DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute (NCI)

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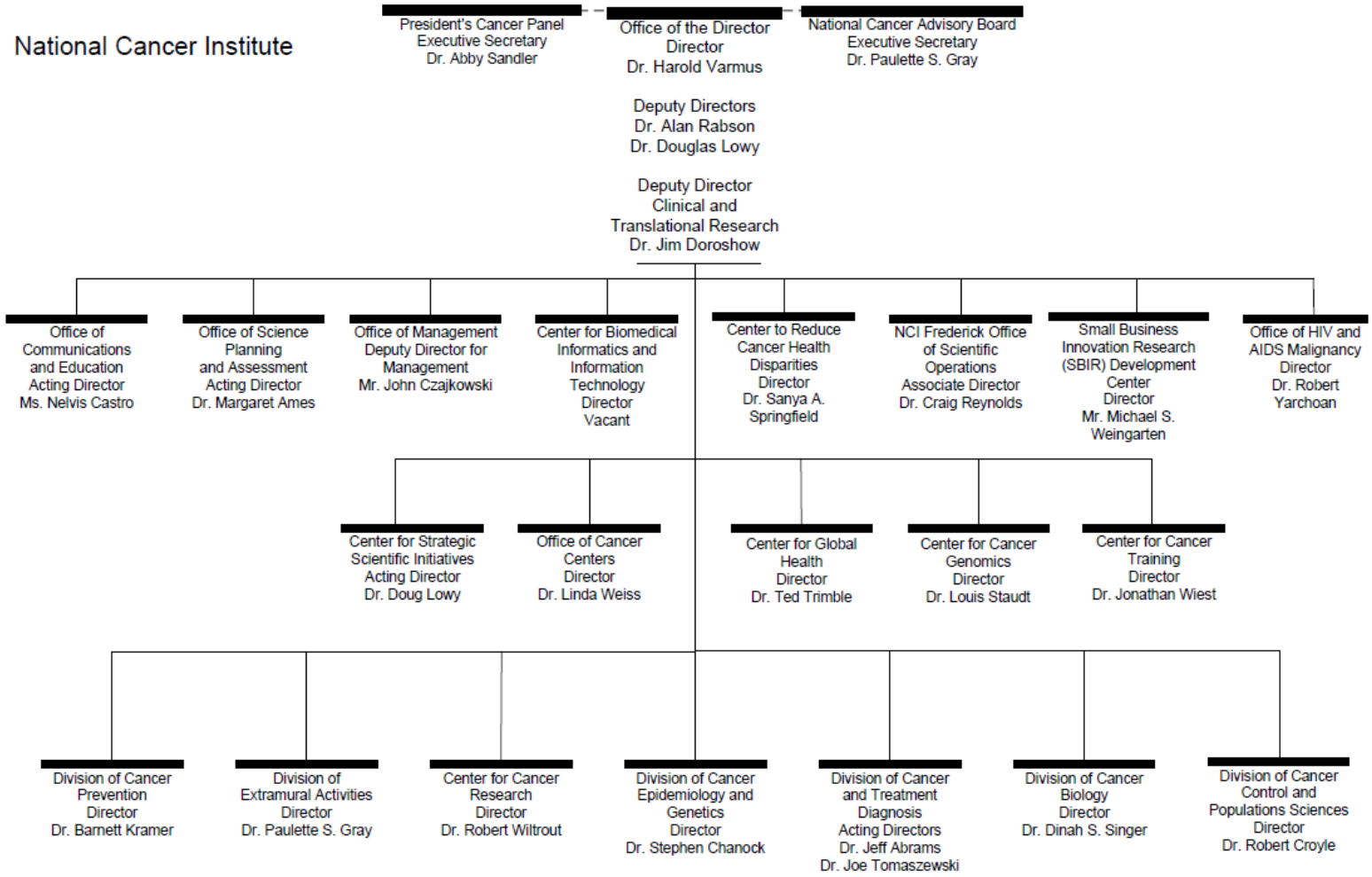
National Cancer Institute



NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out section 301 and title IV of the PHS Act with respect to cancer, ⟦$4,923,238,000⟧ *$4,930,715,000*, of which up to $8,000,000 may be used for facilities repairs and improvements at the National Cancer Institute—Frederick Federally Funded Research and Development Center in Frederick, Maryland.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Amounts Available for Obligation[1]

(Dollars in Thousands)

Source of Funding	FY 2013 Actual	FY 2014 Enacted	FY 2015 President's Budget
Appropriation	$5,072,183	$4,923,238	$4,930,715
Type 1 Diabetes	0	0	0
Rescission	-10,144	0	0
Sequestration	-254,589	0	0
Subtotal, adjusted appropriation	$4,807,450	$4,923,238	$4,930,715
FY 2013 Secretary's Transfer	-28,044	0	0
OAR HIV/AIDS Transfers	5,637	6,307	0
Comparative transfers to NLM for NCBI and Public Access	-5,678	-6,774	0
National Children's Study Transfers	4,077	0	0
Subtotal, adjusted budget authority	$4,783,442	$4,922,771	$4,930,715
Unobligated balance, start of year	0	0	0
Unobligated balance, end of year	0	0	0
Subtotal, adjusted budget authority	$4,783,442	$4,922,771	$4,930,715
Unobligated balance lapsing	-106	0	0
Total obligations	$4,783,337	$4,922,771	$4,930,715

[1] Excludes the following amounts for reimbursable activities carried out by this account:
FY 2013 - $36,779 FY 2014 - $60,000 FY 2015 - $60,000

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Budget Mechanism - Total[1]

(Dollars in Thousands)

MECHANISM	FY 2013 Actual		FY 2014 Enacted[2]		FY 2015 President's Budget		FY 2015 +/- FY 2014	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Projects:								
Noncompeting	3,562	$1,486,513	3,356	$1,482,108	3,175	$1,453,041	-181	-$29,067
Administrative Supplements	*(214)*	38,444	*(216)*	32,437	*(216)*	28,901	*(0)*	-3,536
Competing:								
Renewal	156	79,644	158	80,838	160	81,646	2	808
New	939	324,301	951	329,166	960	332,458	9	3,292
Supplements	0	0	0	0	0	0	0	0
Subtotal, Competing	1,095	$403,945	1,109	$410,004	1,120	$414,104	11	$4,100
Subtotal, RPGs	4,657	$1,928,901	4,465	$1,924,549	4,295	$1,896,046	-170	-$28,503
SBIR/STTR	159	71,260	159	77,357	159	77,003	0	-354
Research Project Grants	4,816	$2,000,161	4,624	$2,001,906	4,454	$1,973,049	-170	-$28,857
Research Centers:								
Specialized/Comprehensive	261	$533,951	261	$549,970	261	$566,414	0	$16,444
Clinical Research	0	0	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0	0	0
Comparative Medicine	0	0	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0	0	0
Research Centers	261	$533,951	261	$549,970	261	$566,414	0	$16,444
Other Research:								
Research Careers	387	$67,525	387	$69,551	387	$71,630	0	$2,079
Cancer Education	96	34,466	96	35,500	96	36,561	0	1,061
Cooperative Clinical Research	120	235,443	181	255,506	181	263,146	0	7,640
Biomedical Research Support	0	0	0	0	0	0	0	0
Minority Biomedical Research Support	4	376	4	388	4	399	0	11
Other	98	49,728	98	51,220	98	52,751	0	1,531
Other Research	705	$387,538	766	$412,165	766	$424,487	0	$12,322
Total Research Grants	5,782	$2,921,650	5,651	$2,964,041	5,481	$2,963,950	-170	-$91
Ruth L Kirchstein Training Awards:	FTTPs		FTTPs		FTTPs		FTTPs	
Individual Awards	416	$17,103	411	$17,563	419	$17,914	8	$351
Institutional Awards	943	48,685	938	50,351	957	51,358	19	1,007
Total Research Training	1,359	$65,788	1,349	$67,914	1,376	$69,272	27	$1,358
Research & Develop. Contracts	433	$610,474	433	$658,282	433	$667,426	0	$9,144
(SBIR/STTR) (non-add)	*(66)*	*(38,877)*	*(66)*	*(38,250)*	*(66)*	*(43,250)*	*(0)*	*(5,000)*
Intramural Research	1,863	811,572	1,863	835,645	1,863	841,809	0	6,164
Res. Management & Support	1,240	366,054	1,240	376,530	1,240	380,258	0	3,728
Res. Management & Support (SBIR Admin) (non-add)	*(0)*	*(244)*	*(0)*	*(2,000)*	*(0)*	*(2,000)*	*(0)*	*(0)*
Construction		0		0		0		0
Buildings and Facilities[3]		7,904		8,000		8,000		0
Total, NCI	3,103	$4,783,442	3,103	$4,922,771	3,103	$4,930,715	0	$7,944

[1] All items in italics and brackets are non-add entries. FY 2013 and FY 2014 levels are shown on a comparable basis to FY 2015.

[2] The amounts in the FY 2014 column take into account funding reallocations, and therefore may not add to the total budget authority reflected herein.

[3] The appropriations act provides that "up to $8,000,000 may be used for facilities repairs and improvements" at the NCI Federally Funded Research and Development Center in Frederick, Maryland.

Major Changes in the Fiscal Year 2015 President's Budget Request

Major changes by budget mechanism and/or budget activity detail are briefly described below. Note that there may be overlap between budget mechanisms and activity detail and these highlights will not sum to the total change for the FY 2015 President's Budget for NCI, which is $7.944 million more than the FY 2014 level, for a total of $4,930.715 million.

Non-Competing Research Project Grants (RPGs: -$29.067 million; total $1,453.041 million): During FY 2015, NCI will continue to support its established commitment base for non-competing Research Project Grants (RPGs). However, NCI's noncompeting RPG commitment base for FY 2015 is declining by 3.1 percent due to the declining number of RPGs that NCI approved during previous fiscal years.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Summary of Changes[1]

(Dollars in Thousands)

FY 2014 Enacted				$4,922,771
FY 2015 President's Budget				$4,930,715
Net change				$7,944
CHANGES	**FY 2015 President's Budget**		**Change from FY 2014**	
	FTEs	**Budget Authority**	**FTEs**	**Budget Authority**
A. Built-in:				
1. Intramural Research:				
a. Annualization of January 2014 pay increase & benefits		$312,558		$770
b. January FY 2015 pay increase & benefits		312,558		2,309
c. Zero more days of pay (n/a for 2015)		312,558		0
d. Differences attributable to change in FTE		312,558		0
e. Payment for centrally furnished services		126,909		354
f. Increased cost of laboratory supplies, materials, other expenses, and non-recurring costs		402,341		1,157
Subtotal				$4,590
2. Research Management and Support:				
a. Annualization of January 2014 pay increase & benefits		$189,137		$466
b. January FY 2015 pay increase & benefits		189,137		1,397
c. Zero more days of pay (n/a for 2015)		189,137		0
d. Differences attributable to change in FTE		189,137		0
e. Payment for centrally furnished services		30,616		85
f. Increased cost of laboratory supplies, materials, other expenses, and non-recurring costs		160,505		773
Subtotal				$2,721
Subtotal, Built-in				$7,311

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Summary of Changes - Continued[1]

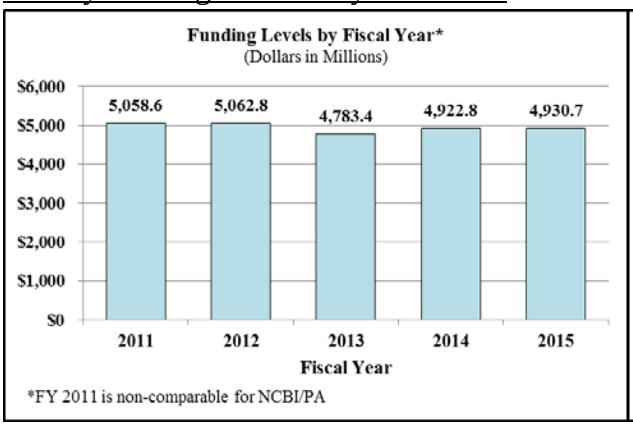
(Dollars in Thousands)

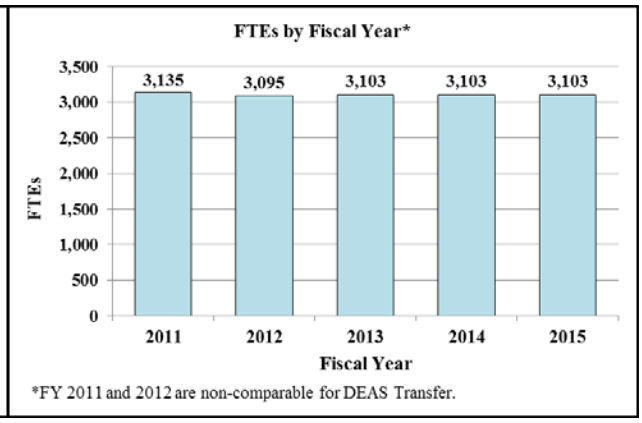
CHANGES	FY 2015 President's Budget		Change from FY 2014	
	No.	Amount	No.	Amount
B. Program:				
1. Research Project Grants:				
a. Noncompeting	3,175	$1,481,942	-181	-$32,603
b. Competing	1,120	414,104	11	4,100
c. SBIR/STTR	159	77,003	0	-354
Subtotal, RPGs	4,454	$1,973,049	-170	-$28,857
2. Research Centers	261	$566,414	0	$16,444
3. Other Research	766	424,487	0	12,322
4. Research Training	1,376	69,272	27	1,358
5. Research and development contracts	433	667,426	0	9,144
Subtotal, Extramural		$3,700,648		$10,411
	FTEs		FTEs	
6. Intramural Research	1,863	$841,809	0	$1,574
7. Research Management and Support	1,240	380,258	0	1,007
8. Construction		0		0
9. Buildings and Facilities		8,000		0
Subtotal, Program	3,103	$4,930,715	0	$12,992
Total changes				$7,944

[1] The amounts in the Change from FY 2014 column take into account funding reallocations, and therefore may not add to the net change reflected herein.

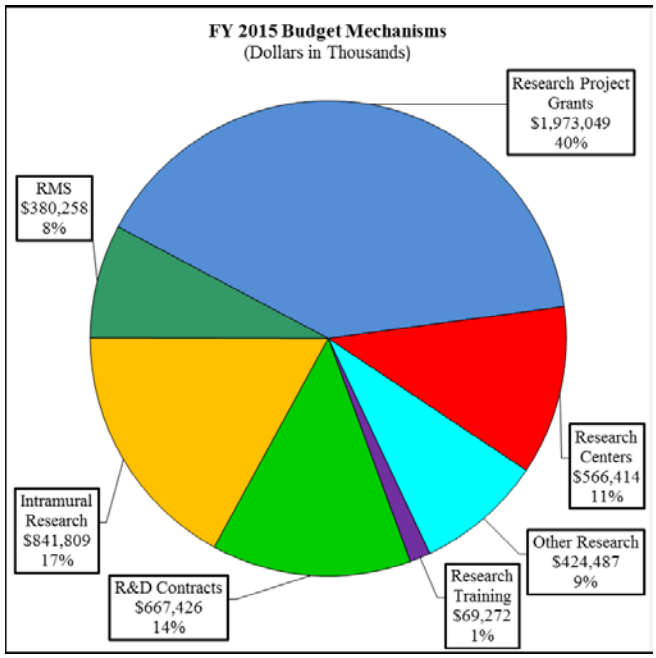
Fiscal Year 2015 Budget Graphs

History of Budget Authority and FTEs:

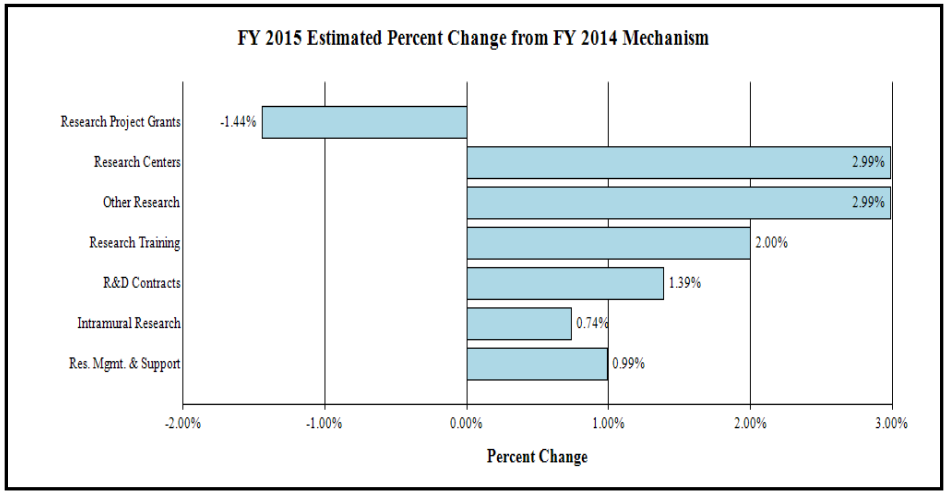




Distribution by Mechanism:



Change by Selected Mechanism:



NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Budget Authority by Activity[1]
(Dollars in Thousands)

	FY 2013 Actual		FY 2014 Enacted [2]		FY 2015 President's Budget		FY 2015 +/- FY 2014	
Extramural Research	**FTE**	**Amount**	**FTE**	**Amount**	**FTE**	**Amount**	**FTE**	**Amount**
Detail								
Understanding the Mechanisms of Cancer		$712,790		$731,605		$734,285		$2,680
Understanding the Causes of Cancer		1,212,295		1,244,296		1,248,853		4,557
Improve Early Detection and Diagnosis		438,179		449,746		451,393		1,647
Develop Effective and Efficient Treatments		1,146,684		1,176,954		1,181,264		4,310
Cancer Prevention and Control		176,853		181,522		182,187		665
Cancer Centers		560,123		574,909		577,014		2,105
Research Workforce Development		162,559		166,850		167,461		611
Buildings and Facilities		7,904		8,000		8,000		0
Subtotal, Extramural		**$4,417,388**		**$4,533,882**		**$4,550,457**		**$16,575**
Intramural Research (non-add)	***1,863***	***$811,572***	***1,863***	***$835,645***	***1,863***	***$841,809***	***0***	***$6,164***
Research Management & Support	**1,240**	**$366,054**	**1,240**	**$376,530**	**1,240**	**$380,258**	**0**	**$3,728**
TOTAL	**3,103**	**$4,783,442**	**3,103**	**$4,922,771**	**3,103**	**$4,930,715**	**0**	**$7,944**

[1] Includes FTEs whose payroll obligations are supported by the NIH Common Fund.

[2] The amounts in the FY 2014 column take into account funding reallocations, and therefore may not add to the total budget authority reflected herein.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2014 Amount Authorized	FY 2014 Enacted	2015 Amount Authorized	FY 2015 President's Budget
Research and Investigation	Section 301	42§241	Indefinite	$4,922,771,000	Indefinite	$4,930,715,000
National Cancer Institute	Section 401(a)	42§281	Indefinite		Indefinite	
Total, Budget Authority				$4,922,771,000		$4,930,715,000

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
2005	$4,870,025,000	$4,870,025,000	$4,894,900,000	$4,865,525,000
Rescission				($40,267,000)
2006	$4,841,774,000	$4,841,774,000	$4,960,828,000	$4,841,774,000
Rescission				($48,418,000)
2007	$4,753,609,000	$4,753,609,000	$4,799,063,000	$4,797,639,000
Rescission				$0
2008	$4,782,114,000	$4,870,382,000	$4,910,160,000	$4,890,525,000
Rescission				($85,437,000)
Supplemental				$25,559,000
2009	$4,809,819,000	$4,975,039,000	$4,958,594,000	$4,968,973,000
Rescission				$0
2010	$5,150,170,000	$5,150,170,000	$5,054,099,000	$5,103,388,000
Rescission				$0
2011	$5,264,643,000		$5,256,409,000	$5,103,388,000
Rescission				($44,810,787)
2012	$5,196,136,000	$5,196,136,000	$5,001,623,000	$5,081,788,000
Rescission				($9,604,579)
2013	$5,068,864,000		$5,084,227,000	$5,072,183,421
Rescission				($10,144,367)
Sequestration				($254,588,730)
2014	$5,125,951,000		$5,091,885,000	$4,923,238,000
Rescission				$0
2015	$4,930,715,000			

Justification of Budget Request

National Cancer Institute

Authorizing Legislation: Section 301 and title IV of the Public Health Service Act, as amended.
Budget Authority (BA):

	FY 2013 Actual	FY 2014 Enacted	FY 2015 President's Budget	FY 2015 + /- FY 2014
	$4,783,442,221	$4,922,771,000	$4,930,715,000	+$7,944,000
FTE	3,103	3,103	3,103	0

Program funds are allocated as follows: Competitive Grants/Cooperative Agreements; Contracts; Direct Federal/Intramural and Other.

Director's Overview

This is a time of remarkable opportunity in cancer research. Armed with broad knowledge about how various kinds of cancer arise and with powerful new research tools, the NCI is well equipped to accelerate progress towards preventing, diagnosing, and treating cancer more effectively. The NCI budget for FY 2015 will allow the NCI to build on the tremendous progress already made in many areas of cancer research, with the aim of improving outcomes for patients with all types of cancer.

Because the NCI's mission is ambitious – to reduce the incidence, morbidity, and mortality of all types of cancer – and requires a deep understanding to better control these disorders, its research program spans a wide range of disciplines (from behavioral to molecular to clinical research). Furthermore, the NCI must balance resources to: maintain its 68 NCI-designated cancer centers and its large intramural research program; fund thousands of grants to individual scientists and teams in many fields; support a national infrastructure for clinical research; and train the next generation of researchers in diverse disciplines.

The following brief summaries discuss some recent accomplishments and new vistas in five areas of NCI-supported research – genomics, cancer immunology, targeted therapeutics, bioinformatics, and prevention – to illustrate the breadth and pace of progress.

Cancer genomics is a collection of "high throughput" methods used in the study of cancers to identify small mutations, rearrangements, and chemical modifications of DNA and to detect changes in the production of RNA and protein. These methods have dramatically altered our understanding of how cancer develops, identified the molecular signatures that can be used to diagnose cancer more precisely, and provided new targets for therapeutic intervention. Two major initiatives – TCGA (The Cancer Genome Atlas) and TARGET (Therapeutically Applicable Research to Generate Effective Treatments) – have addressed nearly twenty common adult cancers and several less common cancers that occur in adults and children, revealing both

tissue-specific patterns of genetic changes and changes that are common to several types of cancers. These findings have been recently reported in leading publications.

In the past year, TCGA provided comprehensive characterizations of acute myeloid leukemia, endometrial cancer, and clear cell renal carcinoma (ccRCC), among others. The ccRCC study, for example, showed that certain mutations can produce changes in enzyme levels that affect cell metabolism in ways that correlate with clinical outcomes. As these massive surveys come to conclusion, the NCI's Center for Cancer Genomics (CCG) is leading efforts to define all of the genes likely to be altered in as few as two percent of common types of cancer; to incorporate genomic findings into the design of clinical trials; to extend genomic methods to the analysis of early tumors, metastases, and individual cancer cells; and to develop new approaches that better define the functional consequences of the identified mutations. Furthermore, some of the surprising findings from the TCGA and TARGET projects – such as the involvement of genes that govern the chemistry of chromosomal proteins, that influence cell metabolism, and that guide the processing of RNAs and proteins – are influencing the study of cancer biology throughout the NCI's programs. These new efforts are likely to enlarge our understanding of carcinogenesis and open new frontiers for preventing, diagnosing, and treating cancers.

Cancer immunology is a rapidly advancing field that, in just the past few years, has dramatically altered our understanding of host defenses in response to cancers. It has also produced new and well-validated methods for treating cancer – (i) with antibodies that attack proteins on cancer cell surfaces and (ii) with techniques that modulate the complex behavior of the immune system.

For several years, monoclonal antibodies against cancer cell proteins have been used to treat lymphomas, leukemias, and several cancers, such as breast and colorectal cancer; more recently, immunotoxins have been created by genetic engineering to fuse antibodies with parts of bacterial toxins to selectively kill cancer cells. Several immunotoxins developed in the NCI intramural program have induced remissions in late stage cases of mesothelioma, ovarian, triple-negative breast cancer, drug-resistant hairy cell leukemia, and childhood acute lymphoblastic leukemia.

There is also great optimism within the science community about modulating the immune system by introducing novel antigen receptors into cancer-killing T cells and, especially, by infusing antibodies that interfere with a system that impedes the response to cancer cells. In 2011, for treatment of advanced melanoma, the FDA approved a monoclonal antibody, called ipilimumab, that inhibits a molecule called CTLA-4, a "brake" on immune cells. Some melanoma patients treated with ipilimumab are still alive several years after completing treatment. Other inhibitory antibodies suppress a protein called PD-1, another immune system "brake." In 2013, one PD-1 inhibitor (lambrolizumab) received "breakthrough" designation by the FDA, enabling its rapid use in clinical trials. For these accomplishments and the promise of further developments, "immunotherapy of cancer" was named this year's Breakthrough of the Year by *Science* magazine.

Targeted therapies, based on the use of drugs that inhibit specific proteins implicated in the behavior of cancer cells, are now being developed and tested for their effects in patients with many types of cancer. Over the past few years, several such drugs have been approved by the

FDA to treat cancers of blood cells, lung cancer, melanoma, and other cancers, and many more are in development. This activity has accelerated because of discoveries by TCGA and other genomics work, by cancer biologists working on cell signaling pathways, and by chemists and structural biologists identifying new ways to inhibit proteins.

These targeted therapies add to the existing arsenal for treating cancer – surgery, radiotherapy, and conventional chemotherapy – and, like the new immunotherapies, they require an enhanced infrastructure for performing clinical trials. To accommodate these needs, the NCI's Cooperative Groups for the conduct of clinical trials has been transformed into a more efficient, highly integrated network better able to address rapid advances in cancer biology. In March 2014, NCI will formally launch the new system, called the NCI National Clinical Trials Network (NCTN). Trials with targeted drugs also require molecular tests and interpretation of results, and tools to accomplish these goals have been incorporated into the NCTN in the design of new trials, in conjunction with the NCI's CCG. For instance, the NCI has launched NCI-MATCH (Molecular Analysis for Clinical Choice) to test a wide repertoire of new targeted agents in patients with refractory cancers that have undergone molecular analysis for genetic changes that can be targeted.

The NCI is also organizing a retrospective study of "Exceptional Responders" – patients whose cancer responded unexpectedly to drug treatment. A few such cases have already revealed unexpected mutations that appear to explain the unusual responses. Still, while pursuing a path that leads to "precision medicine," the NCI must also maintain its capacity to test new ways to deploy the currently dominant means of therapy. For instance, a recent study of 790 patients with metastatic prostate cancer showed markedly increased survival in men who received chemotherapy when starting anti-androgenic hormone therapy, a result that is likely to change clinical practice for a cancer that continues to kill about 30,000 American men annually.

Two important obstacles to precision medicine are the difficulties of (i) interfering with certain common cancer-causing mutations and (ii) overcoming the resistance to targeted agents that occurs frequently during treatment with targeted agents.

(i) Mutant RAS proteins are perhaps the most prominent potential targets for new therapies that the academic and commercial research sectors have failed to target with inhibitory drugs. Yet the importance of the RAS gene family in cancer has been clear for over thirty years; one family member, K-RAS, is mutated in more than 90 percent of pancreatic adenocarcinomas, about 40 percent of colorectal cancers, and about 25 percent of lung adenocarcinomas. For this reason, the NCI recently launched the RAS Project, a large-scale collaboration between investigators at the NCI's Frederick National Laboratory for Cancer Research and those in NCI's intra- and extramural communities. The RAS Project is motivated in part by new developments in the study of RAS proteins, including new information about their structural properties, binding of specific RAS proteins to mutant-specific inhibitors, interactions with other cellular proteins required for function, and new tests for genes required to allow RAS mutants to exert their effects.

(ii) Drug resistance commonly emerges in cancers being treated with targeted therapies, allowing disease to progress. Over the past decade, NCI-supported studies have revealed several

mechanisms by which resistance occurs, including additional mutations affecting the target molecules, mutations in related genes, and changes in gene expression. In some cases, especially chronic myeloid leukemias, drugs that overcome resistance have been identified, developed and FDA-approved. But in other situations, resistance to targeted drugs remains a major impediment to success, and the NCI is making major investments to study this problem.

Bioinformatics, the management of enormous sets of molecular and clinical data, has emerged as a critical component of NCI's toolkit to study cancer in all of its manifestations. In work that ranges from cancer genomics, to cell signaling, and to clinical trials, the proper collection, analysis, storage, retrieval, and distribution of "big data" are critical elements of the Institute's charge. The NCI's Center for Bioinformatics and Information Technology (CBIIT), especially in conjunction with the CCG and the Division of Cancer Treatment and Diagnosis (DCTD), is responsible for addressing these responsibilities. Part of the current effort involves the use of "cloud computing" to work with the vast (petabyte) amounts of genomic data generated by TCGA and TARGET projects and to assemble and ultimately integrate clinical data in manageable forms. In addition, the NCI has announced its intention to join the emerging Global Alliance for Genomics and Health and expects to be engaged heavily in Alliance activities designed to share genomic and clinical data about cancer in ethically responsible ways.

Prevention of cancer remains the most desired goal of the NCI. While complete avoidance of cancer may be impossible to achieve, since cancers often arise through spontaneous mutations, the control of tobacco use, vaccination against cancer-causing viruses (human hepatitis B virus and human papillomaviruses), sunlight avoidance, and regulation of dietary and carcinogenic occupational substances (such as asbestos) have already reduced the incidence and hence the mortality rates of many cancers. For instance, between 2001 and 2010, largely due to the earlier reductions in tobacco use, there was a 25 percent decrease in male death rates and an eight percent decrease in female death rates due to lung cancer, which is the major cause of death from cancer in the United States. Likewise, vaccination with current HPV vaccines can drastically reduce the incidence and mortality of several types of cancer, including cervical, anal, and oropharyngeal cancers.

Still, the NCI recognizes that these successes are incomplete, and therefore invests heavily in efforts to address several pertinent behavioral and biological questions. For instance, despite dramatic declines in the use of tobacco, about 18 percent of Americans continue to smoke; new behavioral approaches are needed to convince young people not to use tobacco and to convince current smokers to quit. Use of HPV vaccines remains far from the desired levels among adolescent girls and boys in the United States, as the February 2014 report from the President's Cancer Panel will discuss. Better methods to promote the use of these potentially lifesaving vaccines are needed, at the same time as the dosing schedules and the protective breadth of the vaccines are improved. Another important aspect of preventing cancer deaths is the use of screening methods to detect cancers early. The U. S. Preventive Services Task Force recently released its recommendation that low dose helical CT scanning be used to screen for lung cancer among elderly smokers and former smokers; this recommendation was based largely on the NCI's National Lung Screening Trial, and the NCI is continuing to analyze the data and materials from this study and to improve the methodology for the screening test. In all of these domains of cancer prevention, the NCI collaborates with other U.S. agencies and with cancer

research organizations to improve cancer control within the United States and around the world. The NCI's new Center for Global Health supports the relevant international activities, partly in conjunction with the NCI-designated cancer centers.

Summary. An important measure of the overall success of NCI's work is the annual "Report to the Nation," which describes trends in the incidence and death rates in the United States for many types of cancer. As has now been true for over a decade, the most reliable indicator – death rates from all cancers combined for men, women, and children – continues to decline by about one and a half percent per year. This reduction represents the savings of an enormous number of years of life and can be ascribed in large measure to the work of the NCI to prevent and treat cancers more effectively. Still, although mortality rates have been decreasing for most cancers, progress has not occurred as rapidly as desired, and for some cancers the numbers have not improved or have worsened. Thus, much work remains. But the overall success apparent from both the public health data and recent achievements in the laboratory and clinical sciences inspires the NCI's conviction that expanded efforts on all frontiers of cancer research will produce better health in the United States and around the globe.

Overall Budget Policy:
The FY 2015 President's Budget request is $4,930.715 million, an increase of $7.944 million, or 0.2 percent above the FY 2014 Enacted level.

Program Descriptions and Accomplishments

NCI conducts basic and applied research across five broad scientific areas:

Understanding the Causes of Cancer
Understanding the Mechanisms of Cancer
Improving Early Detection and Diagnosis
Developing Effective and Efficient Treatments
Improving Cancer Prevention and Control

To achieve its research goals across these five areas, NCI issues grants to support investigator-initiated research, to conduct clinical trials, and to support initiatives that address healthcare disparities. NCI also funds cross-cutting initiatives such as cancer centers and funds programs to develop a strong workforce of cancer researchers. NCI conducts intramural research, operates research facilities at the NCI-Frederick Campus, and provides essential management and support for its cancer research activities.

Investigator-initiated research project grants represent a large portion of the research investment in NCI's five scientific areas. For example, during FY 2013, NCI issued 5,782 new and non-competing grant awards across all grant mechanisms, including 3,306 traditional (R01) grants and 441 exploratory (R21) grants.

The following narratives highlight some of the programs, projects, and progress within each NCI scientific area and identify management and administrative programs that support NCI cancer research.

Understanding the Causes of Cancer: Cancer develops through the complex interplay of genetic background, lifestyle, and environmental factors. In some cases, cancer risk is strongly influenced by inheriting a mutation of a single gene or a combination of genes. More commonly, however, cancer risk is determined by external factors, such as exposure to tobacco or infectious agents. The effects of these factors may differ depending on a person's genetic background.

NCI seeks to better understand the complex interplay of factors that cause or contribute to cancer by supporting investigator-initiated studies through extramural grants and its intramural research programs. These studies range from small scale laboratory research to large scale projects that use population cohorts or case-controlled comparisons of subpopulations. They may also involve modeling to predict cancer risks within an individual or population.

Budget Policy:
The FY 2015 President's Budget request is $1,248.853 million, an increase of $4.557 million, or 0.4 percent compared with the FY 2014 Enacted level.

NCI's past investments in population cohorts provide a robust framework for identifying factors associated with cancer risk. For example, NCI's Cohort Consortium – a large, international collaboration of cohorts that includes data on more than four million people – is evaluating the role of genetic susceptibility, lifestyle, environmental exposures, and gene-environment interactions for a range of cancers. Recent findings uncovered by the Cohort Consortium include:

- The continued increase in risk of death from cigarette smoking among women.
- Many new genetic susceptibility regions for common cancers (breast, prostate, lung, colon, and bladder) and uncommon cancers (osteosarcoma and chronic lymphocytic leukemia).
- A biomarker that may predict head and neck cancers caused by human papillomavirus (HPV).

Looking to the future, the Cohort Consortium offers the promise of answering important questions related to cancer risks in African-Americans, Hispanics, and other understudied populations in the United States, the interaction between environmental and genetic exposures, and the effect of medical procedures, treatments, and practices on cancer risks.

In addition to its association with other health risks, obesity is associated with increased risks of cancers of the esophagus, breast (postmenopausal), endometrium (the lining of the uterus), colon and rectum, kidney, pancreas, thyroid, gallbladder, and possibly other cancer types. Through the National Collaborative on Childhood Obesity Research (NCCOR), NCI is partnering with four NIH institutes, the Centers for Disease Control and Prevention (CDC), the Robert Wood Johnson Foundation, and USDA to improve the efficiency, effectiveness, and application of childhood obesity research. NCCOR seeks to:

- Increase surveillance of childhood obesity.
- Identify, design, and evaluate practical and sustainable interventions.
- Support coordination and collaboration to halt and reverse childhood obesity.

During 2013, NCI developed two web-based NCCOR tools: the Catalogue of Surveillance Systems and the Measures Registry. Combined, these web tools have experienced approximately 527,000 visits by individuals who accessed these tools. Through the Catalogue of Surveillance Systems, for the first time researchers and practitioners can assess a range of childhood obesity resources, identify possible gaps, and plan innovative multilevel obesity prevention research. The Measures Registry contains almost 1,000 measures and is an invaluable resource for researchers interested in using standard measures to describe, monitor, and evaluate interventions, particularly those focused on policy and the environment.

NCI supports research to identify new causes of cancer and to expand understanding about the recognized causes of cancers. For instance, identifying Human Papillomavirus (HPV) many years ago as the causative infectious agent of cervical cancer led to major advances in understanding the mechanism by which cervical cancer develops. This led to development of HPV vaccines and improved screening for cervical cancer using FDA-approved products to test for HPV. NCI-supported research also contributed to guidelines that improved HPV screening.

Understanding Mechanisms of Cancer: Cancer is driven by alterations of the genome (DNA). As a consequence, abnormal kinds and amounts of proteins are made that cause changes in a variety of aberrant molecular processes, and result in inappropriate tumor cell survival and inadequately controlled tumor growth. Achieving a deeper understanding of the changes that take place in the collection of diseases called cancer is critical to developing new and improved approaches to prevent, diagnose, and treat cancer.

To understand the mechanisms of cancer better, NCI supports large-scale, high-throughput studies of the genes, proteins, and pathways altered in cancer. In addition, NCI supports studies related to basic cell biology, cell interactions, angiogenesis, immune responses, and other areas of research that are essential to better understand the mechanisms of cancer. NCI also supports laboratory studies in model systems, including animal models, to investigate the functions of molecules and systems.

Budget Policy:
The FY 2015 President's Budget request is $734.285 million, an increase of $2.680 million, or 0.4 percent compared with the FY 2014 Enacted level.

NCI conducts a number of large and small programs to understand the mechanisms of cancer. These initiatives sometimes bring groups of researchers together to answer scientific questions that a single laboratory cannot easily address. Examples include Program Project grants that support a range of areas of cancer research and disease-specific grants, such as the Specialized Programs of Research Excellence (SPORE) grants.

The Cancer Target Discovery and Development (CTD2) Network is accelerating the use of molecular data gained through TCGA (see box below) and other genome-focused efforts. The

goal of the CTD2 Network is to develop new treatments through gene validation studies, high-throughput screening of molecules, and research on mouse models.

The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative uses high-throughput platforms to identify genetic abnormalities in tumors from pediatric patients. One TARGET project identified a new subclass of acute lymphoblastic leukemia with a high-risk of recurrence that is associated with novel chromosomal translocations, an abnormality that occur when two chromosomes break and then recombine to form novel chromosomes. These findings have the potential to benefit patients in the near term because the translocations often affect genes in signaling pathways for which targeted drugs are already available.

Program Portrait: The Cancer Genome Atlas (TCGA)*

FY 2014 Level: $11.1 million
FY 2015 Level: $8.2 million
Change: -$2.9 million

The Cancer Genome Atlas (TCGA) is a major joint initiative of the NCI and the National Human Genome Research Institute (NHGRI) to catalog the genetic mutations and other alterations that occur in more than 20 human cancers. The goal of TCGA is to increase our understanding of cancer and to improve cancer diagnosis, treatment, and prevention.

Basic research over the past four decades has determined that cancer results from a series of critical changes (mutations) in the genes of the cells that give rise to the tumor. Despite some commonalities in the genes whose abnormalities lead to cancer, recent research has highlighted the complexity of these changes and the heterogeneity of changes that lead to a given cancer. TCGA has therefore undertaken the important task of developing a comprehensive analysis, at the genomic level, of the alterations in DNA and RNA found in various tumor types. TCGA is cataloging the range of these alterations and identifying recurring changes, especially changes that may be vulnerable to inhibitors.

This comprehensive approach, made possible by technical advances in sequencing beyond those used to sequence the human genome, has resulted in substantial progress in understanding the biology of cancer and beginning to apply the findings to the diagnosis and treatment of cancer. For example, TCGA researchers identified four genomic-based subtypes of endometrial cancer and uncovered important similarities between endometrial, ovarian, and breast cancers. In acute myeloid leukemia, they identified at least one key mutation in every case, a finding that has short- and long-term clinical implications. In glioblastoma multiforme, tumor recurrence occurs through pathways that drive epigenetic changes. This finding may have important clinical implications because epigenetic changes, in contrast to genetic changes, are potentially reversible, which suggests the possibility of treatment approaches to prevent recurrences. The extensive sequence information developed by TCGA is stored in databanks that the entire cancer research community can access.

As described in the section devoted to Developing Effective and Efficient Treatments, NCI is initiating several clinical trials of targeted therapies that will use the large TCGA datasets as baseline information and will correlate the response to treatment with the genomic abnormalities found in the tumors.

* The FY 2014 and FY 2015 TCGA budget reflects the maturing of the TCGA program. During FY 2013, TCGA achieved its program goal, accruing 10,000 tumor samples for characterization. Successfully meeting the 10,000-sample milestone allows NCI to reduce funding for TCGA. As this occurs, NCI's Center for Cancer Genomics (CCG) will increase the level of resources devoted to the next phase of activity: characterizing additional tumor samples to identify new therapeutic targets for treating cancer and to understand the impact that the cancer genome has on how a patient responds to treatment.

The Integrative Cancer Biology Program (ICBP) promotes an integrative approach to cancer biology through greater collaboration between cancer biologists and scientists from the fields of mathematics, physics, information technology, imaging sciences, and computer science. ICBP researchers developed a systematic time and dose-dependent method to identify drug combinations that are effective in killing cancer cells. This approach depends on changes in the order and duration of drug exposure. Researchers found that blocking the epidermal growth factor receptor, a protein found in excess quantities or mutated form in many cancers, including breast cancer, dramatically sensitizes a subset of "triple negative" breast cancers to DNA damage if the drugs are given sequentially, but not simultaneously. This provides a deeper understanding of cancer signaling networks and suggests an approach for developing combination therapies.

By using a systems biology approach to study prostate cancer, researchers identified a pattern of gene expression (gene signature) that may help to predict indolent vs. aggressive cancer from early stage tumors and thus could lead to prognostic assays for monitoring patients on active surveillance and thereby avoid over-diagnosis.

The trans-NCI Innovative Molecular Analysis Technologies (IMAT) program exemplifies a high-risk, high-reward investment to catalyze development of highly innovative technology and potentially to transform cancer research. IMAT, which provides seed money to support high-risk research, has resulted in many successful commercialized technologies for clinical application or use in cancer research. Since the program's inception, 657 NCI awards have supported development of nearly 500 technologies. Of these, more than 100 are now commercially available or accessible through collaboration with NCI-supported scientists.

The Tumor Microenvironment Network (TMEN) aims to understand the role of host stromal cells (connective tissue cells of any organ) in the development of tumors and in therapeutic responses. TMEN has three primary scientific objectives:

- Encourage fundamental research to gain a comprehensive understanding of the composition of stromal cells and their role in tumor initiation, progression, and metastasis
- Delineate mechanisms of tumor-stroma interactions in human cancer
- Identify the mechanisms by which tumor stroma may affect responses to treatment.

The Center for Biomedical Informatics and Information Technology, in collaboration with the Center for Cancer Genomics, is coordinating a program to support the design, implementation, and documentation of a new model for computational analysis and sharing very large biological data sets. The goal is to develop a set of Cancer Genomics Cloud Pilots that will provide more open and secure access to genomic data that NCI generates. NCI expects that program outcomes will include the capability for high-priority analysis and a better understanding of how to scale up from cloud pilots to meet future needs. Although cloud computing will be a valuable tool to support studies related to the mechanisms of cancer, this capability will be equally valuable to other NCI scientific areas, including clinical trials and other types of patient-oriented research.

Improving Early Detection and Diagnosis: Many of the deadliest cancers are diagnosed at late stages because of a lack of screening tests to identify cancers earlier, when they may respond to treatment. Investigator-initiated research project grants are the primary mechanism that NCI

relies on to support and improve early detection and diagnosis of cancer, but other larger research programs also play important roles. NCI researchers are working to identify molecules – nucleic acids, proteins, metabolites, and other substances – and develop imaging methods to identify the presence of cancer cells earlier, and thereby help guide decisions about treatment. NCI also supports research to assess the risks associated with screening and early detection, and to ensure that the potential harms of screening do not outweigh the benefits.

Budget Policy:
The FY 2015 President's Budget request is $451.393 million, an increase of $1.647 million, or 0.4 percent above the FY 2014 Enacted level.

In addition to its potential application in other areas of cancer science, nanotechnology has promising potential to support early cancer detection and diagnosis. The NCI Alliance for Nanotechnology in Cancer supports development of materials and instruments for imaging that are capable of recognizing tumors at their early stages. Alliance investigators recently developed a highly sensitive diagnostic system for colon cancer. The system consists of a targeted gold nanoparticle imaging agent and a detection device designed to work with a standard clinical endoscope. Using this approach, endoscopists could quickly distinguish between normal and precancerous tissues and identify lesions that are commonly missed using traditional techniques.

NCI is also working to improve existing approaches for cancer screening. In 2010, the National Lung Screening Trial (NLST) of high-risk current and former smokers announced that screening with low-dose helical computed tomography (CT) decreased lung cancer mortality by 20 percent. However, many abnormalities detected by CT were noncancerous. To help reduce false-positive readings, the NCI Cancer Biomarkers Research Group is working to integrate imaging and biomarker approaches to improve lung cancer screening, detection, and diagnosis.

In 2000, NCI established the Cancer Intervention and Surveillance Modeling Network (CISNET), a consortium of statisticians that use biostatistical modeling to improve the understanding of cancer control interventions in prevention, screening, and treatment. CISNET researchers develop models using data from randomized controlled trials, meta-analyses, observational studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of clinical and public health interventions. CISNET created models for the NLST that the U.S. Preventive Services Task Force used to make recommendations on CT screening. Relying on NCI-supported models, the Task Force recommended screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults between the ages of 50 to 75 years. For adults older than age 75, the Task Force recommendations consider the age of the patient and other patient-specific factors.

Compared to the general population, some HIV-infected individuals who are successfully treated with combination antiretroviral therapy are at increased risk – by more than 100-fold – of developing anal cancer. To address this concern, NCI is supplementing the AIDS Malignancy Clinical Trials Consortium with a study that will determine the effectiveness of treating anal high-grade squamous intraepithelial lesions (HSIL) to reduce the incidence of anal cancer in HIV-infected men and women. In addition to determining whether treating anal HSIL is effective in reducing the incidence of anal cancer, the study will collect specimens to examine

the molecular pathogenesis of progression from HSIL to cancer, to discover biomarkers to identify those at highest risk, and to identify new avenues for treating anal HSIL and cancer.

Developing Effective and Efficient Treatments: Research into cancer therapeutics has many facets that go beyond developing and testing of drugs, radiotherapy, immunotherapy, and surgery, and include many aspects of cancer care, including control of symptoms and palliation of fatal cancers. Developing new knowledge about the molecular fingerprints of tumors and how cancer cells interact with their environments also creates opportunities to design interventions to target specific molecules and signaling pathways. The goal of such studies is to match patients with the treatments most likely to help them based on specific characteristics of their tumors, an effort now termed "precision medicine."

To support the development of effective and efficient cancer treatments, NCI invests in basic and translational research. These investments have identified therapeutic targets, and commercial interests have validated and developed many of these targets. NCI-supported clinical research is developing and testing interventions at many sites through country, at the NIH Clinical Center, and at extramural treatment centers and through clinical research networks.

Budget Policy:
The FY 2015 President's Budget request is $1,181.264 million, an increase of $4.310 million, or 0.4 percent above the FY 2014 Enacted level.

A number of clinical initiatives are taking advantage of cancer genomics and data from TCGA. For example, NCI is developing a new national clinical trial, Molecular Analysis for Clinical Choice (NCI-MATCH) through the NCI-supported Cooperative Group network. The NCI-MATCH trial will determine the genetic profile of tumors for up to 3,000 patients who experience continued tumor growth after receiving standard treatments. The NCI-MATCH profiles will be used to assign targeted treatment therapies to patients. This effort and similar trials could lead to the definitive testing of new drugs and broader uses of available drugs.

The field of cancer immunology is a particularly promising area of research. NCI's intramural program has developed several immunotoxins that induced remission in late stage cases of mesothelioma, ovarian and triple-negative breast cancer, drug resistant hairy cell leukemia, and childhood acute lymphoblastic leukemia. NCI extramural researchers are also improving the feasibility, targeting, and safety of Chimeric Antigen Receptor T cells.

NCI also is investigating ways to harness a patient's own immune system to treat cancer. The Center for Excellence in Immunology is an intramural research program focused on discovering, developing, and delivering novel immunologic approaches – including cell-based therapies, therapeutic vaccines, and novel cytokines – to prevent and treat cancer. Basic discoveries in immunology are moving into early clinical trials through the Cancer Immunotherapy Trials Network (CITN), which performs trials with new drugs that modulate the immune system. These trials emphasize real-time immune system monitoring to predict tumor response and resistance.

Two NCI-supported studies published in 2013 report a beneficial change in treatment for Burkitt's and primary mediastinal B cell lymphomas, two rare cancers of the immune system that

strike children and adults, especially immunocompromised or HIV-positive patients. Intramural scientists at NCI achieved high rates of response to treatment that uses either a shorter course or a lower dose of combination chemotherapy. These promising protocols have increased the time to tumor progression and have increased patient survival. Importantly, these new protocols used less chemotherapy over a shorter period of time and reduced the toxicity that develops in response to current standard of care treatments. The new treatment protocol also eliminated the need for radiation therapy for patients with primary metastinal B-cell lymphoma. Based on this success, larger clinical trials in children and adults are under way.

Program Portrait: RAS Program*

FY 2014 Level: $10.0 million
FY 2015 Level: $10.0 million
Change: $0.0 million

Approximately 30 percent of all cancers involve mutations of RAS genes. The mutant proteins encoded by the three most important RAS genes appear to play an essential role in the origins of a majority of these tumors. For example, mutant KRAS appears in 95 percent of the most common form of pancreatic cancer, 45 percent of colorectal cancers, and 25 percent of the most common form of lung cancer. Many tumors that harbor these mutations have a poor prognosis and respond poorly to standard treatments.

Although basic research in the 1980s identified the critical role of RAS in these tumors, efforts to develop treatments to target mutant RAS have been unsuccessful. However, recent scientific advances offer the promise of new approaches to address these cancers. These advances include chemical approaches to develop inhibitors, knowledge of the signaling networks regulated by RAS, new technology to assess signaling networks, techniques to validate targets, methods to conduct structural analysis, and the availability of mouse models.

NCI launched the RAS Initiative during FY 2013 to harness these and other advances to target tumors driven by mutant RAS. The initiative uses a hub-and-spoke model to connect researchers at NCI's Frederick National Laboratory for Cancer Research to a nationwide network of academic and industry collaborators.

The RAS Initiative differs from the usual disease-specific approach used to develop treatments for organ-specific cancers because the initiative targets a molecular abnormality that is responsible for a range of cancers. Elements of the RAS initiative will develop standardized reagents for the RAS research community and confirm the critical role of RAS in the tumors being studied. The project will also test new therapeutic approaches that have the potential to inhibit the vast majority of mutant RAS proteins, as well as therapeutic approaches that may be effective for specific RAS mutations. Given that three specific RAS mutations occur in nearly 100,000 new tumors per year in the United States, developing of an effective inhibitor against any one of the mutations would be a substantial scientific advance.

*The amounts in this estimate only reflect the FY 2014 and FY 2015 costs associated with the RAS Initiative that NCI launched during FY 2013: connecting researchers at NCI's Frederick National Laboratory for Cancer Research to a nationwide network of academic and industry collaborators. In addition to the amounts in this estimate, NCI also has a broad portfolio of extramural and intramural research related to RAS within many mechanisms of the NCI budget.

The Cancer Therapy Evaluation Program (CTEP) supports an early phase experimental therapeutics clinical trials program that oversees clinical development of new agents. CTEP also assesses various cancer-relevant molecular changes for developing targeted drug agents designed to exploit specific abnormalities. CTEP recently redesigned this program, creating an NCI Experimental Therapeutics Clinical Trials Network (ETCTN) that develops novel anticancer agents for patients most likely to respond to specific agents, based on appropriate biomarkers.

ETCTN clinical trials are designed to identify the dose, schedule, and early evidence of activity to help guide disease-specific clinical trials conducted by the National Clinical Trials Network.

NCI is working to expand access to clinical trials for patients treated in community settings and expand access to trials by minority and underserved populations. The Community Clinical Oncology Programs (CCOPs) enrolls patients into approved trials for cancer prevention, control, and treatment. CCOPs enrolls one-third of all participants in NCI trials nationwide. The 49 current CCOPs represent 340 hospitals and 2,760 physicians. The Minority-Based Community Clinical Oncology Programs (MBCCOPs) enroll patients into approved trials in areas with at least 30 percent underserved or minority populations. The 16 current MBCCOPs represent 50 hospitals and 500 physicians, including 100 minority investigators. MBCCOPs have an average of 64 percent minority participants in trials at their sites. The NCI Community Cancer Centers Program is a network of 21 community hospitals in 16 states dedicated to improving the quality of cancer care for patients from rural, inner city, and underserved communities.

NCI also invests in research to elucidate factors that contribute to cancer health disparities. The Basic Research in Cancer Health Disparities Initiative supports research to understand the biological mechanisms for cancer disparities among racial and ethnic populations. The Centers for Population Health and Health Disparities supports transdisciplinary research involving social, behavioral, biological, and genetic studies to improve knowledge of the causes of health disparities and to devise methods to prevent, diagnose, and treat disease and promote health.

Improving Cancer Prevention and Control: Cancer prevention research draws on knowledge of the mechanisms and causes of cancer. Through education, behavior modification, vaccination, and policy changes, we can reduce cancer risk by reducing exposure to environmental factors. Therapies that interfere with processes that initiate cancer also have the potential to counteract the elevated risk of cancer where genetic or biologic factors are involved. To improve cancer prevention and control, NCI supports research to understand the factors that influence cancer outcomes, quality of care, quality of life, and cancer-related health disparities.

Budget Policy:
The FY 2015 President's Budget request is $182.187 million, an increase of $0.665 million, or 0.4 percent compared with the FY 2014 Enacted level.

HPV vaccination has the potential to drastically reduce or eliminate the incidence and mortality of the several types of cancer caused by HPV infection. However, the currently available vaccines are underutilized in the United States, despite evidence from clinical trials and evidence from the CDC of their efficacy, safety, and potential impact. The President's Cancer Panel, which monitors the development and execution of the activities of the National Cancer Program, has held several workshops and will soon release a report that will make recommendations on how to increase the uptake of the HPV vaccines. In a development that may improve vaccine uptake, NCI research has determined that, compared with older adolescents, younger adolescents mount a stronger immune response to the vaccine. This could make it possible to reduce the number of recommended vaccine doses in this age group from three to two – and perhaps eventually to only one dose.

NCI is working to better understand effective cancer prevention and control interventions, from the molecular level to the policy level. Numerous studies have shown that aspirin can reduce the incidence and mortality rates of several common cancers by as much as 30 percent. The NCI is supporting the ASPirin in Reducing Events in the Elderly (ASPREE) study, sponsored by the National Institute on Aging. ASPREE is testing the effects of aspirin in healthy, elderly participants from the United States and Australia. Biospecimens from the study will be used to examine the molecular mechanisms responsible for the cancer preventive effects of aspirin, including genomic changes. In June 2013, NCI co-sponsored a meeting with NIDDK to assess the possible protective effects of the diabetes drug metformin against some types of cancer.

Program Portrait: Therapy to Stimulate Immune Response*

FY 2014 Level: $184.0 million
FY 2015 Level: $185.8 million
Change: $1.8 million

In the past, several monoclonal antibodies directed at proteins present on the surface of tumor cells have been approved by FDA to treat cancer. More recently, therapeutic antibodies have been developed to target molecules encoded by non-cancer cells, to direct potentially therapeutic cells of the immune system to the tumor cells, or to direct toxins to the tumor cells.

One treatment uses a therapeutic antibody to target a protein called CTLA-4, a normal product of the immune system that decreases immune response. Employing an antibody to inhibit CTLA-4 should increase the body's immune response to the cancer, and thereby help fight the tumor. In March 2011, FDA approved a therapeutic CTLA-4 antibody, known as ipilimumab, to treat advanced melanoma. This is the first FDA-approved treatment directed at a protein produced by a non-tumor target. This approach is being expanded to other experimental treatments directed at non-tumor targets. For example, another therapeutic antibody that is directed to a related protein, called PD-1, has shown promise in early phase clinical trials.

Ipilimumab was the outgrowth of basic research conducted during the 1990s in mice that focused on the regulation of the immune system. NCI-funded researchers identified CTLA-4 and its function, and this work led to the hypothesis that antagonizing this function might be useful for treating cancer. At the outset, this hypothesis was too uncertain to attract interest from the pharmaceutical industry, which led NCI to support much of the early research on the therapeutic antibody that eventually led to the approved treatment. Currently, NCI is supporting further research to understand why ipilimumab works in some patients but not others. Answering this question has the potential to lead to more optimal use of the antibody, and to alternative approaches for non-responsive patients.

Another experimental approach that seeks to harness the therapeutic potential of cells of the immune system is to genetically engineer T cells from the patient to express what are called chimeric antigen receptors (CARs). CARs have the dual property of activating the T cells in which they are expressed and directing the T cells to the tumor cells because the CARs contain both a strong T cell activation domain and antibody domain that recognizes a protein expressed on the tumor cells. The NCI supported this approach since its inception in the 1990's, and excellent clinical responses are now being seen in patients with B cell lymphomas and leukemias.

Attaching a toxin to an antibody that can bind to the surface of tumor cells has also led to long-term therapeutic responses, first in a form of leukemia, and more recently in a solid tumor, mesothelioma. The NCI has provided long-term support for this promising experimental approach.

*The amounts in this estimate reflect extramural and intramural funding for immunology research in areas such as therapeutic vaccines, therapeutic antibodies and non-antibody, non-cellular immune stimuli. The CTLA-4 and ipilimumab examples featured in this program portrait are two of the important results that emerged from NCI's broad immunology research portfolio.

Tobacco use is the leading cause of preventable death and disease worldwide. The World Health Organization has estimated that globally, smoking is responsible for almost six million deaths annually (amounting to 15 percent of male deaths and seven percent of female deaths). Based on current patterns, by the year 2030, smoking-related deaths are projected to rise to more than eight million annually. While tobacco use has been slowly declining in most high-income nations, including the United States, it is increasing in many low- and middle-income countries.

NCI and the Fogarty International Center, together with other partners, launched the International Tobacco and Health Research and Capacity Building Program. This program supports transdisciplinary research and capacity-building projects that address the burden of tobacco consumption in low- and middle-income nations. This collaborative program supports observational, intervention, and policy research of local importance, and builds capacity in these regions for epidemiological and behavioral research, prevention, treatment, communications, health services, and policy research. The program is designed to promote international cooperation between investigators in the United States and other high-income nations that conduct research on tobacco control and scientists and institutions in countries where tobacco consumption is an urgent public health concern.

The global success in controlling infectious diseases suggests that using a similar approach – coordinated basic research, translational research, clinical trials, implementation science, and capacity building – will also be effective against non-communicable diseases such as cancer. With this approach in mind, NCI established the Center for Global Health (CGH) in 2011 to advance global cancer research, build expertise, and leverage resources across borders, in an effort to reduce cancer deaths worldwide, especially in low- and middle-income countries. CGH engages other NCI divisions, offices, and centers, as well as the NIH, to create sustainable international partnerships to address global gaps in research and scientific training. CGH also disseminates information and best practices to improve cancer research and cancer control.

To address emerging developments related to smoking, in November 2013, NCI co-sponsored the NIH Electronic Cigarette Workshop: Developing a Research Agenda. The goal of the workshop was to identify the key research gaps relating to electronic cigarettes and their effects on human physiology and health, the potential for addiction to these products, as well as issues related to smoking cessation and other public health concerns.

Since 1973, the Surveillance, Epidemiology and End Results (SEER) program has been collecting data on cancer incidence, mortality, and prevalence. SEER regularly samples approximately 26 percent of the U.S. population, and it has obtained information on 5.7 million cancer cases. SEER expands the number of samples by 380,000 cases each year. This database is a critical resource for identifying cancer trends. It also serves as a powerful resource for researchers that includes population data associated by age, sex, race, year of diagnosis, and geographic areas. SEER data is used to create the Annual Report to the Nation on the Status of Cancer, a collaboration of the NCI, the CDC, the American Cancer Society, and the North American Association of Central Cancer Registries.

The December 2013 report revealed that overall cancer mortality rates for men and women continued to decline at an average rate of about 1.5 percent per year, after adjusting for age. It

also described the prevalence and impact of comorbidities (other coexisting noncancerous diseases) in patients over 66 years of age with breast, prostate, lung, or colorectal cancer. Because comorbidities affect cancer care and survival, NCI has funded several grants that specifically consider issues related to comorbidities in cancer patients.

Cancer Centers: The NCI-designated cancer centers program recognizes centers around the country that meet rigorous criteria for state-of-the-art programs in multidisciplinary cancer research. These centers put significant resources into developing research programs, faculty, and facilities that will lead to better approaches to prevention, diagnosis, and treatment of cancer.

Budget Policy:
The FY 2015 President's Budget request is $577.014 million, an increase of $2.105 million, or 0.4 percent above the FY 2014 Enacted level.

The 68 NCI-designated cancer centers perform a substantial proportion of the research that NCI supports through various NCI grant and contract programs. This research includes high quality laboratory, clinical, and population science to improve the basic understanding of cancer and cancer prevention, diagnosis, and treatment. NCI center awards support core facilities required for effective research center as well as innovative pilot projects in new investigational areas. Investigators at NCI-designated cancer centers have played central roles in many groundbreaking findings in cancer research in recent decades.

In addition to 68 cancer centers, NCI supports more than 100 other centers that conduct basic and clinical science to advance new and diverse approaches to prevent, detect, diagnose, and treat cancer.

Research Workforce Development: NCI is committed to supporting the training and development of a strong workforce of cancer researchers that spans the career continuum. NCI's investment in early-stage investigators helps attract strong talent and ensure the strength of future cancer research. In addition to NCI's direct support for training, our support for established investigators – scientists that have proven their ability to conduct robust science – also fosters mentoring for the next generation of cancer researchers.

Budget Policy:
The FY 2015 President's Budget request is $167.461 million, an increase of $0.611 million, or 0.4 percent above the FY 2014 Enacted level.

NCI supports many opportunities for training in basic, clinical, and behavioral research through training programs, individual fellowships, research career development awards, and other training and education. NCI training occurs at universities and institutions across the country. In addition, NCI supports research experiences for high school, college, and medical school students; graduate students performing thesis work; and many domestic and foreign post-doctoral fellows in NCI's intramural research programs. Beneficiaries of training and career development grants span the career continuum, including pre-doctoral candidates, postdoctoral fellows, new faculty in independent research positions, and established midcareer investigators.

NCI is committed to enhancing diversity within the cancer research workforce. Many efforts in this area are coordinated through the NCI Center to Reduce Cancer Health Disparities. Initiated in 2001, the Partnerships to Advance Cancer Health Equity (PACHE) aims to create stable, comprehensive, and long-term partnerships between institutions serving underserved populations and NCI-designated cancer centers in the areas of research, training and career development, education, and outreach. Through these collaborations, the institutions that form PACHE work to train scientists from underrepresented backgrounds in cancer and health disparities research, and to reach racially and ethnically diverse communities regarding cancer advances.

The Continuing Umbrella of Research Experiences (CURE) program provides students and trainees educational and career development opportunities that extend from high school through professional appointment. This holistic training program constitutes a pipeline through which students and trainees from groups that are underrepresented in health research gain the skills and knowledge needed to become successful independent scientists.

NCI's Division of Cancer Prevention supports a unique postdoctoral Cancer Prevention Fellowship Program (CPFP) designed to provide a strong training foundation for scientists and clinicians. Trainees earn an MPH degree at an accredited university during the first year, followed by mentored research with NCI investigators. Graduates of the program have varied post-fellowship careers, ranging from academic careers at NCI-designated cancer centers, to research opportunities in industry, to leadership positions at NCI.

Research Management and Support: NCI research management and support personnel fulfill a key and indispensable role by supporting and enabling the activities and success of all NCI-funded activities.

Budget Policy:
The FY 2015 President's Budget request is $380.258 million, an increase of $3.728 million, or 1.0 percent above the FY 2014 Enacted level.

Buildings and Facilities: The renovation and improvement funds support and maintain the operation of facilities at NCI's Frederick, Maryland campus and advance the scientific missions of NCI, NIH, other government agencies, and the extramural community.

Budget Policy:
The FY 2015 President's Budget request is $8.000 million, the same amount as the FY 2014 Enacted level.

NATIONAL INSTITUTES OF HEALTH
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Budget Authority by Object Class[1]
(Dollars in Thousands)

		FY 2014 Enacted	FY 2015 President's Budget	FY 2015 +/- FY 2014
Total compensable workyears:				
	Full-time employment	3,103	3,103	0
	Full-time equivalent of overtime and holiday hours	4	4	0
	Average ES salary	$172	$174	$2
	Average GM/GS grade	12.1	12.1	0.0
	Average GM/GS salary	$99	$100	$1
	Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$98	$99	$1
	Average salary of ungraded positions	$132	$134	$1
	OBJECT CLASSES	**FY 2014 Enacted**	**FY 2015 President's Budget**	**FY 2015 +/- FY 2014**
	Personnel Compensation			
11.1	Full-Time Permanent	$212,818	$214,946	$2,128
11.3	Other Than Full-Time Permanent	119,450	120,644	1,194
11.5	Other Personnel Compensation	5,514	5,569	55
11.7	Military Personnel	4,434	4,478	44
11.8	Special Personnel Services Payments	45,520	45,975	455
11.9	**Subtotal Personnel Compensation**	**$387,735**	**$391,613**	**$3,877**
12.1	Civilian Personnel Benefits	$103,200	$106,812	$3,612
12.2	Military Personnel Benefits	3,238	3,270	32
13.0	Benefits to Former Personnel	0	0	0
	Subtotal Pay Costs	**$494,173**	**$501,695**	**$7,522**
21.0	Travel & Transportation of Persons	$13,437	$13,475	$38
22.0	Transportation of Things	954	956	3
23.1	Rental Payments to GSA	1,624	1,628	5
23.2	Rental Payments to Others	21	22	0
23.3	Communications, Utilities & Misc. Charges	7,753	7,775	22
24.0	Printing & Reproduction	94	94	0
25.1	Consulting Services	$18,605	$18,639	$34
25.2	Other Services	217,185	209,204	-7,982
25.3	Purchase of goods and services from government accounts	$584,859	$604,862	$20,003
25.4	Operation & Maintenance of Facilities	$23,462	$23,528	$66
25.5	R&D Contracts	528,573	529,945	1,372
25.6	Medical Care	3,912	3,923	11
25.7	Operation & Maintenance of Equipment	18,185	18,236	51
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal Other Contractual Services**	**$1,394,781**	**$1,408,336**	**$13,555**
26.0	Supplies & Materials	$33,917	$34,012	$95
31.0	Equipment	17,107	17,155	48
32.0	Land and Structures	25	25	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	2,958,884	2,945,541	-13,343
42.0	Insurance Claims & Indemnities	0	0	0
43.0	Interest & Dividends	0	0	0
44.0	Refunds	0	0	0
	Subtotal Non-Pay Costs	**$4,428,598**	**$4,429,020**	**$422**
	Total Budget Authority by Object Class	**$4,922,771**	**$4,930,715**	**$7,944**

[1] Includes FTEs whose payroll obligations are supported by the NIH Common Fund.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Salaries and Expenses
(Dollars in Thousands)

OBJECT CLASSES	FY 2014 Enacted	FY 2015 President's Budget	FY 2015 +/- FY 2014
Personnel Compensation			
Full-Time Permanent (11.1)	$212,818	$214,946	$2,128
Other Than Full-Time Permanent (11.3)	119,450	120,644	1,194
Other Personnel Compensation (11.5)	5,514	5,569	55
Military Personnel (11.7)	4,434	4,478	44
Special Personnel Services Payments (11.8)	45,520	45,975	455
Subtotal Personnel Compensation (11.9)	**$387,735**	**$391,613**	**$3,877**
Civilian Personnel Benefits (12.1)	$103,200	$106,812	$3,612
Military Personnel Benefits (12.2)	3,238	3,270	32
Benefits to Former Personnel (13.0)	0	0	0
Subtotal Pay Costs	**$494,173**	**$501,695**	**$7,522**
Travel & Transportation of Persons (21.0)	$13,437	$13,475	$38
Transportation of Things (22.0)	954	956	3
Rental Payments to Others (23.2)	21	22	0
Communications, Utilities & Misc. Charges (23.3)	7,753	7,775	22
Printing & Reproduction (24.0)	94	94	0
Other Contractual Services:			
Consultant Services (25.1)	12,082	12,116	34
Other Services (25.2)	217,185	209,204	-7,982
Purchases from government accounts (25.3)	444,956	440,603	-4,353
Operation & Maintenance of Facilities (25.4)	9,026	9,051	25
Operation & Maintenance of Equipment (25.7)	18,185	18,236	51
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**$701,434**	**$689,210**	**-$12,224**
Supplies & Materials (26.0)	$33,917	$34,012	$95
Subtotal Non-Pay Costs	**$757,611**	**$745,544**	**-$12,067**
Total Administrative Costs	**$1,251,784**	**$1,247,239**	**-$4,545**

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Detail of Full-Time Equivalent Employment (FTE)

OFFICE/DIVISION	FY 2013 Actual			FY 2014 Est.			FY 2015 Est.		
	Civilian	Military	Total	Civilian	Military	Total	Civilian	Military	Total
Center for Cancer Research									
Direct:	1,443	25	1,468	1,443	25	1,468	1,443	25	1,468
Reimbursable:	2		2	2		2	2		2
Total:	1,445	25	1,470	1,445	25	1,470	1,445	25	1,470
Division of Cancer Biology									
Direct:	46		46	46		46	46		46
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	46		46	46		46	46		46
Division of Cancer Control and Population Sciences									
Direct:	167	3	170	167	3	170	167	3	170
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	167	3	170	167	3	170	167	3	170
Division of Cancer Epidemiology and Genetics									
Direct:	155	6	161	155	6	161	155	6	161
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	155	6	161	155	6	161	155	6	161
Division of Cancer Prevention									
Direct:	95	1	96	95	1	96	95	1	96
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	95	1	96	95	1	96	95	1	96
Division of Cancer Treatment and Diagnosis									
Direct:	226	3	229	226	3	229	226	3	229
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	226	3	229	226	3	229	226	3	229
Division of Extramural Activities									
Direct:	109		109	109		109	109		109
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	109		109	109		109	109		109
Office of the Director									
Direct:	817	5	822	817	5	822	817	5	822
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	817	5	822	817	5	822	817	5	822
Total	3,060	43	3,103	3,060	43	3,103	3,060	43	3,103
Includes FTEs whose payroll obligations are supported by the NIH Common Fund.									
FTEs supported by funds from Cooperative Research and Development Agreements.	0	0	0	0	0	0	0	0	0

FISCAL YEAR	Average GS Grade
2011	12.0
2012	12.3
2013	12.1
2014	12.1
2015	12.1

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Detail of Positions

GRADE	FY 2013 Actual	FY 2014 Enacted	FY 2015 President's Budget
Total, ES Positions	3	3	3
Total, ES Salary	512,751	516,597	521,763
GM/GS-15	255	255	255
GM/GS-14	469	469	469
GM/GS-13	403	403	403
GS-12	495	495	495
GS-11	200	200	200
GS-10	13	13	13
GS-9	131	131	131
GS-8	104	104	104
GS-7	66	66	66
GS-6	19	19	19
GS-5	14	14	14
GS-4	7	7	7
GS-3	7	7	7
GS-2	4	4	4
GS-1	1	1	1
Subtotal	2,188	2,188	2,188
Grades established by Act of July 1, 1944 (42 U.S.C. 207)	0	0	0
Assistant Surgeon General	0	0	0
Director Grade	22	22	22
Senior Grade	8	8	8
Full Grade	5	5	5
Senior Assistant Grade	7	7	7
Assistant Grade	0	0	0
Subtotal	42	42	42
Ungraded	888	888	888
Total permanent positions	2,213	2,213	2,213
Total positions, end of year	3,121	3,121	3,121
Total full-time equivalent (FTE) employment, end of year	3,103	3,103	3,103
Average ES salary	170,917	172,199	173,921
Average GM/GS grade	12.1	12.1	12.1
Average GM/GS salary	98,314	99,051	100,041

Includes FTEs whose payroll obligations are supported by the NIH Common Fund.