can be found here: http://www.cbsnews.com/video/watch/?id=7398478n

ST. JUDE Children's Research Hospital was honored by Tennessee Gov. Bill Haslam, who declared February "St. Jude Month" in the state, in recognition of its 50th anniversary. The hospital was founded Feb. 4, 1962, by the late entertainer Danny Thomas.

"In the nearly four decades I've been at St. Jude, I've had the privilege of watching the organization grow from one star-shaped building to a sprawling campus of about 2.5 million square feet of research, clinical and administrative space," said William Evans, director and CEO of St. Jude. "When I started, there were a few hundred people on staff. Now we have more than 3,700 employees."

MOLECULARHEALTH Inc. has entered into a five-year research agreement with FDA to evaluate and refine the company's Molecular Analysis of Side Effects software system, intended to support mechanism-based drug safety assessment and prediction.

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NATIONAL INSTITUTES OF HEALTH

(dollars in millions)

	2011	2012	2013	2013 +/- 2012
Institutes				
National Cancer Institute	5,050	5,066	5,069	+3
National Heart, Lung and Blood Institute	3,065	3,075	3,076	+1
National Institute of Dental and Craniofacial Research	409	410	408	-2
Natl Inst. of Diabetes & Digestive & Kidney Diseases	1,939	1,945	1,942	-3
National Institute of Neurological Disorders and Stroke	1,619	1,624	1,625	–
National Institute of Allergy and Infectious Diseases	4,768	4,485	4,495	+10
National Institute of General Medical Sciences	2,368	2,427	2,379	-48
Eunice K. Shriver Natl Inst. of Child Health & Human Dev	1,316	1,320	1,321	+1
National Eye Institute	700	702	693	-9
National Institute of Environmental Health Sciences:				
Labor/HHS Appropriation	683	685	684	-1
Interior Appropriation	79	79	79	–
National Institute on Aging	1,099	1,102	1,103	+1
Natl Inst. of Arthritis & Musculoskeletal & Skin Diseases	533	535	536	–
Natl Inst. on Deafness and Communication Disorders	414	416	417	+2
National Institute of Mental Health	1,475	1,479	1,479	+1
National Institute on Drug Abuse	1,049	1,052	1,054	+2
National Institute on Alcohol Abuse and Alcoholism	458	459	457	-2
National Institute of Nursing Research	144	145	144	–
National Human Genome Research Institute	511	512	511	-1
Natl Institute of Biomedical Imaging and Bioengineering	345	338	337	-1
Natl Institute on Minority Health and Health Disparities	276	276	279	+3
Natl Center for Complementary and Alternative Medicine	127	128	128	–
National Center for Advancing Translational Sciences	554	575	639	+64
Fogarty International Center	69	70	70	–
National Library of Medicine	371	373	381	+8
Office of the Director	1,454	1,457	1,429	-28
Buildings and Facilities	50	125	125	–
Total, Program Level	**30,926**	**30,860**	**30,860**	–
Less Funds Allocated from Other Sources				
PHS Evaluation Funds (NLM)	-8	-8	-8	–
Type 1 Diabetes Research (NIDDK) /1	-150	-150	-150	–
Total, Discretionary Budget Authority	**30,767**	**30,702**	**30,702**	–
Labor/HHS Appropriation	**30,688**	**30,623**	**30,623**	–
Interior Appropriation	**79**	**79**	**79**	–
FTE	18,573	18,573	18,387	-186

1/ These mandatory funds were pre-appropriated in P.L. 110-275, the Medicare Improvements for Patients and Providers Act of 2008, and P.L. 111-309, the Medicare and Medicaid Extenders Act of 2010.

From the HHS 2013 Budget Briefing

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FDA's Center for Drug Evaluation and Research will work with MolecularHealth to incorporate non-proprietary molecular and clinical endpoints of regulatory interest into the program, along with non-proprietary information on patient populations, drug promiscuity, molecular modes of action and mechanisms of disease.

The software system uses information about drug modes of action and the molecular implications of interacting treatments, co-morbidities and genetic profiles to enable a more precise assessment of drug safety. It enables the exploration and analysis of adverse event information from both statistical and molecular perspectives and provides analytical and visualization tools to support the detection and validation of drug-related safety issues.

"Drug safety monitoring and detection have become increasingly important and complex endeavors that depend heavily on a static, binary, observational system," said David Jackson, chief scientific officer of MolecularHealth. "We believe that MolecularHealth's predictive approach to understanding the molecular basis of adverse events will complement the agency's current mode of drug safety assessment to advance the promise of precision medicine."

THE CLEVELAND CLINIC has entered into an affiliation agreement with **Cadence Health**, a merger of the Central DuPage and Delnor hospitals in Illinois. The agreement covers adult medical oncology services.

The agreement will provide Cadence Health with access to evidence-based protocols and treatment plans, expanded research and clinical trials, and additional resources in training and education. Patients will be able to access subspecialty care and expanded support services.

"Our affiliation with Cadence Health will help enhance patient care by providing the latest treatments available along with greater access to clinical trials," said Brian Bolwell, chairman of the clinics's Taussig Cancer Institute.

"We will work together to achieve the highest standards of care and the best outcomes for our patients."

In 2010, it had nearly 300,000 patient visits and enrolled approximately 1,300 patients in 247 clinical trials.

THE OHIO STATE UNIVERSITY Medical Center was renamed Feb. 10, to the **Wexner Medical Center at The Ohio State University,** after benefactor Leslie Wexner.

In over 30 years, Wexner and his affiliates have donated more than $200 million to the university. Last year, Wexner and the Limited Brands Foudnation made a gift of $100 million to the university's medical center, the James Cancer Hospital, and the Wexner Center for the Arts.

Wexner has served 16 years on the university's board of trustees. As the current board chair, he helped guide a $1 billion expansion of the medical center.

As a founding member and the first chair of The Ohio State University Foundation Board, and later as a member of the University Campaign Steering Committee, Wexner helped grow the university's endowment, which now totals more than $2 billion.

The Wexners have been lead supporters of Pelotonia, an annual bike tour research fundraiser, that in three years raised more than $25 million for cancer research at the university's Comprehensive Cancer Center—James Cancer Hospital and Solove Research Institute.

Ohio State's medical center includes the college of medicine; six hospitals; a unified physician practice; a network of primary and specialty care practices; more than a dozen research centers and institutes; and 20 core laboratories.

MICHAEL SEVERINO was named senior vice president of global development and corporate chief medical officer of **Amgen Inc**.

Formerly vice president of global development, Severino will replace **Sean Harper**, who was made executive vice president of research and development.

Severino joined Amgen eight years ago as senior director of Inflammation Early Development. Subsequently, he held the role of head of the proof-of-concept group in medical sciences.

In 2006, he took on leadership of the Inflammation Therapeutic Area in Global Clinical Development and was promoted in 2007 to vice president of global development.

Prior to joining Amgen, Severino held positions at Merck Research Laboratories across a wide range of therapeutic areas, including: vaccines and infectious diseases, oncology, diabetes and metabolic disorders, and neurosciences.