Goal 2. Objective A: Accelerate the process of scientific discovery to improve health

Medical breakthroughs, fueled by scientific discovery, have made the difference between life and death for countless Americans. Nevertheless, the need for better health interventions remains. Continuing to improve the health and well-being of Americans requires ongoing investments, with goals that range from improving our understanding of fundamental biological processes to identifying the best modes of prevention and treatment. HHS investments have improved the health of many Americans, but the path from basic discovery into safe, effective patient care can be long. This is why HHS is expanding the knowledge base in biomedical and behavior sciences and investing in fundamental science and service system research to improve detection, treatment, and prevention. HHS will continue to support ethical and responsible research practices, including ensuring the protection of the humans and animals participating in health research.

The Department has identified several leverage points to accelerate movement along the pipeline from scientific discovery to more effective patient care. NIH supports basic, clinical, translational, and early-stage drug development for promising new therapies. In addition, research and dissemination activities through NIH and other HHS components will help enhance the evidence-base for preventive, screening, diagnostic, and treatment services and facilitate the use of this information by clinicians, consumers, and policymakers.

Many HHS components, including ASPE, ASPR, CDC, NIH, and OASH support the Department's efforts toward scientific discovery. Below is a sample of performance measures that HHS will use to guide activities and achieve improved results for patient care. The Office of the Secretary led this Objective's assessment as a part of the Strategic Review.

Objective 2.A Table of Related Performance Measures

Provide research training for predoctoral trainees and fellows that promotes greater retention and long-term success in research careers. (Lead Agency - NIH; Measure ID - CBRR-1.1)

	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Target	N ≥ 12%	N ≥ 10%	N ≥ 10%	N ≥10%	N ≥ 10%	N ≥ 10%
Result	Award rate to comparison group reached 11%.	Award rate to comparison group reached 11%.	Award rate to comparison group reached 10%	Award rate to comparison group reached 10%	Dec 31, 2016	Dec 31, 2017
Status	Target Not Met	Target Met	Target Met	Target Met	In Progress	In Progress

Provide research training for postdoctoral fellows that promotes greater retention and long-term success in research careers. (Lead Agency - NIH; Measure ID - CBRR-1.2)

	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Target	N ≥ 12%	N ≥ 10%	N ≥ 10%	N ≥ 10%	N ≥ 10%	N ≥ 10%
Result	Award rate to comparison group reached 13% and exceeded the target by 1%.	Award rate to comparison group reached 13% and exceeded the target by 3%.	Award rate to comparison group reached 14% and exceeded the target by 4%.	Award rate to comparison group reached 14% and exceeded the target by 4%.	Dec 31, 2016	Dec 31, 2017
Status	Target Met	Target Met	Target Exceeded	Target Exceeded	In Progress	In Progress

By 2015, make freely available to researchers the results of 400 high-throughput biological assays screened against a library of 300,000 unique compounds, and the detailed information on the molecular probes that are developed through that screening process. (Lead Agency - NIH; Measure ID - CBRR-10)

	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Target	Deposit chemical structure and biological data for 200 new small molecule probes in PubChem.	Establish 400 primary biochemical, cell-based or protein-protein interaction assays that can be miniaturized and automated as high throughput screens in the Molecular Libraries Program (MLP) Portfolio.	Increase the Molecular Libraries Program (MLP) inventory to 375 small molecule probes that can be used in biological research to interrogate basic biological processes or disease.	Make freely available to researchers the results of 400 high-throughput biological assays screened against a library of 300,000 unique compounds, and the detailed information on the molecular probes that are developed through that screening process.	Discontinued	Discontinued
Result	The Molecular Libraries Program deposited chemical structure and biological data for 294 new small molecule probes in PubChem since the program began.	Established 570 primary biochemical, cell-based or protein-protein interaction assays that were miniaturized and automated as high throughput screens in the Molecular Libraries Program (MLP) Portfolio.	Increased the Molecular Libraries Program (MLP) inventory to 375 small molecule probes that can be used in biological research to interrogate basic biological processes or disease.	The Molecular Libraries Program (MLP) completed 448 HTS assays screened against a library of 300,000 compounds and generated 382 small molecule probes. The information on the probes and assays was deposited in PubChem.	N/A	N/A
Status	Target Exceeded	Target Exceeded	Target Met	Target Exceeded		

By 2020, identify two molecular-targeted therapies for disorders of the immune system in children. (Lead Agency - NIH; Measure ID - SRO-3.9)

	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Target	Complete genetic, biochemical, or cellular studies aimed at identifying a molecular pathway underlying the disease in the patient cohort.	Identify at least one molecular pathway suitable for targeting in the patient cohort by performing detailed genetic mapping and confirmatory analyses for markers and pathways identified through genome-wide association.	Design a clinical trial testing an agent for a disorder of the immune system in children (e.g., Still's disease).	Complete a clinical pilot study in a cohort of pediatric patients with a disorder of the immune system.	Identify at least one molecular pathway based on genetic analysis suitable for therapeutic targeting in a pediatric cohort of patients with an immune-mediated disease.	Design a clinical study testing an agent for a disorder of the immune system in children.
Result	A genome-wide association study has been performed on the cohort of 982 systemic-onset juvenile idiopathic arthritis patients and over 7000 healthy controls for 1.4 million genetic markers.	Researchers have identified a genetic variant that confers an increased risk of developing systemic juvenile idiopathic arthritis (sJIA) and that indicates the CD4+ T cell activation pathway as a therapeutic target.	Researchers have designed a compassionate use study to evaluate a novel class of drugs Janus Kinase (JAK) inhibitors in pediatric patients with the immune disorder, Chronic Atypical Neutrophilic Dermatosis with lipodystrophy and elevated temperature (CANDLE).	Researchers have completed a compassionate use study to evaluate treatment with Janus Kinase (JAK) inhibitors in pediatric patients with the immune disorder CANDLE.	Dec 31, 2016	Dec 31, 2017
Status	Target Met	Target Met	Target Met	Target Met	In Progress	Pending

By 2015, establish and evaluate a process to prioritize compounds that have not yet been adequately tested for more in-depth toxicological evaluation. (Lead Agency - NIH; Measure ID - SRO-5.13)

	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Target	Test 10,000 compound main library in 50 qHTS and test 50 compounds in mid-throughput assays.	Test 10,000 compound main library in 25 qHTS and test 180 compounds in densely sequenced human lymphoblastoid cell lines to assess genetic diversity in response to toxicants.	Test 10,000 compound main library in an additional 15 qHTS and test 20 subsets of possible high risk chemicals in high-content screens.	A formal process of prioritizing compounds for more extensive toxicological testing will be evaluated and used.	Discontinued	Discontinued
Result	The library containing 10,000 compounds was screened in 65 quantitative high throughput screens (qHTS) or assays. Fifty compounds were screened in approximately 600 mid-throughput assays.	The 10,000 compound library was screened in 33 qHTS assays and data was analyzed on 179 compounds screened for cytotoxicity across 1086 human lymphoblastoid cell lines representing 9 racial groups to assess genetic diversity in response to toxicants.	The 10,000 compound library was screened in 42 qHTS assays and 22 subsets of possible high risk chemicals were screened in high content screens using cells (e.g., cardiomyocytes, neuronal cells) and alternative organisms (zebrafish, *Caenorhabditis elegans*).	A formal process for evaluating HTS results for use in prioritization of compounds for additional testing has been developed, and a model was developed to evaluate the estrogenic potential of chemicals and has been proposed for use.	N/A	N/A
Status	Target Met	Target Met	Target Met	Target Met		

By 2018, (a) identify genetic factors that enhance or reduce the risk of development and progression of chronic obstructive pulmonary disease (COPD) and (b) validate new genetic and clinical criteria that may be added to COPD classification and contribute to better and/or earlier diagnosis or prognosis of the disease. (Lead Agency - NIH; Measure ID - SRO-5.2)

	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Target	N/A	N/A	Complete Genome-wide Association analysis of the original 10,000 subjects to discover 3 statistically significant genetic risk factors for COPD.	Using analysis of genetic and clinical data from the original 10,000 subjects, identify 1-3 COPD sub-classes that can then be tested for prognostic potential.	Analyze longitudinal data for the first 1000 five year follow-up visits to identify 1-3 predictors of disease progression.	Complete exome chip genotyping of 10,171 COPDGene subjects and identify 1 to 5 new rare and common genetic determinants of COPD.
Result	N/A	N/A	A meta-analysis was published FY 2014 using COPDGene as well as other studies to identify three known loci and three new loci marking genetic risk factors.	Identified four clusters that show robust associations with clinical characteristics of COPD and known COPD-associated genetic variants.	Dec 31, 2016	Dec 31, 2017
Status			Target Met	Target Met	In Progress	In Progress

By 2018, complete pre-commercial development of a point-of-care technology targeted for use in primary care setting. (Lead Agency - NIH; Measure ID - SRO-5.5)

	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Target	N/A	N/A	Identify 6 enabling technologies with potential clinical use in primary care setting.	Establish feasibility of use of 3 to 4 identified technologies through preliminary testing.	Complete pilot clinical studies on 1 to 2 prototype devices.	Support research on continued development of one or two prototype devices that will begin to initiate the regulatory process.
Result	N/A	N/A	Six technologies were identified that have potential for clinically focused solutions to improve primary care.	Identified and established the feasibility of 3 technologies through preliminary testing for potential use as point of care technology in the primary care setting.	Dec 31, 2016	Dec 31, 2017
Status			Target Met	Target Met	Pending	Pending

By 2015, identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations. (Lead Agency - NIH; Measure ID - SRO-6.4)

	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Target	Investigate the role of mucus gel formation in healthy controls and asthma patients.	Conduct investigations to elucidate the dynamic, pathophysiologic phenotypes of severe asthma.	Investigate the disease processes involved in asthma exacerbations and/or severe asthma using state-of-the-art pulmonary imaging techniques.	Identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations.	Discontinued	Discontinued
Result	Researchers investigated two proteins associated with mucus formation, CLCA1 and TMEM16A, that may serve as potential targets for treating asthma.	The Severe Asthma Research Program is conducting investigations.	The Severe Asthma Research Program (SARP) is using state of the art imaging techniques to help define disease phenotypes and endotypes, which will enable the development of tailored interventions for the appropriate patient populations.	Identified and characterized two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations.	N/A	N/A
Status	Target Met	Target Met	Target Met	Target Met		

By 2017, identify circuits within the brain that mediate reward for 1) drugs, 2) non-drug rewards such as food or palatable substances, and 3) aversion to drug effects, and 4) determine the degree of overlap between these circuits. (Lead Agency - NIH; Measure ID - SRO-8.2)

	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Target	N/A	N/A	Identify drug-activated reward circuits.	Identify non-drug activated reward circuits and compare with drug-activated reward circuits.	Support research to compare and contrast rewarding versus aversive pathways in response to substances of abuse.	Identify morphological and functional neuroplastic modifications due to drugs at the level of dendritic spines and electrophysiological indices and their persistence during the development of drug dependence (or during repeated intermittent drug administration).
Result	N/A	N/A	Classical and pharmacological dissection of the central drug reward system was confirmed, extended to demonstrate projections which had two or more transmitters with functional significance for drug reward, and identified the rostromedial tegmentem as a GABAergic nucleus which could functionally inhibit the dopaminergic pathway.	NIH-funded researchers defined circuits and portions of circuits that are important for the perception of reward that are activated in the presence or absence of drugs of abuse.	Dec 31, 2016	Dec 31, 2017
Status			Target Met	Target Met	In Progress	Pending

Analysis of Results

HHS recognizes that a high-quality workforce is crucial to the effective delivery of health and human services. The Department has a number of activities that focus on addressing current workforce issues and the strategic development of workforce capacity. For example, HHS seeks to ensure that our country not only maintains, but enhances its capacity for innovative health-related research. A critical part of the NIH mission is the education and training of the next generation of biomedical, behavioral, and clinical scientists. In FY 2015, NIH pre-doctoral Ruth L. Kirschstein National Research Service Award (NRSA) trainees and fellows were 10 percent more likely to remain active in biomedical research than non-NIH trainees and fellows; this result matched the annual target of 10 percent. Each year's target represents the proportion of NIH trainees and fellows who go on to apply for and receive subsequent NIH support in comparison to non-NIH trainees and fellows. Subsequent support is an indicator of

retention success in the research arena, and reflects the impact of NIH-funded training on the ability of trainees and fellows to be competitive and sustain a research career with independent funding.

NIH also routinely monitors the career outcomes of former postdoctoral fellows. In FY 2015, NIH postdoctoral fellows were 14 percent more likely to remain active in biomedical research than non-NIH fellows; this result exceeded the annual target of 10 percent. Former NIH-trained postdoctoral fellows are more likely to remain in research careers and are better able to compete for funding. Kirschstein-NRSA fellows from 1994 to 2004 were nearly twice as likely to receive NIH research project grant support within ten years of completing their training as compared to other postdoctoral fellows who did not received NRSA support.

Accelerating the process of scientific discovery for the purpose of improving health outcomes is important to Americans' well-being and health. The Molecular Libraries Program (MLP) made exceptional progress and exceeded the annual performance target during the closeout period of the program. In FY 2015 the results of 448 high-throughput biological assays screened against a library of 300,000 unique compounds, including the assay results and the detailed information about the 382 molecular probes that were developed through that screening process, were made publicly available in PubChem by the MLP. By disseminating results in PubChem, the NIH enables one of the largest sets of publicly available chemical biology information to be used by researchers in the public and private sectors.

Advances in technology and reductions in cost have made it possible to identify the causes of certain genetically complex diseases. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE) is a novel rare pediatric autoinflammatory syndrome that is predominately characterized by inflammation, attacks of fever, skin lesions, and fat loss. NIH researchers, along with an international team of collaborators, identified in a group of affected patients mutations in a gene causing cells to be unable to recycle or remove waste products. During FY 2015, researchers completed a compassionate use study to evaluate treatment with Janus Kinase (JAK) inhibitors in pediatric patients with the immune disorder CANDLE, meeting the target.

In addition to the cataloging of data about naturally occurring biological chemicals, NIH manages a program to investigate and catalog the potential health effects of many of the estimated 125,000 man-made chemicals in use commercially. NIH and the EPA began the program, titled Tox21, in early 2008 to collaborate on the research, development, validation, and translation of new and innovative test methods that characterize how chemicals interact with cellular pathways, determining chemical toxicity, as well as danger to human health. This is important for the development of prevention and mitigation strategies. Tox21 has a library of over 10,000 compounds. NIH met its target in FY 2015 by developing a formal process for evaluating high throughput screening (HTS) results for use in prioritization of compounds for additional testing, which consists of a data analysis pipeline and a protocol developed for evaluating HTS results. A model was developed to use 18 of the HTS assays to evaluate the estrogenic potential of chemicals and has been proposed for use in Endocrine Disruptor Screening Program (EDSP) evaluations. Furthermore, NIH met expectations in FY 2015 by screening the Tox21 10K library in 30 quantitative high throughput screening (qHTS) assays with a subset of the 10K library evaluated in a validation mode in an additional 54 assays that focused on measuring agonism/ antagonism in nuclear receptor assays and the activation of various stress response pathways. In addition, data obtained on 22 sets of possible high risk chemicals were screened for activity in a variety of mid to high throughput screens utilizing stem cell derived tissue models and alternative organisms (zebrafish, Caenorhabditis elegans).

COPD is characterized by airway obstruction and/or emphysema. COPD is known to have both environmental (e.g., tobacco smoke) and genetic risk components. Current and former smokers are at highest risk, although only a minority of smokers ever develops COPD. Why some smokers develop COPD while others do not is unknown, as is why some non-smokers develop COPD. The COPDGene study, in which 10,000 current and former smokers with or without COPD were studied to identify clinical and genetic markers of the disease, was begun in 2008 to address some of these questions. NIH met its target in FY 2015 by identifying four clusters that can be characterized as 1) relatively resistant smokers; 2) mild upper zone emphysema predominant; 3) airway disease predominant; and 4) severe emphysema. These clusters show robust associations with clinical characteristics of COPD and known COPD-associated genetic variants.

As the number of primary care providers diminishes and the need for primary care increases, there is an urgent need to increase the capacity of providers to care for more patients without a decrease in the quality of care and without unduly burdening the providers. Primary care providers are also being tasked with providing increasingly complex care as the population ages and the burden of chronic disease grows. Point-of-care technologies have emerged as scientific knowledge has grown. An early example of a point-of-care technology is the home pregnancy test. More recent tests for diagnosing strep throat at the point-of-care have become available. Emerging microfluidic, nanotechnology, and sensor miniaturization technologies are making it possible to develop a new generation of point-of-care test systems designed to improve the efficiencies of primary care practices. NIH is supporting efforts to define and prioritize unmet clinical needs in primary care where technology-enabled solutions could be of benefit. In FY 2015 NIH met its target by identifying and establishing the feasibility of three technologies through preliminary testing for potential use as point-of-care technology in the primary care setting: a microchip for diagnosing multiple infectious agents, a rapid fluorescence-based determination of antibiotic susceptibility, and an optical device for diagnosing otitis media (middle ear infection).

Asthma attacks are a significant cause of morbidity in patients with asthma and represent a substantial public health burden. The Severe Asthma Research Program (SARP) unites transdisciplinary teams in a collaborative platform to foster an understanding of severe asthma and its phenotypes at genetic, molecular, cellular, and clinical levels over time. HHS is tracking SARP and other severe asthma research through a series of annual milestones. In FY 2015 NIH achieved its milestone, with investigators in the Centers for Advanced Diagnostics and Experimental Therapeutics Program (CADET II) identifying and characterizing two molecular pathways of potential clinical significance (smooth muscle myosin polymerization and YKL-40), that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations.

Decades of neuroscience research have shown how substances of abuse impact the brain in many ways, with effects on reward pathways, motor function, cognitive abilities, etc., yet scientists still know very little about the specific brain circuits that signal rewarding effects in response to drugs vs other natural rewards (e.g., food, sweets, water). Scientists also know that substances of abuse can have both rewarding and aversive effects, but the brain circuitry that signals one response vs. the other remains unclear. Recent advances in the development of tools to probe the central nervous system such as multi-array recording electrodes, in vivo fast scan electrochemical voltammetry, and optogenetics, stand to increase dramatically our understanding of this brain circuitry. These data will generate new scientific knowledge that may help to define the basis of individual differences in the responsiveness to reward/aversion- producing substances, including substances of abuse and may help to identify novel targets for the development of anti-addiction medications. In FY 2015, NIH-funded researchers defined

circuits and portions of circuits that are important for the perception of reward that are activated in the presence or absence of drugs of abuse, meeting the target.

Plans for the Future

NIH expects to maintain the retention targets of both pre- and post-doctoral trainees and fellows in FY 2016 and 2017, despite challenges. It is taking a number of steps to bring this about, including encouraging the routine use of individual development plans to guide the career development of graduate students and post-doctorates supported by NIH, and establishing a new office to address biomedical workforce issues. To assess its performance, NIH routinely monitors degree completion by its pre-doctoral Kirschstein-NRSA trainees and fellows and tracks the extent to which the graduate students and post-doctorates it supports are subsequently involved in research, using data from the national Survey of Earned Doctorates and the NIH IMPAC II administrative database.

FY 2014 Strategic Review Objective Progress Update Summary

Please note that this section summarizes the result of the FY 2014 HHS Strategic Review process, limiting the scope of content to that available prior to spring of 2015. Due to this constraint, the following may not be the most current information available.

Conclusion: Noteworthy Progress

Analysis: Significant scientific progress has been achieved by the Department and its Divisions. Accomplishments in 2014 included Ebola research. The Ebola outbreak that began in 2014 in West Africa is the largest such outbreak in history. More than 20,000 cases and almost 8,000 deaths were reported by the end of the year. Scientists used genomic sequencing technologies to identify the origin and track transmission of the Ebola virus. Research intensified efforts to develop a protective vaccine. A clinical trial to assess two experimental vaccines to prevent Ebola virus infection opened to volunteers in Liberia.

Sickle cell disease in adults was reversed by stem cell transplants. Sickle cell is an inherited blood disorder that affects more than 90,000 Americans. In 2014 researchers successfully treated adults using a modified stem cell transplant approach that does not require extensive immune-suppressing drugs. A drug candidate to treat Sickle Cell that was developed in part by HHS researchers was acquired by Baxter International's BioScience business for further clinical development. The compound is the first specifically developed to target the underlying molecular mechanism of sickle cell disease.

Paralyzed men regain movement with spinal stimulation. Four young men paralyzed below the chest because of spinal cord injuries were able to regain control of some movement after receiving an experimental spinal stimulation therapy. The fact that all 4 patients were able to regain voluntary movement suggests that a large number of patients with paralysis might benefit from spinal stimulation.

Another indicator of scientific accomplishment is the award of the Nobel Prize. An HHS grantee, Dr. William E. Moerner, shared the Nobel Prize in Chemistry for work on optical microscopy that enable scientist to visualize structures in living cells beyond the resolution of conventional light microscopy.

HHS is exploring opportunities to strengthen health disparities research efforts including using community-based participatory research (CBPR). The implementation of CBPR projects requires building strong relationships between academic institutions and community partners. It can take considerable time and effort, and progress is difficult to measure. A key need in health disparities research is the

necessity of consistent measurement tools. Non-standardized methodologies for measuring differences between and within populations make it very challenging to compare across population and studies to measure progress to reduce health disparities. The current health environment emphasizes team based care which can include health care practitioners who are geographically dispersed. The training and development needs of these "virtual teams" could benefit from further discussion.

Currently being evaluated by HHS, the implementation of a single institutional review board (IRB) for multi-site research has the potential to enhance and streamline the process of IRB review and reduce inefficiencies so that research can proceed efficiently without compromising protections. The Department is developing a Priority Goal related to Combating Antibiotic-Resistant Bacteria. The Accelerating Medicines Partnership is exploring the utility of tau imaging and fluid biomarkers for tracking responsiveness to treatment and/or disease progress in Alzheimer's disease in three large ongoing clinical trials.