June 9, 2014

Help Us Solve
The Cruel Mystery
LUPUS™
FOUNDATION OF AMERICA

The Honorable Fred Upton
Chairman

The Honorable Diana DeGette
Ranking Member

Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

RE: 21st Century Cures Initiative – A Patient Advocacy Perspective

Dear Chairman Upton and Representative DeGette,

Thank you for the opportunity to comment on the 21st Century Cures initiative. The Lupus Foundation of America is the only national force dedicated to improving the quality of life for all people affected by lupus through programs of research, education, awareness, and advocacy. The Committee's interest in addressing head-on the discovery, development, and delivery process paradigm through the 21st Century Cures initiative is a welcome approach. The Foundation is confident your efforts will yield policy solutions and actions that will accelerate the drug development pipeline and bring forward promising new treatments for people with lupus.

Make Lupus a Priority

A well-known and respected lupus clinician and researcher once opined that "part of the reason why lupus remains so challenging and mysterious to people is because it doesn't fit the classic disease paradigm. There isn't one clinical feature or symptom."[1]

Lupus is not an orphan disease nor is it a disease impacting tens of millions of Americans. Lupus is an overlooked and chronically underfunded, serious, debilitating, and disabling disease impacting more than 1.5 million Americans. Lupus is missing from the national health care agenda; and, it needs special attention from policy makers to help bring the disease to the forefront of research, scientific discovery, and drug development.

What is Lupus

Lupus is an unpredictable and misunderstood autoimmune disease that ravages different parts of the body. It is difficult to diagnose, hard to live with, and a challenge to treat. In lupus, the body's immune system becomes unbalanced, causing inflammation and tissue damage to

[1] S. Sam Lim, as quoted in Von Tesoriero, H. Drugs in testing show promise for lupus. Wall Street Journal, January 23, 2007.

virtually any organ system in the body including the skin, joints, heart, lungs, kidney, and brain. The symptoms and impact of lupus range in severity from mild to life-threatening.

An estimated 1.5 million Americans live with a form of lupus. Ninety percent of the people with lupus are women. African American, Hispanics, Asians, and Native Americans are two to three times more likely to develop lupus - a health disparity that remains unexplained.

An accurate diagnosis of lupus can take four or more years and require visits to three or more physicians. Late diagnosis and delayed treatment contribute to poor outcomes and increased morbidity and mortality. Improved knowledge of lupus among health professionals will result in earlier and more accurate diagnoses; this, in turn, will help to improve disease management, diminish adverse effects, and increase quality-of-life among those affected.[2]

To-date, there are only four FDA-approved medications to treat lupus – Benlysta®, hydroxychloroquine (an antimalarial), prednisone (a steroid), and aspirin. Benlysta®, approved by the Food and Drug Administration (FDA) in March 2011, is the first and *only* drug designed specifically to treat lupus. All other medications used to treat lupus are prescribed off-label such as chemotherapies and immunosuppressants. Current medications only treat lupus symptoms and often have harsh side-effect profiles.

The Financial Burden of Lupus

Lupus annually costs the nation an estimated $31.4 billion in direct and indirect expenditures. A recent study found that the average annual cost per person with lupus (without kidney involvement and between the ages of 18 and 65) was $21,161. For patients with kidney involvement, the costs are estimated at $64,195.[3]

The inability to work is also a frequent consequence of living with lupus. One study found that more than 40% of people with lupus were no longer employed an average of 3.4 years after their diagnosis. As a result, many people apply for Social Security Disability. In addition because lupus affects people in their prime working years, those with the disease are often unable to work in the period of life typically associated with highest earnings.[4]

***Overcoming Barriers to Drug Development*: The Lewin Report**

The Foundation is a leader in spearheading efforts to better understand the challenges and barrier to drug development in lupus, and we have made significant strides in addressing those challenges. In 2009, the Foundation commissioned a landmark report by The Lewin Group, Inc. to gain a better understanding of that lupus drug development landscape and the obstacles standing in the way of new treatments for people with lupus. The Lewin Group brought

[2] Lupus Foundation of America, *Survey of People with Lupus Reveals the Disease Remains Difficult to Diagnose and Manage*, Summer 2000.
[3] Direct and Indirect Costs to Employers of Patients With Systemic Lupus Erythematosus With and Without Nephritis, Carls, et. al., JOEM, Volume 51, Number 1, January 2009
[4] *Ibid.*

together stakeholders from across disciplines to examine the barriers to drug development and approval and made recommendations to overcome those barriers.

The report, entitled *Overcoming Barriers to Drug Development*, identified steep barriers to drug development that include "poorly understood biology of the disease, difficulties in clinical trial participant selection, challenges to selection of appropriate clinical endpoints, adapting instruments and tools for measuring disease activity in clinical trials, and the confounding role of background medications."[5] The report continues to serve as a roadmap and the underpinnings for the Foundation's research program and advocacy agenda.

The Foundation recommends the Committee examine the *Overcoming Barrier to Drug Development* report in detail. While the report outlines barriers unique to lupus, there are concepts which can be applied across disease states to help foster a better discovery, development, and delivery process paradigm.

LUPUS RESEARCH

Current Status and Challenges

Lupus is a heterogeneous and complex disease. The precise causes of lupus are unknown. While there is strong evidence suggesting a genetic component and infectious and non-infectious environmental contributors, any combination of these appears to differ across individuals. The limited understanding of the biological basis of the disease among different patients hinders identification of molecular targets and disease pathways for new drug development.[6]

Some research has been conducted to learn more about environmental triggers – including certain medications or ultraviolet light, hormones, toxins, and air pollution—but much remains unknown about the etiology of lupus in order to help inform the development of targeted therapies. The heterogeneity of its presentation across patients and a clinical course characterized by flares and remissions that are difficult to predict exacerbate the challenges of conducting clinical trials of investigational therapies.[7]

The overall lack of funding and coordination for basic, clinical, and translational lupus research has long hampered efforts to move molecules through the drug development pipeline resulting in treatments for lupus. Furthermore, lupus has never been prioritized. Funding for lupus at the National Institutes of Health (NIH) decreased from $108 million in FY 2012 to $92 million in FY 2013. A recent internal study conducted among the Foundation's Medical and Scientific Advisory Council found that of the $108 million NIH recorded as lupus research funding in FY 12, only $61 million was actually lupus specific or lupus targeted research. The remaining $47

[5] The Lewin Group, Inc. *Overcoming Barriers to Drug Development in Lupus*, September 28, 2014. Prepared for The Lupus Foundation of America. Page 2.
[6] The Lewin Group. Page 11.
[7] *Ibid.*

million actually had no relevance to lupus suggesting the actual dollars going specifically to lupus are much lower than stated by the NIH. These limited resources have hampered advances in lupus research, important research was halted, and lupus researchers have left the field.

Lupus researchers have been forced to leave their labs behind because of the lack of research funding. In response to the current lupus research funding environment and the potential decline in scientific momentum and loss of current and future lupus investigators, the Foundation recently established its LIFELINE grant program™ in support of the lupus research community and the advancement of lupus research. The program provides five one-year grants offering temporary support for those who have experienced a gap in external funding for a specific, previously funded research project due to the decreased funding available from government sources. The award is intended to keep an investigator's project on track while they reapply for funding. This program is limited in scope and does not begin to address the losses for the community of the most seasoned lupus researchers.

The response by researchers to the LIFELINE grant program was overwhelming. While anecdotally, the Foundation knew lupus research funding and labs were in crisis, the number of applications - and from whom they came underscored the sense of urgency to address the significant cuts under sequestration and push hard for new funding for lupus research.

The February 2014 announcement of the new Accelerating Medicines Partnership (AMP) program, a public-private collaboration of the NIH, drug industry, and non-profit organizations, finally thrusts lupus into a national research spotlight. The Foundation is excited about the possible opportunities provided through AMP, and the Foundation is honored to serve on the lupus project steering committee. However, there is no new funding for AMP, and the Foundation remains very concerned that the NIH portion of the AMP funding for lupus pulls vital funding away from much needed RO1 grants that keep basic research moving forward and lupus researchers focused on lupus.

Proposed Solutions

Historically, a robust effort at the NIH produced basic scientific findings that were then developed by industry. **Investing and funding in basic biomedical research at the NIH and throughout the federal government is vital to moving biomedical innovation forward. It is time to make biomedical research and innovation a priority.**

In many cases, industry finds investments just too risky, or they are funding basic research to achieve their goals (adding to the cost of research and development and increasing the cost of the approved therapy). **The NIH should be investing in more translational research to help de-risk investments in drug development by private industry.** This federal investment can help bring down the overall costs of drug development benefiting all stakeholders, especially the patients taking the medications.

With lupus specifically, **the federal biomedical research effort should be greatly expanded to develop a better understanding of the biological mechanisms of lupus, including more basic and translational research on the pathophysiology and pathogenesis of the disease.** This effort should focus on the integration of bench research with clinical investigation.[8]

The NIH suggests lupus is a prototypical autoimmune disease, and research breakthroughs in lupus will also likely benefit the more than 23 million Americans living with autoimmune diseases.[9] With 14 different NIH institutes funding lupus research in FY 2013, coordination is a must. If, as suggested by NIH, lessons learned can be applied beyond lupus, then **NIH should make lupus research funding a priority and develop a national coordinated research strategy** to address lupus broadly and specific issues such as biomarker identification and validation.

Public-private partnerships are integral to improving the discovery, development and delivery paradigm. Congress and the federal government have made great strides in creating innovative public-private partnerships such as AMP. However, it is **essential to provide information and ease of access to existing public-private partnership infrastructure and programs that can help advance research for a disease like lupus.** Furthermore, federal funding for such partnerships must be new funding or at a minimum not re-directed from current essential funding for disease specific research.

LUPUS TREATMENTS

Current Treatments

In the absence of a cure for lupus, the primary goal with medication therapy for people with lupus is to see an improvement in their quality-of-life. Most medications used to treat lupus: (1) have not been approved by the FDA; (2) have side-effects profiles that often prove worse than the disease itself; and, (3) are untenable for long-term use.

Currently, there are only four FDA-approved medications to treat lupus – Benlysta®, hydroxychloroquine (an antimalarial), prednisone (a steroid), and aspirin. Benlysta®, approved by the FDA in March 2011, is the first and *only* drug designed specifically to treat lupus. All other medications used to treat lupus are prescribed off-label such as chemotherapies and immunosuppressants.

While these drugs do provide benefits to people with lupus, they have significant side effect profiles and can be connected with increases in infections, cancer, significant bone loss and osteoporosis, sterility (in children as well as adults), and stroke among many other adverse health consequences. Some off-label treatments also are known to be teratogenic (causing birth defects) and over longer periods of use often compromise fertility in men and women.

[8] *Ibid.* Page 14.

[9] Progress in Autoimmune Diseases Research, National Institutes of Health Autoimmune Diseases Coordinating Committee, Report to Congress, March 2005.

While there is only one drug designed and approved for use in lupus, there is hope for people with lupus. Industry is finally looking at lupus despite the risk. With approximately 30 drug companies investing in lupus, it is all the more critical that the FDA understands the complexity and intricacies of lupus.

Challenges in Lupus Drug Development

Developing new treatments for lupus that are safe, effective, and tolerable has been particularly challenging. Even beyond the complexity of the disease, the persistent lack of a success and clarity along the FDA regulatory pathway has consequences for the willingness of drug companies to invest in lupus. Some in industry perceive there is no clear pathway or system in place for the development of lupus therapies. Other have forged ahead, but face significant road blocks in demonstrating the effectiveness of new lupus therapy - including the difficulty of demonstrating clinical superiority against a non-approved standard of care, confounding effects of background medications, and challenges of selecting clinical endpoints.[10]

In the absence of approved treatments for lupus and a formal standard of care, physicians have no choice but to treat a patient's symptoms and choose among medications approved for other diseases. As a result over the years, the current "unapproved" standard of care for people with lupus involves extensive use of off-label medications.[11] This lack of a standard of care is just one challenge to drug development in lupus, and yet is the common thread among the many barriers. For example, the FDA considers primary outcome measures that assess the disease itself, which is made more difficult in lupus considering a drug in clinical trial is evaluated against potent background medications such as steroids and chemotherapies.

As the diverse symptoms of lupus wax and wane unpredictably, it is complex to determine what, how, and when to measure.[12] Measuring patient reported outcomes (PROs) such as fatigue and steroid sparing are crucial. Other patient reported outcomes to consider include bone density and cardiovascular health.

In a disease like lupus, PROs measuring quality of life through concepts such as fatigue or pain can have a significant impact on the development and approval of new treatments. Furthermore, a clinical trial endpoint measuring the reduction, whether small or large, of the use of steroids in a person with lupus would result in a significantly positive impact on quality of life and should be considered key in the development of future treatments.

Another challenge is the ability to enroll a sufficient numbers of patients to conduct statistically valid clinical trials. The heterogeneity of lupus makes it virtually impossible to assemble uniform patient groups. An individual's disease activity can complicate clinical trial enrollment that may be based on presence or level of disease activity or assessment of outcomes at any particular duration of follow-up. In addition, the pool of lupus patients available for enrollment

[10] The Lewin Group. Page 8.
[11] *Ibid.* Page 1.
[12] *Ibid.* Page 11.

in clinical trials is small, which can increase the difficulty of enrollment and delay and lengthen clinical trials.[13]

Furthermore, as lupus is a systemic disease impacting every organ system in the body, it is not transparent as to how lupus treatments are evaluated at the FDA. It is unclear the expertise the FDA has in lupus. The lupus guidelines desperately need to be updated. The lupus nephritis guidelines, pulled almost two years ago under a cloud of secrecy, have yet to be re-issued. In addition, cutaneous lupus guidelines need to be developed to help advancing skin lupus therapies. There is much work to be done at the FDA on lupus.

Proposed Solutions

Drug development is extremely challenging in lupus. Under many circumstances, the FDA has the authority as authorized by Congress to help usher forward drug development for lupus. **The Committee should ensure the FDA is using its authority, while being transparent and inclusive in its efforts.** The FDA must update and create lupus guidelines if patients are to have a variety of lupus treatments available.

The FDA must be appropriately educated and fully engaged in understanding the complexities of lupus, which is imperative if there are to be an arsenal of safe and effective treatments for people with lupus. **Engagement with the scientific and patient community outside the FDA is crucial** for the success of the future of drug development in lupus.

The scientific community and federal stakeholders such as the FDA and the NIH should collaborate on a research agenda to provide a clear pathway to drug development in lupus. A series of workshops and related expert meetings should address the design of clinical trials. Topics should include, but should not be limited to: clinical trial participant selection, clinical trial endpoints, clinical measures/instruments and tools, and the role of background medications and the placebo effect, which are understood to have played critical roles in the failure of lupus clinical trials.[14] In addition, **flexibly in clinical trial design is essential. Adaptive or smaller clinical trials are a must** as a large trail and all its requirements are not representative of the real-life clinical setting.

Clinical trials now have to measure their unapproved treatment against the current standard of care which is not approved for use in lupus. **The FDA should conduct a systematic review of cyclophosphamide to assess its treatment effect.** Cyclophosphamide, a chemotherapy, is used to treat moderate-to-severe flares, and is considered the standard of care, but has not been approved by the FDA for the treatment of lupus. If the treatment effect of cyclophosphamide could be established, it would offer an alternative validated path to FDA approval by allowing for a non-inferiority study of a drug candidate for lupus nephritis. The findings could be used to

[13] *Ibid.* Page 11.
[14] *Ibid.* Page 15.

inform decisions regarding whether, and if so, how, to approach the FDA, and to pursue further clinical trials or other studies.[15]

Enhance the FDA's clinical and statistical capacity to address PROs both as primary and secondary endpoints in clinical trials and new drug submissions. A PRO measuring quality of life for people with lupus is a very important way to assess the disease and potential individual benefits made by taking a new drug.

For example, debilitating fatigue is one of the most common symptoms experienced by people with lupus. Fatigue often means that a person with lupus is unable to complete their activities of daily living and their quality of life suffers. Using fatigue as PRO to measure quality of life has the potential to serve as a clinically significant endpoint in the development of lupus drugs. If a drug is able to lessen the impact of fatigue on a person with lupus, then that would be an incredibly important step towards improving their overall quality of life and a significantly positive measure. Demonstrating that a new treatment can improve quality of life is extremely important to people with lupus. PROs offer a way to speed the approval of better and more targeted treatments.

Congress Can Help

Recently, the Foundation set forward a new strategic direction aimed at reducing the time to disease diagnosis; ensuring people with lupus have an arsenal of safe and effective treatments; and, access to treatments, supports and services. Congress can help us achieve these goals for this overlooked and underserved disease with a primary goal of improves the lives of Americans with lupus. Congress can:

- Raise critical awareness of hidden diseases like lupus and shift the discovery, development and delivery paradigm;
- Evaluate lupus to the national health care agenda;
- Robustly fund the NIH and the FDA making biomedical research, regulatory science, and innovation a top priority for the United States;
- Provide creative ways to incentivize investment in lupus as an overlooked disease;
- Support protections for the development of dormant therapies and drug repurposing;
- Support funding research to update lupus disease classification criteria and the development diagnostic criteria that will help build the fundamental pillars of lupus;
- Ensure the FDA is using its existing authority and being transparent in its activities;
- Ensure that once treatments for lupus do come to market, they are accessible to patients by evaluating and addressing such issues as co-insurance and robust formularies; and,
- Safeguard against overly strict interpretation of FDA drug labeling as a predicate for health insurance coverage leading to excessively restrictive medical policies and access challenges for emerging lupus treatments.

[15] *Ibid.* Page 16.

Thank you for spearheading such an important effort. The Foundation is a passionate advocate for people with lupus and our work has gone a long way to improve the lives of people with lupus. However, we cannot do it alone. The 21st Century Cures initiative will take important steps towards improving the lives of all Americans. If you have any questions or wish to discuss our ideas further, please contact Kim Cantor, Vice President of Advocacy and Government Relations at [redacted].

Sincerely,

[redacted]

Sandra C. Raymond
President & CEO
Lupus Foundation of America

June 9, 2014

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Diane DeGette
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Upton and Representative DeGette:

On behalf of the Society for Women's Health Research (SWHR), we want to thank you for launching the 21st Century Cures Initiative to help Congress identify ideas and strategies on how it can help accelerate the discovery, development, and delivery of promising new treatments to patients. SWHR thanks the Committee for providing the opportunity to submit comments. We are writing to suggest that the Committee consider examining the important issue of how access to real world data on medication use is shared with health care providers and patients, particularly with respect to medically accepted alternative uses of medicines (prescribing off-label).

SWHR is a national nonprofit organization based in Washington, D.C. dedicated to improving women's health through advocacy, education, and research, and is widely recognized as the thought leader in women's health research and sex-based biology. Since its founding almost 25 years ago, SWHR has been a strong advocate of greater public and private funding for basic science and biomedical research that can advance scientific knowledge, transform the quality of medical care received, and enable personalized evidence-based treatment options for women. SWHR actively supports research into how biological sex differences impact chronic diseases such as, cardiovascular disease, obesity, urological issues, sleep disorders, as well as its role in health outcomes for victims of domestic violence.

Collection, analysis and usage of data is a key priority issue for SWHR. SWHR has long advocated for the reporting and analysis of demographic data by our federal agencies, particularly subgroup analysis, to help inform research and innovation, drug labeling and medical decision-making. While advances in this effort were made by the inclusion of Section 907 within the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), we

are concerned that not all available post market data generated by biopharmaceutical companies is reaching health care providers and patients due to restrictions from the Food and Drug Administration (FDA). We are particularly concerned with availability of data on off label use of drugs as this has a unique impact on pregnant women for whom all drugs are generally prescribed off label.

Companies collect data directly through clinical research, observational studies, exposure registries and medical record research in order to help inform them on the medical decision process and to drive new research and innovation. They examine comparative data on the actual real world use of approved medicines and look at comparisons between two or more therapies. Further, companies look at sub-populations for safety and effectiveness, including sex and race, to advance scientific knowledge and the opportunity to potentially help healthcare professionals tailor their treatment to meet the needs of individual patients. Companies are generally restricted by FDA, however, from proactively sharing much of the data that they collect that exists outside of the package insert (PI) and may not add it to the labeling information for usage as this would be considered a new indication and such data may not have been generated as part of the clinical trials for drug approval. New indications for another use of a product already on the market as safe and effective are most often approved based on additional randomized controlled trials, which require significant time and resources. This has a particular impact on off-label usage of drugs.

We believe open and transparent communication of important scientifically accurate data is important to advancing medical treatments in the digital age. Access to company data should be established in a way that provides for appropriate communication to health care professionals and patients on medication usage that could improve patients' health outcomes. In particular, subgroup analysis can shed light on important sex differences that will help physicians tailor treatments differently to their male and female populations. For example, companies are required to collect this data in exposure registries by the FDA when a medication is used by pregnant women (as all medications used during pregnancy are off-label) but they are not allowed to discuss any of their findings from their registries directly with health care providers or patients.

SWHR believes that enabling greater use of real-world evidence will significantly impact diagnosis and treatment options for patients and their providers. Further, we would suggest that by providing open equal access to all stakeholder from researchers, clinicians, patients and the government to the data collected with systems in place to ensure the collection and analysis is rigorous and transparent will have a positive impact on helping to inform care and treatment in the digital age.

TRANSFORMING SCIENCE
SWHR
SOCIETY FOR WOMEN'S HEALTH RESEARCH

SWHR urges the Committee to hold a hearing on the issue of open and transparent access to scientific evidenced based data collected by biopharmaceutical companies on real world medication use as it directly impacts communication between health care providers and patients, quality of care received, and informed medical decisions on the off label usage of drugs, particularly in pregnant women as sick women get pregnant and pregnant women get sick and their health care providers need better guidance. SWHR believes this data should be accessible and transparently shared as it is critical to ensuring that patients are receiving the most effective care possible.

Sincerely,

[redacted]

Martha Nolan
Vice President, Public Policy

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette
Committee on Energy and Commerce
2322A Rayburn House Office Building
Washington, DC 20515

Re: 21st Century Cures White Paper on Patients

Dear Chairman Upton and Congresswoman DeGette:

The Alzheimer's Association appreciates the opportunity to comment on the white paper and applauds you both for your visionary leadership in developing the 21st Century Cures Initiative. Founded in 1980, the Alzheimer's Association is the world's leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease and other dementias through the advancement of research, and as the world's largest nonprofit funder of Alzheimer's research, the Association is committed to accelerating progress of new treatments, preventions and, ultimately, a cure. Through our funded projects and partnerships, we have been part of every major research advancement over the past 30 years.

No single organization can surmount a challenge as great as Alzheimer's. To help achieve our vision of a world without Alzheimer's, the Association partners with key government, industry and academic stakeholders in the global race to end Alzheimer's. We believe in the value of collaboration and work toward the day when we will have disease-modifying treatments, preventive strategies and gold-standard care for all people affected by Alzheimer's disease.

The Association has included answers to the questions raised in the white paper, and would like to highlight some points.

- Today, Alzheimer's disease is the 6th leading cause of death and the only cause of death in the top 10 without a way to stop, slow or prevent.
- Alzheimer's disease is the most expensive disease in America, and nearly one in five Medicare dollars is spent on a person with Alzheimer's
- Alzheimer's disease is woefully underfunded compared to the magnitude of the number of people affected daily, as well as the cost of care for individuals with Alzheimer's and related dementia.
- Beyond funding basic research in Alzheimer's, the government should incentivize private investment into biotechs working on Alzheimer's and related dementias. Private investment has moved away from the biotech industry which is seen as too risky.

- The federal government must also ensure that there is regulatory certainty that accommodates the risk-benefit of therapies unique to this disease state, as well as certainty that there will be access and coverage of new diagnostics and treatments that are developed.

The Association appreciates the steadfast support of the Committee and the great endeavor in which they are engaged. We look forward to continuing to work with the Committee in order to address the Alzheimer's crisis and hope that the Association will be called upon for our expertise in this area.

Sincerely,

Robert Egge
Vice President, Public Policy

1. **What is the state of discovery of cures and treatments for your disease? Are there cures and treatments now or on the horizon?**

- Today, Alzheimer's disease is the 6th leading cause of death and the only cause of death in the top 10 without a way to stop, slow or prevent. The last approved medication for Alzheimer's was approved over a decade ago and it is a symptomatic treatment, meaning it treats only the disease symptoms. We desperately need therapies to stop or slow the progression of the disease. There are over 150 clinical trials on-going today in the United States at different stages of development; however, we also critically need to continue to develop the pipeline for new therapeutic strategies to increase the probability of success for a cure or treatment on the horizon.

2. **What programs or policies have you utilized to support and foster research, such as patient registries, public-private partnerships, and venture philanthropy?**

- The Alzheimer's Association partners with EmergingMed and Association chapters across the US to offer the Alzheimer's Association TrialMatch®, a clinical studies matching service for individuals interested in identifying trials in their local community or across the US.
- In addition to funding infrastructure for studies such as the Dominantly Inherited Alzheimer's Network – Trials Unit (DIAN-TU), the Alzheimer's Association and the Fidelity Biosciences Research Initiative (FBRI) co-lead a collaborative effort to synergize prevention efforts in AD by facilitating comparative data and assessment efforts throughout collection and analysis. Studies in this effort include DIAN-TU, the TOMMORROW trial, the Anti-Amyloid Asymptomatic Alzheimer's study (A4), and the Alzheimer's Prevention Initiative (API).
- The Alzheimer's Association established the Global Biomarkers Standardization Consortium (GBSC) to develop standards for biomarkers studies used in research and clinical care; the GBSC is focused on cerebrospinal fluid standardization. Through the Worldwide Alzheimer's Disease Neuroimaging Initiative (WW-ADNI), the Alzheimer's Association convenes ADNI efforts from around the world to synergize data harmonization and spur research collaborations. The Alzheimer's Association also hosts the annual Alzheimer's Association International Conference® (AAIC), the largest meeting of AD researchers in the world. More than 5,000 attendees from nearly 70 countries utilize this platform to exchange and accelerate information on new diagnostic tools, the results of drug trials, and data on risk factors; and to convene related meetings for the dementia medical and scientific research community. Both the GBSC and WW-ADNI convene during AAIC.

3. **How can Congress incentivize, coordinate, and accelerate basic research for diseases we know relatively little about?**

- Alzheimer's disease is woefully underfunded compared to the magnitude of the number of people affected daily, as well as the cost of care for individuals with

Alzheimer's and related dementia. The Alzheimer's Association convened an international panel of experts to evaluate the needs of the field and determine the investment needed to achieve significant successes by 2025.

- Foster an environment that encourages open sharing of information and data.
- The government should incentivize private investment into biotechs working on Alzheimer's and related dementias. Private investment has moved away from the biotech industry which is seen as too risky. Even big pharma has moved away from Alzheimer's research and development. The federal government could provide tax incentives to companies and investors for supporting Alzheimer's R&D. This could create a strong eco-system of innovative biotech companies working to bring Alzheimer's treatments to the clinic.

4. How can we work together to better translate advances in science into safe and effective new therapies for patients?

- The Alzheimer's Association, other non-profit foundations and the NIH fund AD research but more support is needed for translational research in order to convert the research discoveries of today into the effective treatments of tomorrow. Congress could provide more funding to the NIH SBIR grant program with money specifically targeted to small companies doing AD research. Many of these companies are spun out of government or Alzheimer's Association funded academic research. These small companies need funding to translate their academic discoveries into clinical candidates.

5. What is the role of government in your work, including any barriers to achieving your goals and advancing breakthroughs?

- The Association is an active collaborator with many government entities around the world.
- The Alzheimer's Association, in partnership with NIA/NIH and Alzheimer's Research UK, convenes over 30 AD research funding organizations from 10 countries through the International Alzheimer's Disease Research Funder Consortium (IADRFC) to enable information sharing and collaborative efforts that leverage investments made around the world to advance AD and dementia science.
- The Alzheimer's Association also collaborated with the NIA/NIH to develop the Common Alzheimer's Disease Research Ontology (CADRO) to catalogue international research funding. Many federal and nonprofit organizations have coded their funded research by the CADRO and contributed their data to the International Alzheimer's Disease Research Portfolio (IADRP), a database housed on the NIH Library's website. Participating organizations include Alzheimer's Australia, Alzheimer Society of Canada, Alzheimer's Society, Alzheimer's Research UK, Ellison Medical Foundation (EMF), Alzheimer's Drug Discovery Foundation (ADDF), Alzheimer Nederland, Patient Centered Outcome Research Institute, and Cure Alzheimer's Fund.
- The Alzheimer's Association and the Centers for Disease Control and Prevention's (CDC) Healthy Aging Program have partnered since 2005 under the Healthy Brain

Initiative (HBI), a multi-faceted collaboration that seeks to educate the public, public health community and health professionals about Alzheimer's disease as a public health issue. Under the HBI, the Association and the CDC Healthy Aging Program have developed the second in a series of road maps that contain actions public health officials can take to address cognitive health, Alzheimer's disease, and the needs of caregivers. The first Road Map was released in 2007, and the latest update – The Healthy Brain Initiative: The Public Health Road Map for State and National Partnerships, 2013-2018 – was released in July 2013. The Alzheimer's Association, together with the Reagan-Udall Foundation (RUF) for the FDA launched a new fellowship to allow an experienced physician, dedicated to treating and studying Alzheimer's disease, the opportunity to work collaboratively with the FDA.

6. **How should regulators evaluate benefit-risk? How do you work with regulators regarding benefit-risk? Can this process be improved?**

- Alzheimer's disease is fatal, and currently there are no treatments, preventative measures or cures.
- Treatments that would halt the progression of cognitive and physical decline would benefit both patients and caregivers. We acknowledge that it is difficult to determine to what extent the patient population as a whole would weigh potential side effects and benefits of new treatments but we believe more can and should be done to better measure the value of new therapies to patients with cognitive disease.

7. **What is the role of public and private funding in the research and development of cures and treatments?**

- As the largest non-profit funder of Alzheimer's research in the world, the Alzheimer's Association looks to make significant impact in high risk, high reward projects and scientific ideas; to provide seed funding for innovative ideas that will give rise to larger projects; and to foster the early career scientist as they establish themselves in the dementia research space.

8. **What is the financial burden of your disease? How would better treatments and cures help save money for your family and the federal government?**

- The financial burden of Alzheimer's disease is huge and getting bigger. Medicare and Medicaid are expected to pay $150 billion in 2014 for health care, long-term care and hospice for people with Alzheimer's and other dementias. By 2050 these costs are projected to be $1.2 trillion (in 2014 dollars). This dramatic rise includes a six-fold increase in government spending under Medicare and Medicaid and a five-fold increase in out-of-pocket spending.
- Families still provide a large percentage of support to people with Alzheimer's. In 2013 Americans provided 17.7 billion hours of unpaid care to people with

Alzheimer's disease and other dementias. This is the equivalent value of $220 billion in unpaid care.
- Effective treatments for Alzheimer's could dramatically improve the financial burden on the government and on families. In addition, an effective treatment would relieve the stress placed on families by Alzheimer's disease.

9. How can Congress help?

- Basic research remains the key to addressing Alzheimer's disease. A disease-modifying or preventive therapy would not only save millions of lives but would save billions of dollars in health care costs. Specifically, if a treatment became available in 2015 that delayed onset of Alzheimer's for five years (a treatment similar to anti-cholesterol drugs), savings would be seen almost immediately, with Medicare and Medicaid spending reduced by $42 billion in 2020.
- Today, despite the federal investment in research, we are only just beginning to understand what causes the disease.
- Along with a robust investment in Alzheimer's research, there must also be regulatory certainty that accommodates the risk-benefit of therapies unique to this disease state, as well as certainty that there will be access and coverage of new diagnostics and treatments that are developed.
- For example, last fall CMS had determined that a new PET Imaging product aimed at supporting the diagnosis of Alzheimer's disease did not provide adequate benefit to patients and was granted coverage with evidence development (CED) despite strong evidence to support full coverage from the clinical, research and patient community.
- This determination not only has the effect of limiting access to this critically important diagnostic tool, but it also sends the message to developers that there is uncertainty in CMS coverage for new diagnostics in this space.

Home Dialyzors United
Dialysis Support and Advocacy

June 9, 2014

The Honorable Fred Upton, Chairman
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Re: 21st Century Cures Initiative

Dear Chairman Upton and Congresswoman DeGette:

Home Dialyzors United (HDU) appreciates the opportunity to provide comments to the Energy and Commerce Committee about the 21st Century Cures Initiative. The members and board of directors of HDU share the goals to "accelerate the discovery, development and delivery of new treatments to patients." We also look forward to assisting the Committee to ensure that these goals are met for home dialysis patients.

Home Dialyzors United (HDU), a 501(c)(3) non-profit organization, is the only dialysis patient group dedicated to home dialysis. Our mission is to educate, support, and advocate for home dialysis. We believe that patients and care partners can live a normal life including employment, education, volunteerism, family life and leisure pursuits. We further believe that Congress can help their constituents with chronic kidney failure (ESRD) reach those goals.

Both peritoneal dialysis and home hemodialysis offer advantages over in-center treatment. Studies have shown that more frequent dialysis at home means potentially lower risk of death and hospitalization, increased energy, lower cost, fewer medications, and less stress on the heart. In addition, home hemodialysis usually offers more frequent and/or extended time dialysis, which translates into quicker recovery time after treatment, fewer side effects, and a more normal diet. Home patients enjoy more freedom and flexibility to live a normal life.

Despite proven benefits, too many patients are unaware of this option largely because Medicare policies are not making home treatment fully accessible to Medicare beneficiaries and new machines designed to be used in the home are often not being approved in a timely manner. Yet, the Social Security Act specifies that it is the intent of Congress that "any patient who is a suitable candidate for home dialysis should be so treated." Consider the following statistics:

- Currently, just 10% of U.S. dialysis patients receive treatment at home, a method that is a lower cost option than treatment in traditional centers. Less than 2% of those patients use home hemodialysis treatments.

- Only 24% of centers are certified to offer home hemodialysis (HHD), which means access to home hemodialysis may be dependent on such arbitrary factors as where the patient lives. Rural areas are traditionally underserved.

- Only 12% of patients report receiving education about HHD despite the fact that Medicare requires education about all options.

- Nephrologists believe that a much higher percentage of patients would be good candidates for HHD but less than 2% are currently using this treatment modality.

While HDU believes that well designed studies and the resultant statistical data are a vital component of research, development and delivery of better treatment, we also feel that one aspect is glaringly lacking—that of patient and care partner involvement. While scientific data derived from RCTs contribute to improvements, they do little to assess quality of life and the ability of patients and families to lead a normal life. There is no other chronic disease that, on a daily basis, affects literally every single aspect of life from the kitchen table to the bedroom and even into the broader community. Due to the nature of treatment, chronic kidney failure (ESRD) directly impacts the entire family. Therefore:

- HDU strongly urges all those involved in the 21st Century Cure Initiative to include patients and care partners in every aspect of the process. Who better to offer input than those who live with chronic kidney failure every single day? With the increased emphasis on patient engagement and patient empowerment, the 21st Century Initiative has the chance to be a leader in making a real paradigm shift.

- HDU also requests that the 21st Century Initiative carefully consider the alignment of new discoveries with regulatory policy to facilitate the development and approval of home dialysis friendly innovations. We urge the Initiative to expedite the delivery of new developments. A recent example of this is the FDA fast tracking of research projects and clinical trials, three of which are dialysis related.

- HDU urges movement in the direction of real patient-centric quality measures. For example, collecting data on patients who are employed and incentivizing facilities to keep those patients employed would have a nearly immediate effect on care and innovation. Not only would such a measure help meet the psychosocial needs of patients, but it would also save government dollars. According to 2010 USRDS statistics, only about 20% of chronic kidney failure patients, ages 18-54, are currently employed.

- In order to foster patient and care partner engagement, HDU employs a “Buddy System” of peer mentoring. HDU also requests that peer mentoring be included in the delivery of new developments.

- Lastly, we ask that the 21st Century Initiative support a “home first” culture by fostering not only new developments but also the education of all patients about the advantages of home dialysis therapies.

Home Dialyzors United is a voice for many patients and care partners who are living a normal life despite chronic kidney failure. In the process of developing these comments, HDU has solicited opinions from a cross section of our individual members through our social media sites. A sampling of these opinions is attached in the addendum.

HDU thanks the committee for the opportunity to comment on the 21st Century Cures Initiative.

Sincerely,

Home Dialyzors United Board of Directors

Jim Smith
Denise Eilers, RN, BSN
Benjamin Ruback
Patricia Colongione
Melissa Sondergaard

21ST CENTURY CURES INITIATIVE
HDU ENERGY & COMMERCE LETTER
[1]PATIENT COMMENTS

What is the state of discovery of cures and treatments for your disease? Are there cures and treatments now or on the horizon?

Dialysis machines have evolved extremely slowly for about 50 years. I usually say that if the evolution in consumer electronics had followed that of dialysis machines, my laptop would be the size of Manhattan.

Then NxStage came along and changed the game. They made a machine that was (somewhat) portable so people could enjoy just a modicum of freedom. Now we are 1000's of patients enjoying the freedom this machine gives us.

But many of us are waiting for truly portable dialysis machines, just like we're waiting for devices that can be worn and/or implanted to help us overcome our kidney disease.

Henning Sondergaard

At this time, there is no cure for end-stage renal disease, only treatments. There are two treatment options, transplantation or dialysis. Not everyone is eligible for transplantation, many people cannot afford the expense of medication after the period of time when they become in-eligible for Medicare coverage, and furthermore, there are simply not available organs to meet the need of those waiting.

The other treatment option currently available is dialysis. The majority of patients dialyze in dialysis units, generally three times a week. Kidneys function twenty-four hours a day, seven days a week; most dialysis patients get twelve hours a week of dialysis to clean their blood. Between these intervals, toxins and fluids build up in their bodies, and systemic long-term health effects commonly occur. Immediately post dialysis, most patients who dialyze in this manner, have severe intra-cellular fluid shifts, resulting in low blood pressure that gives rise to cramping, dizziness, and a generalized feeling of exhaustion.

A small percentage of patients perform dialysis at home, either doing peritoneal or hemo-dialysis. Peritoneal dialysis uses the body's own peritoneal membrane within the abdominal cavity to act as a filter. It is a continuous treatment and provides a reasonable standard of dialysis. However, its effectiveness tends to rely on a person have residual urine output, again, not everyone is a candidate, and after a time, the peritoneal membrane tends to lose its capability to filter effectively.

The remaining number of home patients do hemo dialysis using either a standard full-size machine, or a smaller, portable (still very heavy) machine. Home dialysis allows patients to do more frequent treatments in the comfort of their own home. This gives better long-term outcomes, lower mortality rates and a much better quality of life. The best outcomes are achieved from overnight treatments. This is currently no machine on the market that is FDA approved for home nocturnal use.

There are facilities who are endeavoring to make wearable and implantable artificial kidneys, and although on the horizon, probably within the next few years, at this time are either in the design and/or trial phase.

I personally do home hemo, using the more portable machine. Although listed for a transplant, a high antibody level means a transplant is an unlikely option. In the past I have done peritoneal dialysis, but this no longer works for me. I elected to do home hemo, because although onerous on time, it gives me the greatest flexibility, I feel well doing it, and it allows me greater control and independence over my life. In addition, get to spend more time with my family and it is also relatively easy to travel.

Amanda Kirkby Wilson

More money and emphasis needs to be put on WAK and the small implantable kidney. In this day and age it shouldn't be taking so long for this big improvement.

Debi Barnard

Unfortunately we are still in the dark ages when it comes a cure, a real cure, for kidney failure, either the hereditary type (PKD) or from high blood pressure and diabetes. The best near-term hope seems to be a wearable or implantable device using sorbent technology, which may be a decade or less off and offer round-the-clock dialysis for many waiting for a transplant or those for whom a transplant is not feasible.

Renal failure is fast approaching epidemic proportions, worldwide. Yet, the emphasis and funding continues to be placed on treatment and not basic research into why kidneys fail. It's a very sad comment that dialysis treatment has focused on an out-moded modality and an unproven treatment standard (3x/wk.), while too little has been spent on original research. The reason for this, I believe, is the heavy reliance on a for-profit treatment system in the U.S., which offers little incentive to innovate and seek a cure. The current dialysis system is too lucrative. Unlike other diseases, like some forms of cancer, where huge gains have been made in the last forty years, dialysis is still back in the 1970s.

David Rosenbloom

What programs or policies have you utilized to support and foster research, such as patient registries, public-private partnerships, and venture philanthropy?

In the last year I have participated in two research programs trying to better dialysis machines. One was by a Swedish designer who wanted to make the home hemo machines more 'humane' the other one was by two Danish engineer students who were very keen on advancing home hemo dialysis to the next level - whatever that is.

I have also closely followed the development of the WAK and talked to its designer a few times. And lastly I keep a very keen interest in all the other technologies out there so we can get better treatment.

Unfortunately it seems like most researchers in nephrology are afraid of patient voices. There is way too little exchange between doctors and patients in our field. Patients have so much experience from their own bodies that many of us are better specialists than our physicians. Now we just need those physicians to stop being afraid of us and listen to the experts - their very own patients!

Henning Sondergaard

I believe we need more accurate patient attitude research on rehabilitation - on how patients feel about the present dialysis system's limitations on lifestyle and quality of life issues. We have tons of rather irrelevant medical data, which divorces the person from their medical histories. I have just finished a project with the public policy school at USC, and am seeking financial support for a very extensive kidney patient attitude study in Southern California.

David Rosenbloom

Some doctors might say there are plenty 'quality of life' (QOL) studies. But they all are focused on irrelevant medical data that have been determined by medical staff to reflect QOL but that are really just poorly disguised data on how well people hold up to in-center treatment. We need real life data, a.k.a. qualitative data that is based on what patients find is important for them, and NOT what doctors and nurses have pre-determined should be researched about us.

Henning Sondergaard

How can Congress incentivize, coordinate, and accelerate basic research for diseases we know relatively little about?

The most major issue I have with dialysis and renal disease in general is that the questions that they are all trying to ask are so obviously made for doctors by doctors. Nobody ever asks what is important for patients.

Nobody ever looks at quality of life (QOL) issues. There are 1000's of research papers that claim to focus on QOL but they are all looking at medical issues that doctors have determined must be QOL issues – NOT what patients really think about their life and their situation as dialysis patients.

Then, of course, there's the issue of home dialysis. When is somebody going to take a good hard look at the benefits of it over in-center treatment? We all know how much better it is so why is it only 1.3% on HHD and 7.3% who are on PD at home? This is appalling numbers and something serious needs to be done to make this (all the more humane) treatment option available to EVERYONE who is eligible and willing. And it needs to be done yesterday!

Henning Sondergaard

Shoulda been done yesterday!

Jennifer Shufelt

As you said the majority of the machines are made so health personnel can STAND and control the machine. The way I see it machines need to be able to be controlled by patients lying or sitting down….we have a long way to go….now we are not just surviving….but actually live good lives. That is surely the new goal…bringing patients into the game.

Malene Madsen

Addressing education about treatment choices: When and how are these choices presented?

"My husband was never told of any options. He started hemo in the hospital last April and was never given any option of hemo or PD. Then once he was out and in center he was never given any other options. I was the one who did all of the research online to figure out his best options and to find places that did home hemo and sit down to talk with them about the training process, etc."

"We found it [home HD] on our own and pursued the option on our own with a little help from our PCP. They may have mentioned PD at first, but more or less pushed for hemo. PD was something they later told us was an option but I don't know of anyone who went to the center who ever actually did it...even now I only know of two people in our area who do PD and one of them travels an hour away to the same center that we go to. IMO if what they offer is the best option for you that's fine but if there's another option, especially a better option, they should at least give you the opportunity to make your own choice even if they don't offer it themselves!"

"We were told about PD in our initial nephrology visit but in-center hemo seemed to be their main push. I think they anticipated that my Mom would be on dialysis almost immediately after her first visit based on numbers. But, at 81, she still wants to have all her questions answered before making a decision. So we looked for answers to her questions and ended up on PD after three years of clinic visits. I believe that part of the challenge in our case was that their clinic is segmented. You have in-center dialysis nurses and then you have home dialysis nurses."

"My center gave me options: in-center, PD, or no treatment! They had not heard of Buttonholes or told me, 'They are not safe or effective.' I had a VERY difficult access AND a very real needle phobia. My Neph agreed HH would be better for me. My clinic REFUSED to allow me to do a Buttonhole b/c they had no techs trained in it! After 8 years the clinic got a new director. She was appalled that I had NEVER been told my HH options AND that when I asked, I was routinely told it is waaaaaaay more dangerous to do HH! As I look back, my heart is sad that I stayed in that stupid center 9 years total!"

"I was offered in center only, PD was mentioned briefly, but only in a passing manner while I was in the middle of a treatment. I was never told about NxStage. I researched it myself and switched centers to get it. I think I found out about it from ihatedialysis.com. I also got a load of garbage from my old center about how I was going to die if I did home hemo with NxStage. I know it's because I

was still in the middle of my 30 month coordination period and they were raking in the cash from my insurance company."

"I had to change centers to one that offered HH. The Neph who treats me when I am in hospital told me 'under NO circumstances would I recommend HH. You need to trust the people who are TRAINED to care for you!' Since then, he has said my experience CHANGED HIS OPINION of HH!!! WHAT? Ugh! Imagine HIS patients who missed this AMAZING gift b/c of his misguided belief!"

Someone above commented about us being given choices based on what was perceived as "best for us", but according to WHO? The very people who stand to make money from us being there? I was 36 years old w/3 kids 4-9 I was homeschooling! I had no other health issues AT All (PD was not option b/c of scar tissue). I should have been the EXACT candidate they recruited for HH! I missed so much time with my kids (1 of whom was 8 & had just finished a 2 year battle w/cancer when my transplant failed). NOT BEING GIVEN INFORMATION impacted me—and THEM—forEVER! Please let's do something!

Anonymous Quotes as excerpted from: *(*http://www.homedialysis.org/news-and-research/blog/45-dialysis-options-education-is-not-optional)

I don't remember exactly when the options were introduced (I was in center just under a year and remember having a first real conversation about home hemo briefly early on, and re-visited towards the end), but I was told initially that I would not be able to do home hemo because I was single and did not have a "caregiver". Within a year, I wanted to get out of the center environment so badly, I proved them wrong and completed the training! I just celebrated a year of doing home hemo solo. My home team is learned, accessible, and supportive. It is like night and day, and although there were trade-offs (more work, more time on the machine, etc....), at least I can concentrate on my health and my sanity. I have not infiltrated or bruised myself and my fistula is thankful for it. I am extremely grateful for home hemo, and wishful for better solutions for all kidney patients in the future.

Two years ago, I was told there was no hope of a cure, my disease was progressive, and my expected average mortality rate was 3 years. I've been told a transplant has a 5 year wait time for my blood type with a high probability that the disease will return to the new kidney.

Robin Franzi

On behavioral psychology and measuring the benefits of dialysis.

I am all about promoting and educating people on the BENEFITS of proper dialysis treatment. This section of a lecture from Harvard on US Health Policy had some examples about Organ Donation and how many more organs are available with an OPT OUT system, and some behavioral psychology notes that I think have everything to do with the problems involving the current treatment models of dialysis. 1) One is that we know that human beings have trouble processing large numbers of options. So that would include both physicians and patients. If you give them a lot of choices they may actually make worse choices than if you give them a few choices. 2) it's also true that people have trouble making choices that have different consequences over time. 3) Another bias is that people really like what they have, in particular, and they are particularly averse to losses, in a way that's not symmetric with the way they look forward to potential gains, in terms of things that they don't have. 4) Here's another important phenomenon called the status quo bias that people are likely to avoid a choice where they can. And so they favor wherever they are now versus any other option to a degree that is not optimal. 5) We know one rule of thumb that people use is pick the top plan or pick the top choice. It's easy. It's at the top of the list so organization and presentation of information matter

These behavioral situations totally scream KIDNEY & DIALYSIS to me, and how it is currently presented to anyone dealing with it.

Mikey Hann

National Breast Cancer Coalition

The Breast Cancer Deadline 2020

1101 17th Street, NW, Suite 1300, Washington, DC 20036 | P 202.296.7477 | F 202.265.6854

June 12, 2014

The Honorable Fred Upton
Chair, House Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515

Sent via email to cures@mail.house.gov

Dear Chairman Upton:

On behalf of the National Breast Cancer Coalition (NBCC), I would like to thank you for undertaking the 21st Century Cures initiative and reaching out to the patient advocacy community for guidance and input. We look forward to working with you, your staff and the other members of the Energy and Commerce Committee on our shared goal of ending diseases such as breast cancer.

As NBCC advocates from Michigan have shared with you and your staff, in 2010 NBCC set a deadline to know how to end breast cancer and launched a plan to achieve it. **Breast Cancer Deadline 2020®** is a call to action for all stakeholders - policymakers, researchers, breast cancer advocates and others - to concentrate their efforts on knowing how to end the disease by the end of the decade. Like the 21st Century Cures initiative, **Breast Cancer Deadline 2020®** intends to shift the focus toward what will truly benefit patients, to encourage new approaches, to look at disease differently.

NBCC undertook **Breast Cancer Deadline 2020®** after reviewing the progress that has been made in knowing how to prevent breast cancer or how to prevent deaths from the disease. While new ways to treat breast cancer have been discovered, they have not had a great effect on the important outcomes: preventing breast cancer and making certain no one dies of it. In the United States, the chance of a woman developing breast cancer during her lifetime has increased from 1 in 11 in 1975 to 1 in 8 today. In 1991, 119 American women died of breast cancer every day. This year, that number is estimated to be 110, adding up to about 40,000 lost lives.

The financial realities of the disease are also staggering. The National Cancer Institute estimates that breast cancer care in the United States cost $16.5 billion in 2010. It estimates if the status quoi continues, this care will cost $20.5 billion by 2020.

To change these outcomes, NBCC has developed a strategic plan which will leverage existing financial resources to harness the knowledge and experience of years of research to catalyze innovation. **Breast Cancer Deadline 2020®** will capitalize on the investments made by our nation which have resulted in the knowledge, tools and technologies needed to end breast cancer.

NBCC's strategic plan requires all stakeholders involved in research, particularly the scientific community, to work together to build synergies and partnerships to advance the pace of research. In order to assess the extent of the problems, identify meaningful questions and the individuals and tools needed to answer, NBCC began with strategic summits bringing together stakeholders and other visionaries.

Over the course of NBCC's **Breast Cancer Deadline 2020®** work two such summits have been conducted: one on primary prevention, the other on preventing metastasis. The recommendations from these summits were then refined and prioritized, those priorities likely to achieve the Deadlines goals identified and catalytic projects known as Artemis Projects were launched.

The Artemis Projects are innovative, advocate-led, mission-driven models which ensure appropriate focus on the end result. For each catalytic project, collaborations are formed on specific issues to define solutions and implement research plans to achieve them. Research plans are being developed, implemented and overseen by project participants and the work will include in-person meetings and use of the web and social media to exchange data and information and facilitate collaboration.

The topic chosen for the first Artemis Project, launched in 2011, was a five year development plan for a breast cancer preventative vaccine. It was chosen because of the potential impact on breast cancer and the progress made in the field of immunology. A research plan is in place and being implemented and multiple NBCC seed grants to allow researchers to begin the research required in each of the key areas identified in the collaborative research plans have been awarded. In addition, annual meetings and issue-focused meetings to address specific issues that are raised at the annual meeting have been held. A second Artemis Project on tumor dormancy was launched in 2013 and will follow the successful model of the first such project.

Just as NBCC is leveraging existing scientific knowledge towards knowing how to end breast cancer in its Artemis Projects, the *Accelerating the End of Breast Cancer Act* (S. 865/H.R. 1830), seeks to build on the decades of our nation's medical and scientific investment and achievement and apply these towards ending breast cancer deaths and learning how to prevent the disease.

Specifically, the *Accelerating the End of Breast Cancer Act* focuses on identifying strategies for primary prevention, stopping women from getting breast cancer, and understanding and preventing metastasis (the spread of cancer), which is responsible for 90% of breast cancer deaths. It would create the Commission to Accelerate the End of Breast Cancer comprised of a few representatives of biomedical research, business, breast cancer advocacy, and other related and unrelated disciplines, who have demonstrated an ability to be innovative. This tactical Commission would be tasked with identifying promising opportunities, tools, technology and ideas not currently being prioritized for breast cancer by the public and private sectors, but which hold true promise in ending breast cancer. It will implement strategies to leverage these opportunities and maximize prior investments in these areas.

The *Accelerating the End of Breast Cancer Act* would not duplicate the efforts of other government agencies and programs, but instead help ensure our nation's limited research dollars are leveraged to accelerate progress already begun. It would seek to harness the nation's continued drive for innovation, and help ensure our position as the worldwide leader in medical and scientific advancement.

Like **Breast Cancer Deadline 2020®**, the 21st Century Cures initiative appears to share the desire to apply the knowledge and advances that have been made by our nation to answer the many questions that still remain in so many diseases, including breast cancer. Through its ongoing Artemis Projects, NBCC is challenging the existing scientific paradigm and making real progress towards answering the questions necessary to end a disease that is annually taking the lives of over 40,000 US women and 430 men. The *Accelerating the End of Breast Cancer Act* takes another step towards this goal by defining a necessary and important role that the federal government must play in this effort.

We look forward to working with you and your staff as the 21st Century Cures initiative moves forward.

Sincerely,

Fran Visco
NBCC President

National Kidney Foundation™

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New York, NY 10016

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The National Kidney Foundation appreciates the opportunity to respond to select questions, where we can lend our expertise, contained in the House Energy and Commerce Committee's 21st Century Cures – Patients white paper. The National Kidney Foundation has a patient and patient family membership of over 50,000. To solicit input for some of the patient experience questions we surveyed some of these members and their input is incorporated into NKF's responses below.

What is the state of discovery of cures and treatments for your disease? Are there cures and treatments now or on the horizon?

Chronic Kidney Disease (CKD) is a significant public health problem in the US, with an estimated 26 million people having measureable kidney dysfunction and another 73 million at risk, yet there are currently no medications that are specifically indicated for the treatment of chronic kidney disease (CKD). Current clinical management of CKD relies on the effective treatment of risk factors associated with kidney disease such as hypertension and diabetes, or minimizing exposure to potentially kidney toxic drugs such as non-steroidal anti-inflammatory drugs (e.g. ibuprofen, naproxen) and contrast agents used in radiology studies.

The progression of CKD is often slow, and there are few specific symptoms until the final stages of kidney failure have been reached. This makes the development of treatments specific for CKD both complex and costly. Because the treatment benefits of primary interest to the patient are not expected to manifest for many years, clinical trials evaluating a CKD treatment rely on a surrogate outcome such as glomerular filtration rate (GFR).

There are currently a couple of experimental agents for the treatment of CKD that have progressed to the later stages of clinical development. However, due to the difficulty in recruiting study subjects, who are frequently unaware of their CKD, and the length of time it takes to establish efficacy based on current FDA requirements, even if found to be efficacious these drugs are many years from receiving market approval. There are several other therapies in earlier stages of clinical development, but it is uncertain if any will move forward due to the lack of understanding of the natural course and biomarkers to assess progression of CKD.

As previously mentioned in our response to the Call to Action, the biggest barrier to approval of a drug to slow the progression of CKD is the length of time it takes to reach the current FDA endpoint, which is the doubling of serum creatinine (57% decline in kidney function based on glomerular filtration rate). The trial design required to reach that endpoint can take well over five years and

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are excessively expensive to conduct, making studies in CKD drugs less attractive to manufacturers. Just last year the FDA did not approve a drug shown to reduce the size of cysts in patients with autosomal dominant polycystic kidney disease (APKD) because it did not meet the endpoint for delaying kidney failure in patients and had risks of causing liver disease. Despite these risks, some patients with APKD stated that they would be willing to take the drug because of the evidence that it would reduce the size and number of the cysts, which causes significant pain and discomfort. The FDA stated further studies would be required before approval would be considered. The drug has since been approved in Japan.

A recent meta-analysis published in the Journal of the American Medical Association, shows a lesser decline in kidney function, such as 30% over 2 years, is a strong predictor of progression to ESRD or higher mortality. This published meta-analysis was one of the outcomes of the clinical endpoints workshop led by NKF and FDA, where data was presented that showed the lesser decline in kidney function could improve the efficiency of clinical trials for drug approval.[1] Hopefully, these results will lead to action to improve the design of future clinical trials. Yet it is also critical that further research be conducted to better understand the natural history of CKD and develop better biomarkers to assess the progression of kidney disease.

For people with kidney failure there are treatments in the pipeline to address comorbidities related to ESRD, like anemia, and some new immunosuppressive medications that would reduce the pill burden for kidney transplant recipients. There are also a few devices (home dialysis machines, wearable kidneys, implantable artificial kidneys) being developed. It is anticipated that two new home dialysis machines will be available in the next couple of years with the wearable kidney and implantable artificial kidneys still a number of years away. However, the FDA approved a wearable kidney design for a fast-track review under the FDA's innovation approval pathway, which could make the device available sooner.

What programs or policies have you utilized to support and foster research, such as patient registries, public-private partnerships, and venture philanthropy?

NKF has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD) since 1997 through the NKF Kidney Disease Outcomes Quality Initiative (NKF KDOQI) and is a founding partner in the Kidney Disease Improving Global Outcomes Initiative (KDIGO). Most recently KDIGO released new guidelines for the treatment of CKD, which also created new staging

[1] Coresh J, Turin TC, Matsushita K, et al; for the CKD Prognosis Consortiu, Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. doi:10.1001/jama.2014.6634.

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for CKD to take into account the risk of disease progression. KDOQI published a detailed commentary on the guidelines translating the global work into U.S. practice guidelines.

In the past 45 years the National Kidney Foundation has provided $90 million in research grants mostly to support young investigators work. Moving forward NKF plans to continue its research program by targeting research to address knowledge gaps in the progression of CKD. NKF is seeking public and private funding to further these goals. While many federal grant programs exist it is a time and resource consuming effort to seek out federal dollars to fund these types of projects, particularly when so few grants are specifically earmarked for kidney disease research.

To truly address gaps in knowledge for CKD we need a national patient registry to prospectively evaluate the natural history of kidney disease and how variations in clinical practice affect outcomes. With private funding NKF plans to continue its partnership with Johns Hopkins University to run a global CKD Prognosis Consortium, which has data on 1.7 million people with CKD in 35 cohorts to help answer some of the unknown questions of CKD. However, a robust registry to track CKD in the US is needed to be able to compare data across one system and learn more about CKD and its progression.

How can we work together to better translate advances in science into safe and effective new therapies for patients?

There are a number of research projects underway funded by the Federal government across various agencies. However, there is a need for stronger interagency coordination and communication to share results and address gaps in science so that ultimately barriers in clinical trials can be addressed. Recently introduced legislation, H.R. 4814 the Chronic Kidney Disease Improvement in Research and Treatment Act of 2014, calls for a GAO study of current research in kidney disease and an interagency research coordinating entity.

In addition, innovation in pharmaceuticals for kidney patients could be accelerated if FDA were willing to consider surrogate end points and patient reported outcomes as basis for approval. Given the prevalence of CKD and the Federal government's investment in treating ESRD, it was surprising that the FDA Patient Focused Drug Development Initiative did not select CKD as one of the disease areas to address. NKF believes the FDA should prioritize innovation in CKD by including it in this initiative.

How do you coordinate your research and outreach with other patients?

NKF collaborates with non-kidney groups such as the American Diabetes Association and the Juvenile Diabetes Research Foundation to address gaps in research of diabetic kidney disease. NKF has also worked with the American Heart Association as a workgroup member on a sodium

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consensus conference and with the American Association of Clinical Endocrinologists on a recent obesity conference. This collaboration has helped to draw attention to the need to address kidney disease in research regarding direct and indirect causes.

As a board member of the Kidney Health Initiative (KHI), a public private partnership with the FDA and other Federal agencies, we work together with other kidney patient organizations as well as professional societies, health care providers, and drug and device manufacturers to address research gaps in treatments for kidney disease, particularly kidney failure.

How do you learn about new treatments and cures? How do you communicate with other patients regarding treatments and cures?

NKF surveyed kidney patients and family members using an online survey to answer this question. Out of 745 respondents with email addresses, 64% of patients and family members reported discussing new developments in the treatment of kidney disease with other patients and families in their healthcare providers office, dialysis facility or transplant center and 31% reported using social media to communicate about scientific advancements in kidney disease.

What can we learn from your experiences with clinical trials and the drug development process?

There is a great need for reliable biomarkers to more accurately assess CKD progression and risk, thereby improving the efficiency of clinical trials, and a need for validated survey tools to evaluate patient preferences and quality of life when considering new therapies to treat people with kidney disease. These changes will help spur innovation and expedite the development of new treatments that make meaningful improvements in patients' lives.

Out of 194 survey respondents that reported participating in a clinical study, there was a notable trend that participation led to a better understanding of their individual role in managing their disease through strategies like improvement in diet and medication adherence. However, our survey also identified a greater need to educate and communicate with patients generally about clinical studies and their value.

What is the role of government in your work, including any barriers to achieving your goals and advancing breakthroughs?

The Federal government is the leading payer of treatments for kidney failure and its payment policies have a direct impact on innovation and advancements in care. For example, the Medicare ESRD program pays for dialysis and transplants for most of the 616,000 people with kidney failure. However, if a patient is fortunate enough to receive a kidney transplant Medicare coverage will end

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36 months post-transplant for non-aged or non-disabled Medicare beneficiaries, requiring recipients to seek coverage elsewhere. Kidney transplant recipients must take immunosuppressive drugs for the rest of their lives to reduce the risk of rejecting the kidney. Insurance coverage so that patients can afford these meds is vital. However, even with the expansion of insurance coverage due to the Affordable Care Act not all recipients are able to afford coverage. Without coverage for immunosuppressive drugs those patients are likely to reject their transplants and return to Medicare covered dialysis. Knowing that they may not be able to afford the immunosuppressive drugs post Medicare coverage, some patients do not even seek transplantation or have refused a transplant from a family member who was willing to serve as a living donor.

Payment for dialysis and related medications could also be a barrier to advancement and innovation in treatments for kidney failure. In 2011 the Medicare ESRD program moved to a bundled payment, which includes the dialysis treatment and all related injectable medications (and the oral equivalents). Any new medications developed to treat dialysis patients would be bundled into the payment. Unlike other payment systems, there is no temporary pass through payment or adjustment for new technology to temporarily provide for separate reimbursement of the new therapy.

For earlier stage CKD there is very little incentive for physicians to actually diagnose CKD even when it is detected through a lab test. Private plans often bear little to no responsibility for paying for kidney failure so it's not always a high priority for private quality incentive programs. Often times even when a physician tests for kidney function and receives positive results a diagnosis code is not applied. As a result the patients and other healthcare providers are unlikely to be alerted to the declining kidney function. This is problematic because there are steps a patient and practitioners can take to reduce patients' risk for morbidity, mortality and progression to kidney failure, such as avoiding certain medications and modifying diet. In addition, with CKD dramatically underdiagnosed there is a limited pool of data for drug developers to understand the size of the market and to appropriately target therapies to treat CKD.

Under Medicare Advantage (MA), risk adjustment payment was applied for CKD diagnosis, which improved diagnosis of CKD in MA compared to Medicare Fee For Service. However in 2014, CMS removed the Hierarchical Condition Categories from MA payment for CKD stages 1-3. This eliminated an incentive to diagnose patients earlier as well as removed payment for treating patients known to have higher healthcare costs because of their comorbidities.

Beyond payment policy, the United States Preventative Services Task Force (USPSTF) has sent mixed signals on the value of screening for CKD. In 2012 USPSTF issued recommendations on the value of screening CKD in the general population. These recommendations received a C rating due to

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inconclusive evidence. USPSTF has not evaluated the merit of CKD screening in specific at risk populations, such as those with hypertension, diabetes, or over age 60, as advocated by the NKF. USPSTF recommendations are important because under federal health care programs patients can receive screenings and treatments that receive a grade of A or B without any cost sharing.

How should regulators evaluate benefit-risk? How do you work with regulators regarding benefit-risk? Can this process be improved?

As mentioned previously, patient-reported outcomes are largely dismissed by FDA when considering new therapies for people with kidney disease. Innovation in pharmaceuticals for kidney patients could be accelerated if FDA were willing to consider surrogate end points and/or patient-reported outcomes as basis for approval. The FDA Patient Focused Drug Development Initiative should include chronic kidney disease.

As a Member of KHI we are participating in a workgroup with staff from the FDA, and other kidney organizations to assess patient preferences and risk versus benefit decision making when adopting new device technology. We are hopeful the outcomes of this workgroup can become a basis for evaluating patient preferences in device approvals.

How have you worked with other patients to support one another?

The National Kidney Foundation operates a national, telephone-based peer support program called PEERS. PEERS connects people who want support with someone who has also experienced kidney disease. These trained peer volunteers help people adjust to living with chronic kidney disease, kidney failure, or a kidney transplant by sharing their personal experiences and listening to the callers' concerns, questions, and experiences.

What is the financial burden of your disease? How would better treatments and cures help save money for your family and the federal government?

Medicare spends approximately $77 billion on people with CKD, including $34.3 billion (6.3 percent of the Medicare budget and 1% of Medicare beneficiaries) on people with ESRD. [2] However, investment in research is estimated to be only 1% of federal spending on treatment. Most people with ESRD have Medicare Parts A and B. Medicare Part B covers dialysis treatments and immunosuppressive drugs for transplant recipients. Medicare beneficiaries are subject to a 20%

[2] U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.

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coinsurance for each medical appointment and dialysis treatment. For dialysis treatments this amounts to roughly $50 per treatment and people on dialysis receive at least three dialysis treatments per week. Those Medicare beneficiaries with a kidney transplant also pay a 20% copayment on their immunosuppressive drugs. The out-of-pocket costs vary depending on the combination of medications prescribed. However, Medicare spends on average less than $4,000 per year per transplant recipient for immunosuppressive medications, much lower than the cost of dialysis. However, after 36 months transplant recipients under age 65 lose their Medicare coverage and those who cannot afford health insurance or their medications are likely to reject their kidney and require dialysis again, which will allow them to be re-eligible for Medicare coverage.

Right now the best economical and high quality treatment for kidney failure is a transplant. However, there are over 100,000 people waiting for a kidney transplant and a little more than 15,400 people received kidney transplants last year. Clearly, better treatments and cures to slow or prevent the progression of kidney disease would reduce the excessive economic burden of ESRD requiring dialysis or transplantation.

How can Congress help?

Even in the immediate absence of breakthrough cures and treatments, Congress can take steps to reduce CKD progression and improve mortality and morbidity. To improve outcomes for patients with CKD and spur innovation Congress should:

1. Protect Medicare's investment in kidney transplants, prevent recipients from needing to return to dialysis, and potentially increase the number of kidneys available for transplant, by passing Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act of 2013 (H.R. 1428 and S.323)
2. Pass legislation that seeks to identify research gaps CKD and strengthen kidney disease research coordination across agencies (H.R. 4814).
3. Invest in research specific to kidney disease to address known gaps
4. Encourage the FDA to use a surrogate endpoint of eGFR less than 30 in clinical trials for drugs seeking to prevent or delay progression to ESRD, consider patient reported outcomes for approval of new CKD therapies, and include CKD in the FDA patient focused drug development initiative.
5. Explore solutions to encourage early detection and diagnosis of kidney disease in the Medicare program.
6. Provide funding for a national patient registry to allow evaluation of the course of CKD, the compliance with evidence based treatment guidelines and how clinical practice affects outcomes.

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We hope the 21st Century Cures initiative will help spur solutions to the barriers of innovation in the treatment of kidney disease and the National Kidney Foundation appreciates the opportunity to serve as a resource on kidney disease to the committee.

Sincerely,

[redacted]

Kerry Willis, PhD
Senior Vice President for Health Science and Education

21st Century Cures – Patients

What is the state of discovery of cures and treatments for your disease? Are there cures and treatments now or on the horizon?
There are eleven MPS diseases for which there are four FDA approved treatments. Treatment clinical trials are in progress or in the pipeline for three diseases. There are no cures for any of MPS diseases.

What programs or policies have you utilized to support and foster research, such as patient registries, public-private partnerships ,and venture philanthropy?
The National MPS Society awards approximately $500,000 to research each year. Several grants offered have been partnerships with private MPS foundations. In 2004 the Society developed the Lysosomal Storage Disease Research Consortium jointly between lysosomal disease support groups and the National Institute of Neurological Disorders and Stroke (NINDS). The purpose was a jointly sponsored program associated with the program announcement PARS-04-092: CNS Therapy Development for Lysosomal Storage Disorders. Information from the Society's patient database is utilized to gain better understanding of mortality.

How can Congress incentivize, coordinate, and accelerate basic research for diseases we know relatively little about?
Congress has the advantage of advising on research priorities and setting appropriations for the National Institutes of Health (NIH). The National MPS Society has supported increased funding to the NIH for over 15 years for not just MPS research, but research for all rare diseases. Many rare disease groups, including the National MPS Society, advocate with their legislators and work with the NIH to create awareness about their diseases and encourage research.

How can we work together to better translate advances in science into safe and effective new therapies for patients?
In recent years the NIH has increased the focus and funding for translational research and clinical trials. It's imperative that funding to the NIH for these programs not just continues, but is increased.

How do you coordinate your research and outreach with other patients?
The National MPS Society offers research grants specific to each MPS disease and also general research grants to all the MPS diseases. The Society provides information of grants funded and progress of the research on our website and in our quarterly newsletter. As noted, the Society also works in partnership with private family foundations to provide research grants.

How do you learn about new treatments and cures? How do you communicate with other patients regarding treatments and cures?
The National MPS Society has a Scientific Advisory Board who provides peer review for the grant funding process. Basic research funded has moved forward to translational research and, in

some cases, clinical trials. In addition, the Society collaborates with biotechnology companies investing in research for MPS treatments, advising them about the patient population and providing information to our patients about these treatments. The Society provides information about potential treatments, clinical trials and approved treatments on our website, in our quarterly newsletter and through email and social media.

What can we learn from your experiences with clinical trials and the drug development process?
The voice of the patient and/or their caregivers can provide valuable information on symptoms that most impact the patients quality of life along with the level of treatment tolerance they are able and willing to manage to alleviate symptoms or slow disease progression. In depth understanding of the patient/caregiver perspective is invaluable to successful clinical trial participation along with drug development, education, and marketing. The Society has been integral in bridging trusting networks between researchers, drug development companies, and patient/caregiver community.

What is the role of government in your work, including any barriers to achieving your goals and advancing breakthroughs? Rare disease advocates have created forums and networks to share information about legislation and regulations that may benefit or hinder the advancement of research, innovation, and clinical trials. The National MPS Society has a working Committee on Federal Legislation which educates and mobilizes patients and caregivers to advocate on their on behalf with key decision makers. The biggest barrier to educating and then mobilizing the MPS community is the intense complexities and caregiving needs of patients with MPS. The Society continues to build their advocacy presence through advocating one-on-one with legislators, building relationships within the government and providing valuable patient/caregiver testimony on incentives that are successfully driving research, drug development and regulations that may be slowing patient access to innovative research.

How should regulators evaluate benefit-risk? How do you work with regulators regarding benefit-risk? Can this process be improved?
Families who have a child with a progressive, lethal, rare disease with no treatment are willing to accept high risk. The possibility that the known outcome for their child, invasive medical care and ultimately an untimely death, could be alleviated translates to acceptance of potential risk, including death. In fact, many parents are willing to undergo high risk in order to maintain their child's current level of function. This is because they know the outcome of these devastating diseases: progression, loss of functions and death.

The National MPS Society supports legislation expediting approved FDA treatments, and our board of directors met with FDA in February 2014 to discuss the topic of benefit-risk. Requiring FDA professionals knowledgeable about rare diseases to work with investigators and companies submitting INDs (and throughout the approval process) will streamline the process for new treatments. The society applauds FDA's efforts for regulators to better understand the benefit-risk ratio through the series of Patient-Focused Development meetings with patients and caregivers. This is an invaluable step to improving the process through understanding the disease, benefit v risk, and treatment tolerance beyond the data and statistics.

What is the role of public and private funding in the research and development of cures and treatments?
Without funding, research stagnates. Both public and private funding are critical to move research toward development of treatments and cures. Often much of the private foundation or

patient group funding is sufficient to prove efficacy but not to ultimately move the research to treatment approval. NIH funding provides the necessary boost to move the basic research to translational research and ultimately clinical trials. Biotechnology companies have the resources to develop the treatments, and their increased interest bringing treatments to FDA approval correlates with the inception of the Orphan Drug Act. We must continue our support of the tenets of this historical piece of legislation.

Are there success stories the committee can highlight and best practices we can leverage in other areas? Each clinical trial and drug development for treating four of the MPS types have only been able to move forward because of the Orphan Drug Tax Credit incentive. Without this incentive, the development of a drug for a rare disease is unlikely. Most recently, a small biotech company that developed the 1st FDA-approved treatment for MPS IVA secured a Rare Pediatric Disease Priority Review Voucher. This voucher was an incentive piece of legislation, also known as Creating Hope Act, which was included in Section 908 of the 2012 FDA Safety and Innovation Act ("FDASIA"). The voucher has potential to lead more investment in rare disease drug research and development.

How have you worked with other patients to support one another?
In 2004 the Society developed the Lysosomal Storage Disease Research Consortium jointly among lysosomal disease support groups and the National Institute of Neurological Disorders and Stroke (NINDS). The purpose was a jointly sponsored program associated with the program announcement PARS-04-092: CNS Therapy Development for Lysosomal Storage Disorders. The Society is a member of the National Organization of Rare Diseases (NORD), the Rare Disease Legislative Advocates (RDLA) and the Lysosomal Disease Network (LDN). Information regarding research, legislative initiatives and the NIH is shared among the plethora of patient groups associated with these organizations.

What is the financial burden of your disease? How would better treatments and cures help save money for your family and the federal government?
Caring for children with MPS is a full-time job. They cannot care for themselves. Parents need to coordinate with dozens of medical experts, including pediatricians, neurologists, geneticists, ENTs, orthopedists, cardiologists, audiologists, dentists and oral surgeons as well as physical, speech and occupational therapists and home nursing aides. Children with MPS often need specialized medical equipment, such as oxygen pumps, gastrointestinal feeding equipment, therapeutic beds, braces, wheelchairs, and other specialty medical items.

For these reasons, the costs to care for children with MPS are astronomical. The emotional and social impacts are also great. Some children with MPS diseases have significant behavioral problems and sleep infrequently. Siblings are affected in significant ways. School issues impact many children with MPS. Vacations and other "normal" family activities all require special planning and accommodations. Having a child with MPS disease affects nearly every aspect of a family's daily living.

Ultimately, stopping or significantly slowing the disease progression, the financial burdens would greatly decrease. Individuals with MPS would potentially have the opportunity to be contributing, self-sufficient members of society. It is important to understand that children with MPS are born healthy and normal. The disease progression is what changes the course of their lives and those of the ones that love them.

Slowing or stopping disease progression at birth would be ideal and ultimately would allow the individual to live a more "normal" life which would be less medical care, surgical interventions, special accommodations, fulltime caregiving, medical equipment, home modifications, etc. The impact of lessoning the financial burden on the family, insurance providers, private foundations, and government programs would be significant.

How can Congress help?

Congress needs to actively participate and understand that their role can either hinder or promote rare disease research, development, and awareness. NIH funding must significantly increase to support the fast pace of rare disease research, innovation, and breakthroughs. FDA funding must increase to support the growing needs of reviewers' expertise in rare diseases and time allotted to engage with the disease specific populations. Our congress must continue to support translational science and programs that could mean significantly larger impact of research on multiple disease types.

Congress should protect this vulnerable population in every aspect of legislation. Over 7,000 rare diseases affect up to 30 million Americans. 80% are genetic rare diseases, 50% are children, 35% are infants that die within the 1st year of life, and 30% are children do not live past 5 years of age. Every parent that has a child diagnosed with a rare, terminal disease is thrust into a world that is overwhelming and devastating with financial burdens that may be astronomical. Rare disease patients and their caregivers are actively engaging to advocate and raise funds for research because many times, no one else is doing it. There can't be a more vulnerable population that needs the support, compassion, and protection of our Congress.

Congress needs to be aware that individuals with rare diseases often have to travel to get the medical care necessary to manage their disease. More often than not, there may be only one or two medical experts able to provide the medical care for specific type of rare disease. Limiting access through narrow provider networks only hinders best quality of life and outcomes, which ultimately increase cost on many levels. Patients with rare diseases often need life saving drugs to slow or cure their disease. Allowing access to treatments is critical for us to benefit from the innovation and research that we have already invested in as a society.

American Brain Coalition

STATEMENT OF THE AMERICAN BRAIN COALITION TO THE 21ST CENTURY CURES INITIATIVE

The American Brain Coalition is a non-profit organization comprised of many of the United States' leading patient organizations, as well as professional neurological, psychological, and psychiatric associations. Together, we seek to advance the understanding of the functions of the brain, and to reduce the burden of brain disorders through public advocacy.

The ABC is a strong and powerful voice for the 50 million people with disabling brain disorders, bringing together organizations that represent concerned and interested patients, families, and professionals. We advocate for increased support of research that will lead to better treatment; services and support that will improve patients' quality of life; as well as a national commitment towards finding cures for individuals with disabling neurological and psychiatric disorders.

The ABC congratulates the Energy and Commerce Committee, particularly Chairman Upton and Congresswoman DeGette, for their commitment to this important and thoughtful initiative. We are grateful for the opportunity to participate in this process and speak on behalf of our organizational members who represent one sixth of the population of the United States.

We share your initiative's stated goal - to accelerate "the cycle of discovery, development, and delivery of promising new treatments and cures." We believe that as stated, it clearly addresses the continuum of activity from basic to clinical to translational research, through the regulatory processes of approval and ultimately to payment by public and private payers.

Stated another way, we strongly encourage you to focus on the broad-scale research components that are embodied in the activities of the National Institutes of Health and the regulatory aspects of the activities of the Food and Drug Administration and the Centers for Medicare and Medicaid Services. From the perspective of patients, providers and researchers, each of these elements have to work in concert in order to maximize the positive benefits from any of them. Great discoveries in the lab do no good if they are never tested at the bedside. Successful treatments that meet high quality standards are useless if they are not paid for and accessible for patients.

In the field of brain-related disorders, there are "science" problems – things we simply do not know about the functioning of the brain that make dysfunction a mystery. There are regulatory problems – aspects of dealing with the "safety and efficacy" standard that are particularly difficult (yet absolutely essential) with regard to brain research. There are legislative issues related to patent law and exclusivity standards. And there are reimbursement and related payment issues, where our desire to cut costs collides with the need to address real human suffering.

American Brain Coalition

In fact, data show that the process to develop drugs to treat neurological conditions takes longer, is more costly, and has higher failure rates than the development process for drugs to treat other conditions. Accordingly, industry has shifted investment away from treatments for central nervous system diseases and conditions, further exacerbating this situation.

All of these aspects factor into a terrible – and expensive – conundrum for American society. Mental health issues alone are estimated to cost the economy a half trillion dollars per year – an amount equal to one half of the entire discretionary federal budget! Add to that the cost of neurological conditions ranging from Alzheimer's to movement disorders to multiple sclerosis to stroke and more, and we are looking at a one trillion dollar drain on the American economy.

While the problem is huge, the issues can be addressed with a strong will and sustained commitment to do so. Specifically:

- NIH funding must be set at a sustainable level of at least three percent above the rate of increase in the Biomedical Research and Development Price Index (BRDPI).
- NIH and NSF funding must be allocated free from political interference, in a balanced manner through a scientifically-driven peer review system that assures that basic, clinical and translational research are funded in accordance with scientific opportunity and advancement.
- The NIH and NSF should be encouraged to consider alternative models for requesting and funding proposals that target the translation of basic research findings to therapeutic development. A new model should be created that enables rapid review of proposals, prompt funding decisions, frequent review of data driven milestones, and sharing of research findings as rapidly and efficiently as possible.
- Private companies, venture capitalists and philanthropies need to be incentivized to take on the most difficult research tasks – such as mental illness and neurodegenerative disease product development – through the use of creative tax laws, exclusivity provisions, support for patient recruitment for clinical trials, and so forth.
- Congress should consider and take appropriate legislative action that attempts to better align the scientific opportunities for creating new medicines with the intellectual property system intended to address unmet medical needs.
- FDA must be assured sustainable and robust funding – from user fees paid by industry and from government support – to prevent bureaucratic delays in the processing of applications for new drugs, biologics and devices, while assuring safety and efficacy are maintained at the levels American patients have come to expect.
- Congress should empower the Centers for Medicare and Medicaid Services (CMS) to create an expedited payment system for CNS-related products and treatments that assures prompt and fair payment so as to avoid unnecessary delays and further incentivizes investment.
- While not within the Committee's jurisdiction, tax laws must be adjusted to eliminate any unintended penalties that dissuade investment by providing appropriate credits for innovative research and development investments.

The American Brain Coalition and its 82 nonprofit and for-profit members, individually and collectively, stand ready to work with the Energy and Commerce Committee as it continues to investigate this very important area of government responsibility.

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Katie Sale, Executive Director – [redacted]

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CAUSE FOR A CURE
www.hepb.org

June 13, 2014

The Honorable Fred Upton
Chairman
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Diana DeGette
2368 Rayburn House Office Building
Washington, D.C. 20515

Sent via e-mail: Cures@mail.house.gov

Re: Request for Information Regarding the 21st Century Cures Initiative

Chairman Upton, Representative DeGette:

On behalf of all the patients and families affected by hepatitis B and liver cancer that we serve, the Hepatitis B Foundation thanks you for the opportunity to provide input on the *21st Century Cures* initiative. We are the nation's leading nonprofit 501(c)3 research and disease advocacy organization dedicated to finding a cure and serving those affected.

Worldwide 2 billion people have been infected with the hepatitis B virus (HBV), 400 million are chronically infected, and 1 million die each year from its complications. According to the World Health Organization, HBV is the leading cause of primary liver cancer (hepatocellular carcinoma or HCC), which moved up this year to become the 2nd leading cause of cancer deaths in the world. In the U.S. alone, liver cancer is on the rise due to chronic HBV and HCV infections -- it is currently one of the fastest growing cancers in incidence with an overall 5-year survival rate of 16% (and only 10% with advanced disease).[1]

HCC is the most common solid tumor worldwide[2] and the second leading cause of cancer deaths.[3] In the United States, liver cancer is considered one of the deadliest or recalcitrant cancers, which are defined in the Recalcitrant Cancer Research Act of 2012 as those cancers with five-year relative survival rates below 50 percent. In fact, nearly half of the 585,000 cancer deaths expected in 2014 will be caused by eight site-specific cancers: ovary, myeloma, brain, stomach, esophagus, lung, pancreas and liver.

According to the National Cancer Institute, while the incidence of most cancers is decreasing, the incidence of liver cancer continues to increase, at an average rate of 2.9% per year. A recent study[4] projects that in the United States, liver cancer will overtake prostate cancer to become the 5th deadliest cancer by 2020 and the 3rd leading cause of cancer-related deaths by 2030, after lung and pancreatic cancers, which are also considered to be recalcitrant cancers. These projections underscore the need for greater federal investment in research to prevent this dramatic rise in the rankings of cancer killers.

The Hepatitis B Foundation continues to be concerned with the lack of a focused liver cancer research program and therefore urges that the National Cancer Institute initiate funding for a Specialized Program of Research Excellence (SPORE) on liver cancer, as well as liver cancer program projects. The Hepatitis B Foundation also urges that an NCI

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liver disease research program focus more on the development of biomarkers to serve as early detection markers of cancer to offer the prospect of improved outcomes.

Early diagnosis through screening and ongoing surveillance of at-risk populations are critical for improving outcomes in liver cancer, especially because treatment options are so limited and are less effective when patients are diagnosed at an advanced stage.

There is already very strong evidence of the profound impact of effective screening. The projected decrease in the incidence of colorectal cancer is attributed to advances in screening, resulting in earlier detection and initiation of treatment. Equally encouraging is the projected increase in the incidence of thyroid cancer that is not accompanied by an increase in deaths, indicating that earlier diagnosis is helping to improve outcomes.

The Hepatitis B Foundation believes that improvements in the early detection of liver cancer in combination with preventive strategies and early initiation of treatment will reduce both the incidence and the number of needless deaths from liver cancer. A concerted effort by all stakeholders— policy makers, scientists, clinicians, and the public—can change the alarming recent predictions and improve the future outlook for people who will be diagnosed with liver cancer.

Sincerely,

[redacted]

Joan M. Block, RN, BSN
Executive Director and Co-Founder
Hepatitis B Foundation
[redacted]

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Immune Deficiency Foundation

The National Patient Organization Dedicated to Advocacy, Education and Research for Primary Immunodeficiency Diseases

June 13, 2014

The Honorable Fred Upton
2183 Rayburn House Office Building
Washington, DC 20515
Submitted via email to cures@mail.house.gov

The Honorable Diana DeGette
2368 Rayburn House Office Building
Washington, DC 20515

RE: 3rd White Paper -- 21st Century Cures: Patients

Dear Chairman Upton and Representative DeGette:

Thank you for your recent endeavors to examine efforts in which Congress can provide additional direction to Federal agencies to accelerate the discovery, development, and delivery of innovative new treatments and cures, creating more jobs, and maintaining our nation's role as the innovation capital of the world. The Immune Deficiency Foundation looks forward to being a partner with you in developing the appropriate legislative framework in the next several months.

The Immune Deficiency Foundation (IDF) is the national patient organization, founded in 1980, dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency (PI) disease through advocacy, education and research. To provide you with our full perspective, we strive to answer the questions most relevant to our patient population below.

What is the state of discovery of cures and treatments for your disease? Are there cures and treatments now or on the horizon?

Primary immunodeficiency (PI) diseases represent a group of more than 200 rare disorders. Many patients with PI depend on lifelong immunoglobulin replacement therapy (Ig therapy) to replace the antibodies their bodies do not produce. Besides the obvious importance of the safety and efficacy of Ig therapy, people with PI continue to seek therapeutic options that allow them to lead a more normal life while maintaining good outcomes. Improved product choices will benefit patients. We have been pleased that there have been recent new Ig products that have been directed towards more convenient presentations (liquid as opposed to lyophilized, subcutaneous as well as intravenous), higher concentrations (10% and 20% solutions) and products that have greater theoretical assurance of viral safety (additional methods of viral removal or inactivation).

However, we recognize that patients want and deserve additional options in order to minimize existing burdens of their treatment.

- Patients can be limited in the product or routes of administration, which can be used to effectively treat their PI.
    - In a 2008 IDF survey of patients with PI, just one-third of intravenous immunoglobulin (IVIG) users and 28% of subcutaneous immunoglobulin (SCIG) users report that they tolerate all immunoglobulin products similarly.
    - In some patients, it is difficult to achieve appropriate IgG-trough levels despite increased SCIG and IVIG doses.

- For patients whose compliance is optimized with self-administration, SCIG provides an option. Sometimes however, limitations can arise due to the inability to infuse large quantities of Ig into the subcutaneous site in a timely manner. Such limitations include:
    - Frequency of dosing and number of needle sticks.
        - Some patients would prefer less frequent dosing.
        - Some patients require multiple needle sticks per infusion.
        - A number of patients would prefer to reduce the number of needle sticks per infusion.
    - Frequency of local site reactions.
    - Decreased bioavailability can result in increased use in Ig.
- For patients whose compliance is optimized with less frequent administration, IVIG provides a good option. However, limitations do exist, which include:
    - Significant supervision during administration is required by a health care professional.
    - Receiving infusions in a doctor's office or outpatient hospital setting may not be ideal due to the potentially increased risk of exposure to infections.
    - Many patients have difficulty with venous access, which may affect therapy choice and increase discomfort during infusion.
    - IVIG can be less tolerable for some patients due to the increased risk of systemic adverse reactions, which may create additional morbidity or pose additional significant risk.

In summary, some patients would have more favorable treatment outcomes with choices that could alleviate some of the issues outlined above. The Immune Deficiency Foundation is always looking for new and innovative ways to help our patients receive the Ig therapy they need in the least restrictive treatment environment, recognizing that no one treatment is appropriate for all patients.

In addition to the need for products that can make the lives of patients more normal and avoid some adverse reactions, we continue to be concerned with antibody efficacy and diversity for patients with PI, all of whom depend on Ig therapy as replacement, rather than immune modulation.

Additionally, IDF continues to have an issue with insurers who treat Ig therapies as generic, and hope that the FDA could help clarify that these are, indeed, unique products, and that patients do react differently and have distinctive needs.

What programs or policies have you utilized to support and foster research, such as patient registries, public-private partnerships, and venture philanthropy?

IDF provides administrative support for the ***United States Immunodeficiency Network (USIDNET)***, a research consortium established to advance scientific research in the field of primary immunodeficiency diseases, focusing on a primary immunodeficiency disease registry. USIDNET, a program of the IDF, is funded in part by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institutes of Health (NIH). NIAID supports research to advance the understanding of transplantation and to prevent, diagnose and treat infections and Immune-mediated illnesses.

The USIDNET Registry is a national patient consented registry of individuals with primary immunodeficiency diseases. The goals are to advance research in the field and to improve the quality of life of patients. It is managed by leading immunologists and administered by the Immune Deficiency Foundation (IDF). IDF has also created for its patients an electronic personal health record (IDF ePHR) to track their own medical information to improve communication with their providers, and

ultimately, to improve their health. In December 2012, IDF was awarded a contract from the Patient-Centered Outcomes Research Institute (PCORI) to create a **Patient Powered Research Network**, which we are calling ***PI Connect*** that will share patient entered information from IDF ePHR with the clinical information in the USIDNET Registry.

How can Congress incentivize, coordinate, and accelerate basic research for diseases we know relatively little about?

Individuals with primary immunodeficiency (PI) diseases are vulnerable to infection since they lack antibodies to fight these infections. Therefore, resistant pathogens are of great concern to our patient population. IDF believes Congress can incentivize basic research on the most troubling resistant pathogens by addressing current regulatory burdens to antibiotic development. IDF urges the Committee to pass ***H.R. 3742, the Antibiotic Development to Advance Patient Treatment (ADAPT) Act.*** This legislation would establish a new FDA approval pathway to incentivize the study of new antibiotics to treat serious or life-threatening infections for which there is an unmet medical need. It is critical to stay ahead of antibiotic resistance which threatens our patients and the general public every day.

How have you worked with other patients to support one another?

IDF works closely with other patient organizations whose patients use plasma products as part of advocacy efforts of the American Plasma Users Coalition (APLUS). APLUS members work together advocating for public policies which encourage research and increased access to care. APLUS also works closely with the National Organization of Rare Disorders (NORD) on federal legislation and regulatory issues regarding research and regulations of the FDA and the Affordable Care Act (ACA). Collaboration with other patient organizations enable a greater voice to be heard.

IDF is also an active participant in the 28 member Coalition for Accessible Treatments which supports the bipartisan Patients' Access to Treatment Act of 2013 (HR 460) that would place limits on patient co-insurance out-of-pocket costs for specialty drugs placed on specialty tiers.

As a result of an award from the Patient Centered Outcomes Research Institute (PCORI), IDF is actively involved with PCORI and other PCORI awardee organizations. Together, the awardees will be a part of PCORnet: the National Patient-Centered Clinical Research Network. This new national resource aims to boost the efficiency of health research.

IDF is a member of the National Health Council and participates in many of its advocacy committees, especially those that pertain to the ACA implementation, regulatory issues, legislation and other health matters. We also work together to provide our patients the most up to date information and resources for them to navigate the health care system.

IDF also works closely with the medical community such as the IDF Medical Advisory Committee (MAC), American Academy of Allergy, Asthma and Immunology (AAAAI) and the Clinical Immunology Society (CIS) on a number of policy and advocacy issues including access to care, analysis of payer immunoglobulin medical policies and standards of care.

What is the financial burden of your disease? How would better treatments and cures help save money for your family and the federal government?

Currently, one of the biggest obstacles to care for our patients as well as many (if not most) other patients who have a rare and chronic disease is the increasing use of co-insurance cost-sharing policies of insurers. Payers are moving more and more specialty drug treatments, which are primarily used by patients with rare and chronic diseases, out of drug tiers with co-payment arrangements to specialty tiers which require patients to pay a percentage of the cost of treatment. According to a study by Avalere Health of such arrangements in the ACA Marketplaces, over 20% of plans reviewed require patients to pay at least 40% of the treatment costs. The monthly cost of treatment for our patients with PI can range between $5,000 and $10,000 per month for the rest of their lives. For other diseases, the cost of treatment can even be higher.

The annual out-of-pocket (OOP) costs limitation of the ACA is beneficial for most people. However, in conjunction with high co-insurance requirements it is being used to keep people from getting their treatments because all of the costs are front loaded. It is not unusual for payers to require those patients with high cost drug treatments to pay the annual cost cap ($12,750) plus any applicable deductibles at the time of the first (or maybe 2nd) treatment of the year. For those with life-long treatments as our patients with PI, the cost is staggering. How many Americans can afford to pay premiums, deductibles, co-payments and co-insurance *and* come up with nearly an additional $13,000 per year – every year? The use of coinsurance for the most sick in our population with the most expensive treatments is tantamount to economic and health discrimination.

These policies encourage people to forego treatment. There is ample evidence of this behavior by patients if costs are too high. The irony of this situation is that studies show that when patients with PI do not have their treatments, they will get sick many times in a given year, requiring payers to cover the costs of symptomatic treatments while patients incur a fraction of the costs. One study indicated it cost payers twice as much to treat sick patients with PI who are not on Ig replacement therapy as it would if they had received the prophylactic benefit of the drug therapy.

How can Congress help?

IDF urges Congress to pass ***H.R. 460, the Patients' Access to Treatment Act of 2013*** introduced by Representatives David McKinley (R-WV) and Lois Capps (D-CA). Currently, the bill has 127 bipartisan co-sponsors. H.R. 460 would restrain high cost-sharing for specialty medications, thereby enabling more patients with chronic, disabling, and life threatening conditions to access the treatments they need. It would limit cost-sharing requirements applicable to medications in a specialty drug tier (typically Tier IV or higher) to the dollar amount applicable to drugs in a non-preferred brand drug tier (typically Tier III). It will enable patient access to treatments, reduce disability and constrain health care costs.

Again, we strongly appreciate your efforts in this area, and we look forward to continuing to work with you. If you have any questions or would like to discuss our recommendations further, please feel free to contact me at [redacted]

Sincerely,

[redacted]

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IDSA
Infectious Diseases Society of America

June 13, 2014

Representative Fred Upton
2183 Rayburn House Office Building
Washington, DC 20515

Representative Diana DeGette
2368 Rayburn House Office Building
Washington, DC 20515

Submitted electronically to cures@mail.house.gov

RE: 3rd White Paper — 21st Century Cures: Patients

Dear Chairman Upton and Representative DeGette:

On behalf of the Infectious Diseases Society of America (IDSA), thank you for your continued efforts regarding the 21st Century Cures Initiative and multiple opportunities to comment. IDSA recognizes that this third white paper focused on patients' perspectives, and we appreciate the Committee seeking out this important voice. Over a decade ago, IDSA launched policy efforts to address antibiotic resistance and the need for new antibiotics on behalf of our increasing numbers of patients who were contracting and dying from multi-drug resistant infections that we could not effectively treat with existing therapies. Unlike many chronic conditions, there are no large, well-organized groups able to advocate on behalf of patients who suffer from serious or life-threatening infections that are resistant to current antibiotics.

In the past decade, rates of resistance have continued to climb, as have the numbers of patients contracting and dying from infections caused by resistant pathogens, as IDSA has noted in our previous comment letters regarding this initiative. Thus, IDSA has intensified our commitment to advance policy solutions to spur the development of the new antibiotics needed to save our patients' lives.

IDSA spotlights examples of the patients for whom we advocate on our website, including children, adults and seniors who have lost their lives or suffered devastating health outcomes due to resistant infections. For example, you can read the story of 17-year-old Rebecca Lohsen, a healthy high school honor student and swimmer from New Jersey who died of an MRSA infection. Sadly, these stories are a small sampling of the millions of people in the U.S. who struggle with resistant infections and have few or no satisfactory treatment options. With these patients in mind, IDSA offers the following recommendations in response to the questions raised in this third white paper.

What is the state of discovery of cures and treatments for your disease? Are there cures and treatments now or on the horizon?

Antibiotics are generally accepted as the greatest curative development of the 20th century and now credited with a 26 year increase in average longevity. This progress is threatened by the rapid rise of antibiotic-resistant bacteria coupled with a persistent market failure to develop new antibiotics. This public health crisis has been well documented by the Centers for Disease Control and Prevention, the World Health Organization and multiple

other government entities and non-government experts, including IDSA with our 2004 Bad Bugs, No Drugs report and our 2011 Combating Antimicrobial Resistance: Policy Recommendations to Save Lives report. We are on the very real, very frightening precipice of a post-antibiotic era.

Antibiotic research and development (R&D) has plummeted for a variety of reasons. Unlike other types of drugs, the use of antibiotics decreases their effectiveness over time due to the development of resistance by the bacteria that infect us. Companies are lacking sufficient incentives to develop new antibiotics and must answer to stockholders. Antibiotics are typically priced low compared to other new drugs, used for a short duration, and held in reserve to protect their utility, making them far less economically viable investments for companies than other types of drugs used over years to treat chronic diseases. In 1990, there were nearly 20 pharmaceutical companies with large antibiotic research and development (R&D) programs. Today, there are only 2 or 3 large companies with strong and active programs and a few small companies with more limited programs. An IDSA report issued in April 2013 identified only seven new drugs in the development pipeline for the treatment of serious infections caused by multidrug-resistant Gram-negative bacilli with no guarantee that even one will make it to the market, particularly given that the failure rate of bringing drugs at this stage to the market is very high.

What programs or policies have you utilized to support and foster research, such as patient registries, public-private partnerships, and venture philanthropy?

In response to IDSA's advocacy about patients' desperate need for new antibiotics, Congress and various federal agencies have taken initial steps to foster antibiotic R&D. But key stakeholders agree that more must be done/much more be done. … much more is needed?. In 2012, the Committee led successful congressional efforts to enact the Generating Antibiotic Incentives Now (GAIN) Act, which provides an additional 5 years of exclusivity for antibiotics and antifungals that treat serious or life-threatening infections. This legislation was an important first step in revitalizing our nation's antibiotic R&D enterprise.

The National Institute for Allergy and Infectious Diseases (NIAID) recently established the Antibacterial Resistance Leadership Group (ARLG) to develop, design, implement, and manage a clinical research agenda to increase knowledge of antibacterial resistance. The ARLG will focus on antibacterial drug and diagnostic development, optimal usage strategies, infection control and activities to limit the development of resistance. In addition to helping to develop new cures, ARLG research can also help determine the best way to use existing antibiotics to maximize their potential to cure patients and save lives. If properly supported, the ARLG is well poised to help catalyze efforts to bring new antibiotics to patients and reduce the disease burden associated with drug resistant pathogens.

The Biomedical Research and Development Authority (BARDA) is also a critical source of funding for new antibiotics. In the last few years, BARDA has awarded contracts to multiple large and small pharmaceutical companies to develop new antibiotics to treat serious threats, including infections caused by gram negative bacterial pathogens, hospital acquired pneumonia, complicated urinary tract infections, and infections caused by carbapenem-resistant

Enterobacteriaceae (CRE)—infamously termed the "nightmare" or "urgent threat" bacteria by the Centers for Disease Control and Prevention (CDC) Director Tom Frieden. Products supported by BARDA funding have potential use not only in bioterror situations, but also in more traditional healthcare settings.

While these important initiatives are all critical in helping to revive the stagnant antibiotic pipeline, they are not sufficient to thoroughly revitalize antibiotic R&D. Recent federal budget pressures have put serious funding constraints on all federal agencies, including NIH and BARDA, severely limiting the reach of these agencies' efforts.

How can Congress incentivize, coordinate, and accelerate basic research for diseases we know relatively little about?

The National Institutes of Health (NIH) is the driver for a significant portion of basic research in the U.S. New infectious diseases are regularly emerging, and existing pathogens continuously mutate and require additional research to understand the best way to treat infected patients. Congress can best incentivize the necessary basic research by providing the NIH with sufficient funding for them to meet the important missions of its institutes.

Robust, sustained funding is needed not only to spur research today, but also to encourage the younger generations to pursue careers in research to ensure the future of our nation's biomedical research enterprise. IDSA urges the Committee to work with your colleagues on the Appropriations Committee and in congressional leadership to better prioritize funding for the NIH, and specifically the NIAID.

Between Fiscal Year (FY) 1998 and FY 2003, Congress doubled the funding for NIH. Since that time, NIH has received very modest increases some years and even cuts in FY 2011 and FY 2013. For FY 2015, the President proposed a $200 million increase for NIH. However, NIH estimated that the Biomedical Research and Development Price Index for 2015 would be 2.9%. As such, the 0.7% increase requested for NIH in the President's budget continues the 10-year downward trend in purchasing power at the NIH. The overall NIH grant success rate for FY 2013 is likely to be reported as falling to 15%, its lowest level in history. The latest funding line reported by investigators for investigator initiated grants (R01s) is the 9th percentile.

Depressed NIH funding is having a chilling effect on research, causing established researchers to scale back or completely discard promising research, lay off laboratory staff and dismantle research infrastructure that took years to build. Young people are so discouraged by the lack of NIH funding that they are abandoning potential careers in basic research entirely-- seriously jeopardizing our nation's ability to remain a leader in biomedical innovation.

Weakened NIAID funding comes at a particularly problematic time as we are facing an onslaught of emerging, growing and re-emerging infectious disease threats for which patients need researchers to help develop cures. In addition to infections caused by multi-drug resistant pathogens, U.S. patients have now experienced our first cases of the Middle East Coronavirus (MERS). Dengue and chikungunya are becoming more prevalent. We are also seeing a resurgence of measles. College campuses are struggling with meningitis cases. Of course

seasonal and pandemic influenza remain a serious concern.

Congress also has a critical role in fostering research that can prevent disease, including infections caused by rare or emerging pathogens about which we still know relatively little. For example, IDSA urges the Committee to help the Centers for Disease Control and Prevention (CDC) conduct greater research on novel strategies, best practices and evaluation of methods to prevent, control and eradicate antibiotic resistant organisms. CDC's prevention EpiCenters (a partnership with academic investigators) conduct valuable work in this area regarding healthcare associated infections, but flat funding over the last several years is preventing these collaborations from expanding their critical work. CDC's proposed Detect and Protect Against Antibiotic Resistance initiative, which has broad support, would also establish regional prevention collaboratives. These are envisioned to be groups of healthcare facilities in communities across the country that work together to implement and evaluate best practices for antibiotic prescribing and preventing infections. This initiative will also improve antibiotic stewardship by evaluating state-to-state variations in antibiotic prescribing and implementing best practices for antibiotic prescribing. IDSA believes that every healthcare facility should have in place an antibiotic stewardship program to help guide appropriate use. By reducing the overuse and misuse of antibiotics, we can slow the rate at which resistance to these drugs develops, and thus extend the longevity of these drugs' ability to cure patients.

IDSA also urges the Committee to work with your colleagues on the Appropriations Committee to ensure strong funding for CDC. Unfortunately, CDC funding has suffered dramatic cuts in the last several years—most notably a $740 million cut in FY 2011 and an additional $300 million cut in FY 2013 due to sequestration.

How can we work together to better translate advances in science into safe and effective new therapies for patients?

While the NIH funds critical basic research, and some extremely important clinical research through efforts such as the ARLG, Congress must incentivize industry to re-enter antibiotic R&D to ensure that desperately needed new antibiotics are developed and brought to patients. The GAIN Act was a vital first step, but Congress must now build on that foundation.

IDSA recognizes this effort may include collaborative work with colleagues on other committees (particularly Ways & Means and Appropriations). For example, reimbursement mechanisms hold important potential to help stimulate antibiotic R&D, such as through the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act, H.R. 4187. The bill would provide Medicare add-on payments for antibiotics used in inpatient settings to treat infections associated with high rates of mortality. Strong communication between CMS and FDA is critical for the success of such efforts, to help ensure that criteria to determine a drug's coverage and payment are applied in a scientifically appropriate and consistent manner that provides companies with the certainty and predictability they need in order to develop life-saving new antibiotics.

IDSA is also working on proposals for targeted and transferrable R&D tax credits to further stimulate antibiotic and antifungal R&D, and hopes the Committee will collaborate with other

committees to include such tax credits as a complimentary provision to the 21st Century Cures Initiative. While the GAIN Act and DISARM Act provide valuable incentives, companies must fully develop a product before receiving the benefits from increased exclusivity or reimbursement. Economic modeling has indicated that financial support during expensive clinical trials, as provided through tax credits, would be a powerful incentive to complement enhanced exclusivity and reimbursement. In fact, Ernst & Young analysis estimated that our tax credit proposal would result in an additional 5-7 new antibiotics or antifungal drugs to treat serious or life-threatening infections in the pipeline every year.

Lastly, IDSA supports increased direct federal funding to spur innovation through NIAID, BARDA, the Centers for Disease Control and Prevention (CDC), the Defense Threat Reduction Agency (DTRA), and the Defense Advanced Research Projects Agency (DARPA). IDSA encourages Congress to be mindful of CDC's role in research and innovation and provide the agency with strong funding. For example, CDC's proposed Detect and Protect Against Antibiotic Resistance Initiative (mentioned above) includes the establishment of a bacterial isolate library that could be useful to researchers and companies for the development of new antibiotics and diagnostics.

What can we learn from your experiences with clinical trials and the drug development process?

Clinical trials for antibacterial and antifungal drugs to treat serious or life-threatening infections face significant challenges. Some of the most dangerous pathogens are to date occurring in relatively small numbers of patients, making it difficult to impossible to populate traditional, large scale clinical trials. It is important to develop drugs to treat infections caused by these deadly pathogens before they infect larger numbers of people. Moreover, when a pathogen is resistant to all approved antibiotics, there is no effective antibiotic against which to compare the new antibiotic, which is the standard procedure for clinical trials. Compounding the problem is the lack of rapid diagnostic tests to identify patients infected with certain pathogens who may be eligible for antibiotic or antifungal clinical trials.

IDSA urges the Committee to swiftly act upon the Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742, which would establish a new approval pathway for new antibiotics to treat infections that are resistant to current available treatments. Under ADAPT, companies could study new antibacterial or antifungal drugs to treat serious or life-threatening infections for which there is an unmet medical need in smaller clinical trials and receive approval for the limited population in most need of the therapy. The European Union is already developing regulatory schemes to allow for this type of limited population antibacterial drug development, and we strongly urge the U.S. to follow suit.

The ADAPT Act would speed patient access to desperately needed, life-saving new antibiotics and antifungals, and it includes important provisions to help guide the appropriate use of these drugs. IDSA recommends that one additional provision be added to require a prominent and conspicuous visual element, such as a logo, on the labeling of ADAPT drugs to make it as simple as possible for the health care community (including those conducting educational campaigns, such as the CDC Get Smart program) to easily recognize that these drugs have been

approved in a different manner than traditional antibiotics and must be used appropriately. As PCAST noted, a limited population drug approval pathway must be implemented in such a way as to strongly influence behavior. Lastly, a visual element would help give the Food and Drug Administration (FDA) the comfort level it needs to approve new drugs under this pathway, thus increasing the potential success of the ADAPT Act in bringing lifesaving new antibiotic drugs to patients. We believe this issue can be easily addressed as the legislation moves forward.

We are pleased that the ADAPT Act has garnered broad bipartisan support among Committee members. Numerous medical societies and public health organizations share IDSA's view of this important legislation. Given the urgent need for new antibiotics and the broad stakeholder support for a limited population antibacterial drug pathway, we believe that the ADAPT Act should move forward right away.

Importantly, if the U.S. government does not make it feasible for companies to conduct antibiotic clinical trials in the U.S., companies will conduct these trials in other countries with different pathogens and different methods and/or standards of care. Such activities could leave patients in the U.S. still in need of life-saving new drugs.

What is the role of government in your work, including any barriers to achieving your goals and advancing breakthroughs?

Antibiotics are experiencing a market failure, meaning that market forces alone are not sufficient to incentivize companies to develop new antibiotics due to the significant economic and regulatory barriers discussed above. In previous similar situations in which the market failed to yield products desperately needed by patients, such as with orphan drugs, the government took decisive actions to address the market failure in the interest of patients. For example, the government can enact many policies (enhanced exclusivity, improved reimbursement, targeted tax credits) to provide economic incentives to companies to conduct desperately needed R&D in areas where significant economic barriers exist. In many instances, the NIH funds research that the private sector is unable or unwilling to conduct. But Congress must ensure that NIH receives robust funding to meet this need.

How should regulators evaluate benefit-risk? How do you work with regulators regarding benefit-risk? Can this process be improved?

In setting regulatory guidance for antibiotic development, IDSA has strongly urged the Food and Drug Administration (FDA) to balance the public health risks of approving a potentially less effective drug with the risk of having no new, critically needed antibiotics available to treat patients infected with resistant pathogens. While recent FDA clinical trial guidances demonstrate some progress in this area, more work remains.

Already conservative estimates of antimicrobial efficacy relative to placebo/no therapy should not be further "discounted" when setting requirements for non-inferiority margins for clinical trials, as discounting results in excessively large trial (and thus often infeasible) requirements. The treatment effect of antibiotic therapy for serious and life-threatening infections is very large. The primary issue in justifying the non-inferiority margin for a clinical trial is determining how

much of the clinical benefit of antimicrobial therapy must be preserved, which should be based upon an assessment of the relative merits of the specific experimental drug versus currently available therapy. Qualified experts in clinical medicine, who care for patients and know the current challenges and needs for improving treatment, possess the expertise required to define how much of a potential decrease in treatment benefit can be justified as a trade-off against the critical need to develop new efficacious and safe drugs and have them available for clinical use.

Earlier this year, FDA published a draft guidance for industry on developing drugs to treat community acquired bacterial pneumonia, which is an important cause of significant morbidity and mortality in the U.S., particularly among young children and the elderly. IDSA recognized that the draft guidance was a good faith effort to improve upon previous agency guidance in this area. However, IDSA remains concerned about the FDA's selection methodology for non-inferiority (NI) margins. Compelling evidence indicates that there is a real effect of antimicrobial therapy on both death as well as on speed of recovery. The current proposed NI margin of 12.5% is a significant improvement over past proposals. However, IDSA further recommends that consideration be given to expanding the NI margin to 15% under special circumstances. A margin of 15% could be justified if, for example, the study drug has other critically important advantages, such as better safety, better tolerability, shorter treatment duration, or activity against multidrug-resistant pathogens with limited available treatment options.

In short, as new antibiotics are critically needed, we must balance feasibility of conducting studies (and the resultant public health benefit of facilitating approval of effective new antibiotics) against a desire to narrow the non-inferiority margin. While patients may be harmed if less effective drugs are allowed to reach the market, they also may face even greater harm if they have an infection for which no effective antibiotics have been developed. Furthermore, if the criteria for trial conduct are so strict that it is not feasible to enroll meaningful numbers of patients in the US, we run the risk that the observed safety and efficacy of the drug in its pivotal studies will not be informative regarding the safety and efficacy of the drug for patients in the US who are treated with the drug. The key is to create a regulatory path that balances these competing risks.

What is the role of public and private funding in the research and development of cures and treatments?

IDSA firmly believes that a high-level public private partnership (PPP), with representation from the federal government, academia, industry, physicians and other key stakeholders, is needed to promote the discovery, development, and evaluation of new antibiotics. There is an urgent unmet medical need for new antibiotics, and antibiotic R&D faces significant scientific, economic and regulatory challenges. The European Commission (EC) has a successful PPP that should serve as a strong example for the U.S.

In 2012, the EC launched their ground-breaking New Drugs For Bad Bugs (ND4BB) PPP. PPPs are essential to furthering the discovery process for new antibiotics because they convene the required diverse stakeholders to tackle the complex scientific and economic challenges facing antibiotic R&D. For example, ND4BB brings together government leaders, academia, industry and other experts for an unprecedented sharing of information and multi-disciplinary

collaboration. The focus of the overall program is to develop better networks of researchers, create fluid and innovative clinical trial designs and provide incentives for companies to meet the challenges of antibiotic resistance quickly and efficiently. Initial funding for ND4BB (approximately $300 million for the first phase) was nearly equally split between government and industry sources.

The U.S. has begun recognizing the importance of PPPs for antibiotic development, though U.S. efforts have been much more limited in scope than EU activities. For example, the Biomedical Advanced Research and Development Authority (BARDA) has become a critical source of funding for companies developing novel antibiotics. However, discreet projects, while valuable, will likely not yield as powerful an impact as a large-scale, well-coordinated PPP similar to the ND4BB initiative.

IDSA urges U.S. government leaders to establish a large scale PPP, similar to the European effort, to ensure that we do not continue falling further behind. Industry leaders at the forefront of ND4BB have noted that government initiative was vital to the creation of these valuable partnerships.

Are there success stories the committee can highlight and best practices we can leverage in other areas?

The Committee is largely responsible for one of the most compelling success stories in the area of antibiotic R&D—the GAIN Act, mentioned above. This important first step has encouraged companies to consider re-entering the antibiotics market, not only because it provides an additional 5 years of exclusivity for new antibiotics to treat serious or life-threatening infections, but also because it demonstrates to industry that Congress is committed to the urgent public health need for new antibiotics. To ensure greater and continued success, Congress must build upon the GAIN Act by enacting additional incentives, as discussed above.

The European ND4BB initiative, also discussed above, is a best practice that the Committee can leverage by authorizing a similar effort in the U.S.

What is the financial burden of your disease? How would better treatments and cures help save money for your family and the federal government?

The medical and societal costs of antibiotic resistant infections are significant. A study published in 2009, "Hospital and Societal Costs of Antimicrobial Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship," extrapolated that resistant infections result in an additional $35 billion in healthcare and societal costs and an additional 8 million hospital days.

Better, more effective antibiotics will allow patients to be cured more rapidly, decreasing hospital admittance and length of stay. Faster cures can also limit the need for other costly interventions, including administration of less effective drugs, surgeries and physical therapy. Safer antibiotics can also reduce harmful side effects, such as kidney failure, that result in the need for additional costly treatments. Most importantly, more effective, safer antibiotics save

lives and improve the quality of life for patients.

How can Congress help?

As noted above, Congress can help patients by fostering the development of desperately needed new antibiotics. Congress can build upon the success of the GAIN Act to further reduce the economic and regulatory barriers facing antibiotic R&D using the specific recommendations discussed above.

Again, IDSA thanks you for this opportunity to comment. The Society is eager to maintain an ongoing dialogue with you regarding the 21st Century Cures Initiative and policies to incentivize antibiotic R&D. If you would like any additional information, or if IDSA can assist you in any way, please contact Jonathan Nurse, IDSA's Director of Government Relations, at [redacted]

Sincerely,

[redacted]

Barbara E. Murray, MD, FIDSA
President

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

www.LLS.org

June 13, 2014

The Honorable Fred Upton
Chairman
House Energy & Commerce Committee
2183 Rayburn HOB
Washington, DC 20515

The Honorable Diana DeGette
Member
House Energy & Commerce Committee
2368 Rayburn HOB
Washington, DC 20515

Dear Chairman Upton and Congresswoman DeGette:

The Leukemia and Lymphoma Society (LLS) appreciates this opportunity to comment on the *21st Century Cures: Patients* whitepaper. As the world's largest voluntary health agency dedicated to the needs of blood cancer patients, LLS is a strong supporter of action that will facilitate the discovery, development and delivery of new, safe, effective therapies for blood cancer patients. This year, we estimate that more than 150,000 Americans will be newly diagnosed with a blood cancer, accounting for nearly 10 percent of all new U.S. cancer diagnoses. Our mission is to cure leukemia, lymphoma, Hodgkin's disease and myeloma and improve the quality of life of patients and their families. We advocate on behalf of all blood cancer patients to ensure they have sustainable access to quality, affordable, coordinated healthcare.

We applaud the committee for taking this important step to ensure that the US remains at the forefront of innovation, and more importantly, for advancing an initiative that will ensure that patients have access to affordable, quality, life sustaining therapies. We strongly recommend that the committee take the following steps to facilitate this outcome:

- Adequately fund the discovery process, which is essential to keeping the United States at the forefront of biomedical innovation
- Pay special attention to programs that promote translational science research
- Ensure that clinical trial review and FDA drug approval processes are ready for advances in treatments, such as immunotherapy and precision medicine
- Ensure that the patient's voice is heard throughout the drug development process
- Ensure that once novel therapies are approved by the FDA, patients are able to access them

Given our unique position as a large funder of research, and as one of the largest organizations representing cancer patients in the United States, we appreciate the opportunity to comment on the important questions raised. LLS looks forward to continuing this discussion so that we may identify ways to expedite patient access to innovative, safe therapies.

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Question 1 – What is the state of discovery of cures and treatments for your disease? Are there cures and treatments now or on the horizon?

We have seen signifigant advances in the state of discovery of cures and treatments for blood cancer patients. For example, for patients with chronic myeloid leukemia (CML) three oral drugs, imatinib mesylate (Gleevec®), dasatinib (Sprycel®) and nilotinib (Tasigna®) have been approved for newly diagnosed patients. While these drugs do not cure CML, they keep the cancer under control for many patients for as long as the patient is compliant with the treatment regimen.

There are many other exciting advances in the area of blood cancer. For example, LLS is currently funding the pioneering immunotherapy research being done by Dr. Carl June at the University of Pennsylvania, and also at Memorial Sloan Kettering Cancer Center (MSKCC) using genetically engineered autologous T-cells for patients with certain forms of leukemia who have relapsed after standard treatments. In short, T cells, a type of immune cell, are collected from the patient's own blood and genetically engineered to produce special receptors on their surface called chimeric antigen receptors (CARs). These CARs give the T cells the ability to recognize a specific protein (antigen) on tumor cells and kill those tumor cells. Known as CAR T therapy, these treatments have produced 80-90% complete response (CR) rates in patients with formerly incurable acute lymphoblastic leukemia (ALL). Moreover, CR rates as high as 50% have been seen in patients with chronic lymphocytic leukemia (CLL) using a similar therapy, indicating that this approach has a potentially wider utility. Additional forms of CAR T therapy are now being tested for other blood cancers and solid tumors.

Emily Whitehead, a six year old near death from relapsed ALL, is now 9 years old, cancer free and in remission for over 2 years thanks to CAR T therapy. For more on Emily and Dr. June's treatment, please see the linked video entitled *Fire with Fire* (http://focusforwardfilms.com/films/72/fire-with-fire).

While these successes are encouraging, unfortunately, not all blood cancers have seen the same level of focus or advancement. For example, acute myeloid leukemia (AML) is a disease that causes more than 10,000 deaths in the U.S. each year, and where little treatment progress has been made over the past thirty years. As referenced in our comments submitted on May 30th (attached), LLS has made a commitment to address this lack of progress through our *Beat AML* initiative, a multi-institution research initiative designed to unlock the underlying genetic causes of AML, and leverage the advances in personalized medicine to accelerate findings and improve outcomes for AML patients.

Question 2 – What programs or policies have you utilized to support and foster research, such as patient registries, public—private partnerships, and venture philanthropy?

LLS is committed to achieving our vision of a world without blood cancers. To that end, LLS has multiple venues through which it supports and fosters research. In the past year alone, LLS has

committed more than $73 million to fund new grants supporting a wide range of research projects in academic centers throughout the world. This research spans all of the blood cancers and our goal is to advance myriad approaches that could improve outcomes for cancer patients. Examples of these initiatives are as follows:

- The *Quest for Cures* program is a collaboration with Celgene Corporation to fund research focused on the molecular causes of blood cancers and how to identify those patients who are most likely to respond to particular therapies.

- The *Screen to Lead* program is designed to help researchers turn chemicals into drugs that can be tested to further prove their potential effectiveness in treating blood cancers.

- The *New Idea Award* supports researchers with innovative ideas for new and substantially different approaches to the diagnosis and treatment of patients with blood cancers – the kind of early stage3 approaches that often do not receive funding from federal agencies.

- The *Specialized Center of Research* (SCOR) program is an academic grant program that facilitates the creation of teams of leading academic investigators who work together and are focused on a specific research goal. Four SCOR teams were created in September 2013 with a funding commitment of $6.25 million for each team over five years.

- The *Therapy Acceleration Program* (TAP) was created in 2007 to provide a process for getting new therapies to patients faster. This program provides funding to create alliances among biotechnology, pharmaceutical companies and academic research teams that can initiate investigational new drug-enabling studies and clinical-stage projects. The TAP program's goal is to move innovative biomedical discoveries more quickly from the laboratory into clinical trials and ultimately, to patients.[1]

LLS is also exploring ways to create a secure and confidential patient registry – a tool to collect patient data and combine it with the most current blood cancer treatment and research knowledge in order to disseminate personalized disease and treatment information to blood cancer patients, their healthcare providers, and caregivers. The registry will also provide easy access for patients to their medical records, easy access to clinical trials, and possibly genomic and or epigenetic profiling of their tumors that could be used to guide further research or participation in clinical trials.

[1] http://www.lls.org/#/researchershealthcareprofessionals/drugdevelopment/therapyacceleration/

Question 3 – How can Congress incentivize, coordinate, and accelerate basic research for diseases we know relatively little about?

Unfortunately, there is still a dearth of knowledge about the root causes of many diseases, including blood cancers. Federal funds in basic sciences fill a critical funding gap that can yield promising results for future new therapies and diagnostic tools.

As we have stated in earlier comments, the most important way that Congress can incentivize and accelerate basic research is by restoring adequate funding to the National Institutes of Health (NIH), its subinstitutions, and focusing on translational science.

Major gaps in funding exist at all stages of the discovery process. Although LLS and other private stakeholders have developed innovative programs that attempt to fill the gaps, a shortage of Federal funds will lead to a shortage of scientific discoveries. Adequately funding the discovery process is essential to keeping the United States at the forefront of biomedical innovation.

Question 4 – How can we work together to better translate advances in science into safe and effective new therapies for patients?

The Committee should ensure policies that adequately fund all stages of research, but pay special attention to those that promote translational science research. Translational science is essential to the development of new cures, because it bridges the gap between basic scientific discoveries and applied treatments.

Alongside TAP (discussed above), our *Translational Research Program* (TRP) serves as a model for how to drive discoveries from the laboratory into clinical trials, where they can be tested and developed into safe new treatments to prolong and enhance patients' lives.[2] Through TRP LLS identified six areas of unmet medical need and awarded 21 grants totaling $12.6 million. These grants, alongside an additional $11 million other areas, were awarded to research that was clearly clinical in orientation and had an overall goal of resulting in a clinical trial. TRP was developed in consultation with the National Cancer Institute, and representatives from the NCI are invited to participate in the grant review process. This is just one example of how groups can work together to speed effective new therapies to patients. LLS would be happy to discuss other ways to further this goal.

Question 5 – How do you coordinate your research and outreach with other patients?

LLS coordinates its research priorities based on medical need, with a focus on developing new therapies and treatment modalities. For example, as discussed previously, with the Beat AML project

[2] http://www.lls.org/#/researchershealthcareprofessionals/academicgrants/translationalresearch/

LLS is hoping to discover and develop new agents for AML, as treatment options have remained virtually unchanged in 30 years and the disease has a devastating outcome.

LLS also actively engages with its patient community through a variety of other efforts. For example, LLS's information specialists, who staff our Information Resource Center (IRC), are master's level oncology social workers, nurses and health educators who help patients deal with the challenges of their diagnosis, provide information about treatment options, help patients map the best route from diagnosis through treatment and survivorship, conduct individual clinical trial searches, and provide general education materials for patients.

The information specialists also provide information to patients about new clinical trials. For some blood cancer patients, participating in a clinical trial may be the best treatment choice. LLS helps patients understand the clinical trial process, and even provides online search tools for patient to determine if there may be an appropriate clinical trial. We hope that the patient registry (discussed above) will eventually further and strengthen this effort.

Finally, LLS maintains the LLS blog, a destination for blood cancer patients on the internet. Through the blog, LLS updates patients on new research initiatives, drug shortages, and other information that might be of interest to blood cancer patients.

Question 6 – How do you learn about new treatments and cures? How do you communicate with other patients regarding treatments and cures?

LLS-funded research has been part of nearly all of the FDA-approved therapies for blood cancer treatment, and as such LLS is intimately aware of new treatments and cures for blood cancer patients. LLS maintains an active relationship with the research community, not only providing academic and research grants, but also sponsoring research symposia where our investigators come together to share and exchange new ideas.

Upon approval of new therapies by the Food and Drug Administration (FDA), LLS communicates this information to patients through our website, monitored-discussion boards, chapter-led programs across the country, our IRC, and via live teleconference webinars. Our information specialists receive more than 60,000 calls annually from patients and we use these opportunities to communicate about the most up-to-date treatments that are available for specific blood cancers. LLS medical and mission education staff work with a groups of volunteer clinical advisors to review the communications materials that we provide to patients to ensure that they are accurate and up-to-date.

Frequently, our IRC receives calls from patients who are newly diagnosed; who have not had a good response to the standard treatment protocol, or who have simply run out of treatment options. LLS

keeps current on relevant clinical trials through daily updates that it receives from various medical journals. Thus, we are able to inform these patients of the latest treatment options that are available for their disease, as well as any appropriate clinical trials for which they may qualify. .

LLS also communicates with blood cancer patients via each of the 55 chapters that are located across the country. Chapter staff connects patients with local experts and other resources that may be available in their immediate community.

Finally, we also provide national teleconferences and webinars and invite experts in multiple myeloma, leukemia and lymphoma to speak about the latest treatment options and cures. These programs are live, and reach thousands of patients nationally and internationally. These programs are archived on our website for future use by patients.

Question 7 – What can we learn from your experiences with clinical trials and the drug development process?

It is clear that through our better understanding of hematological malignancies and disease progression, there have been significant advances in the treatment of blood cancer patients. However, our experiences throughout the clinical trial and drug development process have also taught us many other things, including:

- The "standard" approach to drug development is difficult for blood cancers. Finding drugs that have a durable complete response is extremely difficult, and meeting the current standard endpoint of an increase in overall survival (OS) is particularly difficult, particularly in AML. In order to bring new agents to market for many diseases, including AML, FDA may need to consider additional endpoints. For example in AML the FDA might consider progression free survival (PFS) or minimal residual disease (MRD).

- Targeted therapies are the future of cancer treatment, and blood cancers in particular need support for additional research into precision medicine. This will require flexibility in clinical trial design and understanding of sub-populations in clinical trials.

- We are unlikely to cure any given cancer with one drug. It is likely going to to take a combination of treatments and approaches. Combination treatments, and therefore clinical trials examining combination treatments, should be encouraged. Getting to combination treatments faster is essential, and will have a significant impact on our diseases. More incentives may be required to invest in research into "tool" compounds that can be combined, and which may provide an approach for seeing significant changes in overall survival.

- Finding patients to populate clinical trials is a challenge for hematological malignancies, not just because the patient numbers are small to begin with, but also because patients are generally older and frequently cannot travel to trial sites. Clinical trials will need to be made more nimble and new designs into clinical trials will needed to ensure that trial accrual is not the reason new innovative drugs do not make it to market.

Question 8 – What is the role of government in your work, including any barriers to achieving your goals and advancing breakthroughs?

LLS actively participates in all aspects of the legislative and regulatory process. Because there are few means for prevention or early detection of most blood cancers, LLS is focused on finding cures and ensuring access to care. For our patient population, getting new treatments to market quickly and safely is of paramount importance and the only available option.

LLS understands the importance of the work performed by the FDA to review and approve new drugs and devices. To that end, LLS advocates for the FDA to to have the resources and funding necessary to meet the challenges it faces.

While the FDA has not been a barrier to advancing breakthroughs, through our own interactions with the agency, and through our partners, we have become aware of certain areas where additional clarity or guidance would be valuable and would speed the advancement of breakthroughs. These areas include:

- the approval of and reimbursement for companion diagnostics
- the regulation of laboratory developed tests
- the approval pathway for biosimilars
- the use of information from the patient focused drug development initiative
- the approval pathway for immunotherapies and other precision medicines
- expanded access
- drug shortages

Question 9 – How should regulators evaluate benefit-risk? How do you work with regulators regarding benefit-risk? Can this process be improved?

LLS appreciates the FDA's recent efforts to provide additional clarity on how it intends to evaluate benefit-risk by implementing a structured benefit-risk assessment framework. The framework, agreed to as part of PDUFA V, seeks to provide better communication of the review team's perspective during review and of the FDA's decision-making when the agency approves a product. However, in evaluating benefit-risk, LLS requests that patient input regarding benefit and risk considerations be considered earlier in the regulatory review process.

For example, as the potential to identify and treat disease variants becomes increasingly sophisticated, LLS requests that the knowledge gained from research in this area be quickly incorporated into benefit-risk evaluations. Increased diagnostic precision will allow the identification of patient sub-populations that will respond to treatments with greater benefit and/or lower risk than members of the larger group. LLS recommends that benefit-risk evaluations be designed to incorporate this additional information during the approval and post marketing process.

Question 10 – What is the role of public and private funding in the research and development of cures and treatments?

LLS is a significant stakeholder in the drug and device development process, and has provided more than $1 billion for research aimed at discovering, developing and delivering blood cancer cures since its founding. LLS provides funding at every level in the search for cures to blood cancer patients. LLS academic grants support and encourage basic and translation blood cancer research. LLS also funds research to help improve the quality of life for patients and their families with our projects studying long-term and late effects.

As discussed above, LLS participates in several drug development partnerships, parterning with organizations whose resources and expertise can help accelerate the process of developing new drugs and making them available to patients.

However, despite LLS's role as a funder of cancer research, we also recognized the critical importance of the NIH, the National Cancer Institute, the Centers for Disease Control and Prevention, the Department of Defense, and the many other voluntary and private institutions and corporations that also help fund cancer research and are intergral to our goal of ending cancer.

Question 11 – Are there success stories the committee can highlight and best practices we can leverage in other areas?

Gleevec®, Sprycel® and Tasigna® all represent transformative steps forward for blood cancer patients. These oral medications have helped to turn a formerly terminal disease, CML, into manageable chronic condition for many patients. The possibility for similar results exist with ibrutinib (Imbruvica®), a drug recently approved by the FDA to treat patients with mantle cell lymphoma and relapsed chronic lymphocytic leukemia (CLL).

Part of the success of ibrutinib is due to the work of LLS-funded researcher John Byrd, M.D., of the Ohio State University Ibrutinib is a drug that targets Bruton's tyrosine kinase (BTK), an enzyme which promotes growth of a variety of B-cell cancers, including CLL, mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia (WM), follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), hairy cell leukemia (HCL) and multiple myeloma. Dr. Byrd has not only helped develop a

greater understanding of how ibrutinib works, but he has also developed a greater understanding of why, for a small portion of patients, treatments such as ibrutinib are ineffective. Building an understanding of why certain treatments do not work for some patients is an important building block to our understanding of how to cure cancer.

LLS would also like to highlight once again the innovative work of Carl June, M.D. and other doctors in the field of immunotherapy and CAR T cell therapy.

Question 12 –How have you worked with other patients to support one another?

Internally, LLS provides support to blood cancer patients through our First Connection Program – a free service that enables patients and their loved ones to connect with a trained peer volunteer who has gone through similar experiences. The program makes an average of 6,000 first connections annually. These volunteers are in a unique position to provide support and community resource information to others facing a similar cancer diagnosis. Because many of our patients, when diagnosed, do not have family members or friends who have experienced blood cancer, this program provides vital support to patients across the country.

Externally, LLS partners with a number of coalitions in the cancer community, and the broader health community, to support our shared priorities. One such partnership is the Cancer Leadership Council[3], a patient-centered forum of national advocacy organizations addressing public policy issues in cancer. A second is the Alliance for a Stronger FDA[4], a group of several hundred patient and industry partners allied around supporting the important work of the agency.

Question 13 – What is the financial burden of your disease? How would better treatments and cures help save money for your family and the federal government?

An example of the financial burden of blood cancers can be seen through the burden on patients with CML. Critical advances in CML research have lead to targeted oral therapies which have transformed what was once a certain death sentence into a chronic, manageable disease. However, this change has led to a larger cost-burden to patients and families. LLS will continue investing in the next generation of therapies and cures; however, access barriers that exist today are preventing patients from affording necessary, life-saving therapies.

Changes in policy that ensure patients have access to therapies can ultimately save the healthcare system hundreds of millions of dollars. Access barriers like “specialty tiers” allow plans to impose high coinsurance, in lieu of a co-payment, for therapies resulting in higher out-of-pocket spending for patients. This policy has a direct, negative impact upon patient access to needed medicines, and

[3] See: http://www.cancerleadership.org/
[4] See: http://strengthenfda.org/

disproportionately affects those prescribed innovative oral therapies. Not only does this place a financial burden on patients, but it has also been shown to discourage adherence to treatment. In fact, in a recent study, patients were found to forgo some more expensive therapies altogether or discontinue treatments based on cost.[5] Another study shows once out of pocket costs exceed$100 approximately 10% of patients abandon treatment and at $500, 25% of patients abandon treatment.[6] The New England Health Institute recently estimated that medication non-adherence results in up to $290 billion annually in increased medical costs in the U.S.[7]

We urge the Committee to consider supporting additional policy changes that will ensure that once novel therapies are approved by the FDA, patients are able to access them. For example, HR 460, the Patients' Access to Treatments Act, is a bill which would require plans to limit cost-sharing requirements for specialty drug tiers to the level of cost sharing required for non-preferred brand drug tiers. Support for this bill would help ensure that patients have access to better treatments and cures.

Question 14 – How can congress help?

At LLS, our mission is to cure leukemia, lymphoma, Hodgkin's disease and myeloma and improve the quality of life of patients and their families. LLS hopes that the Committee, in conjuction with FDA, echos that mission for all diseases. The Committee should ensure that the FDA, NIH, and other relevant agencies have the proper funding to fulfill their missions. The Committee and Congress should incentivize basic and translational research. The Committee and Congress should continue to actively engage the patient community in order to gain an understanding of the changes that are needed to the clinical trial system and engage in changes that will lead to real results and cures for patients.

However, as the Committee and Congress look to bring the most advanced treatments to market, the Committee must not forget that the most advanced treatment means nothing if a patient cannot access that treatment. As the Committeee looks to make sure that America does not lose its lead in innovation, the Committee and Congress must be sure that they are working toward a system of quality, sustainable, healthcare innovation.

[5] Neumann, et al. "Cancer Therapy Costs Influence Treatment: A National Survey of Oncologists." Health Affairs. January 2010. 29:1.
[6] Streeter. S, "Patient and Plan Characteristics Affecting Abandonment of Oral Oncolytic Prescription," Journal of Oncology Practice, Vol7, Issue 3S, p. 49.
[7] New England Health Institute. "Poor Medication Adherence costs $290 billion a year." 2009. See: http://mobihealthnews.com/3901/

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Conclusion

We appreciate the Committee's interest in producing a regulatory environment that will maintain America's position as the leader in biomedical innovation. Discovering, developing and delivering new treatments to patients with blood cancers are central to the LLS mission and we applaud the Committee for proactively undertaking the 21st Century Cures initiative to improve these processes across the entire biomedical industry.

Please do not hesitate to contact me at [redacted] should you or your staff have any questions.

Sincerely,

[redacted]

Brian Rosen
Chief Policy & Advocacy Officer
The Leukemia & Lymphoma Society

Muscular Dystrophy Association (MDA) Congressional Comment
21st Century Cures Initiative

The Muscular Dystrophy Association (MDA) is the leading nonprofit health agency dedicated to saving and improving the lives of individuals affected by more than 40 neuromuscular diseases, including the muscular dystrophies, spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), Friedreich's ataxia (FA), Charcot Marie Tooth disease (CMT), myasthenia gravis (MG), mitochondrial myopathies, and more. The diseases MDA fights are all rare disorders of the muscles or parts of the nervous system that control the muscles. They are progressive and cause the muscles to weaken and atrophy; in some disorders this can happen very rapidly. Individuals with these disorders can lose basic functions that many people take for granted, like walking, standing, speaking, swallowing or breathing. Some muscle diseases appear at birth, while others emerge during early childhood, young adulthood or even late middle age. Most are genetic in origin, and most limit life span and quality of life. **There are few treatments, and no cures.**

MDA is working tirelessly to change this picture by funding worldwide research to develop treatments and cures; by providing comprehensive health care services and support to MDA families nationwide; and by rallying communities to fight back through advocacy, fundraising and local engagement.

Currently serving more than 100,000 Americans representing every state of our nation, MDA supports a national MDA clinic network comprised of 200 hospital-affiliated multi-disciplinary clinical care centers that provide comprehensive, world-class care to people with neuromuscular diseases. In addition to optimization of health outcomes, many institutions that host MDA clinics serve as hubs for basic and translational research, while many MDA clinics themselves conduct clinical research and trials and participate in national clinical trial networks.

Since its inception more than 60 years ago, MDA has provided an unparalleled level of private funding to basic, clinical and translational research; young investigator rants; neuromuscular and research fellowships; a clinical research network infrastructure for ALS, Duchenne muscular dystrophy (DMD), and myotonic muscular dystrophy (DM); and the development and implementation of the U.S. Neuromuscular Disease Registry. While our investment – thanks to the generosity of our donors within the American public – has been substantial, we have not done this alone. The neuromuscular community is a well-organized, collaborative community that has benefited from the contributions of many private organizations, world-renowned academic leaders and federal partners. Furthermore, in recent years, the neuromuscular therapeutic pipeline has attracted biotech and pharmaceutical partners and drug development momentum has hastened.

Despite more than 6 decades of investments, collaborations and research progress, people living with neuromuscular diseases still are in urgent need of comprehensive treatments and cures. Infants diagnosed with spinal muscular atrophy type I (SMA I) typically die before age two. Adults diagnosed with amyotrophic lateral sclerosis (ALS) typically die three to five years from the time of symptom onset. Those with Duchenne muscular dystrophy (DMD) have an average life expectancy in the mid 20's. And, like so many of the other neuromuscular diseases in MDA's program, symptoms from these diseases - such as impaired ability to walk, lift one's arms and head, turn over in bed at night, breathe

independently, maintain cardiac function – have a profound impact on an individual's quality of life and that of their family.

While our therapeutic pipeline continues to move more promising therapies into late phase II and III clinical trials, families anxiously await the ability to access critical treatments, with few answers. **We want nothing more than for safe and effective therapies to be delivered to patient families at the earliest moment possible.** We applaud the House of Representatives and the United States Congress for devoting attention and resources to ensuring this pathway exists and to expediting cures and treatments.

Questions posed by Congress

What programs or policies have you utilized to support and foster research, such as patient registries, public-private partnerships and venture philanthropy?

MDA's U.S. Neuromuscular Disease Registry
MDA has implemented the U.S. Neuromuscular Disease Registry which records types of medical care provided, disease progression and health-related and quality of life outcomes of patients seen in MDA clinics.
The goals of the registry are to 1) gain a better understanding of the course of illness for specific neuromuscular diseases, 2) collect data about genotype-phenotype correlations to allow for better prediction of disease progression based on genetic information, 3) collect longitudinal patient data that will enable benchmarking of best clinical practices 4) use registry data as a platform to develop and implement a clinical quality improvement program for MDA clinics across the country 5) provide outcome-related information about MDA clinics for families seeking medical care and 6) establish a database of individuals eligible for clinical trials in neuromuscular diseases and expedite research by easing the burden of clinical trial recruitment.

MDA's Registry Advisory Board includes membership from a variety of sectors including academia and the patient community, as well as advisors from the National Institutes of Health and the Centers for Disease Control and Prevention. We are also working closely with pharmaceutical industry partners on ways to utilize the registry to inform clinical trial design and implementation and accelerate therapeutic pipelines. (For additional information, see http://www.neurology.org/content/82/10_Supplement/P7.008 for Muscular Dystrophy Association U.S. Neuromuscular Disease Registry – Preliminary Findings.)

Public-Private Partnerships
MDA has many examples of partnerships between our funded programs and federally-funded programs yielding great progress.

An important example is the NIH Centers of Excellence Program (Wellstone Centers). First established by the Paul D. Wellstone Muscular Dystrophy Community Assistance, Research, and Education Act (MD-CARE Act) in 2001, then reauthorized in 2008 and under consideration for amendment currently, they have yielded great advances in understanding the specific causes of the various forms of muscular

dystrophies, the mechanisms of these diseases, identification of therapeutic targets, and now even clinical trial development. These Wellstone Muscular Dystrophy Research Centers serve as a model to follow for best incentivizing therapy development. Wellstone Centers each share core facilities and have unique research specialties about which they communicate and share data frequently and transparently; serve as training and career development grounds for scientists and clinicians; and foster industry collaborations. Further, this network approach to research yields a layered funding approach where government funding serves as the foundation, supplemented by nonprofit and patient advocacy research support and dollars, and further supplemented by private biotechnology and pharmaceutical research investments.

- Supported by four- to five-year NIH awards of $1 million direct cost per year (~$1.5 million total cost)
- Total of six centers
- Funding from National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Child Health and Human Development (NICHD), National Institute of Neurological Disorders and Stroke (NINDS) and National Heart, Lung and Blood Institute (NHLBI)

When the Wellstone Center program was first initiated in 2005, MDA matched the funding provided by NIH to each Wellstone Center ($1.5 million) to ensure that the centers would have the traction needed to launch. Wellstone Centers have contributed to the understanding of significant scientific concepts and technological advances. The Wellstone Centers Program supports high quality translational and clinical research advancing understanding and therapy development for Duchenne muscular dystrophy (DMD), myotonic dystrophy (DM), fascioscapulohumeral muscular dystrophy (FSHD), limb-girdle muscular dystrophy (LGMD), and congenital muscular dystrophy (CMD). Furthermore, several of the Wellstone Centers' current clinical trials in muscular dystrophies were made possible by discoveries that originated within Wellstone Centers.

MDA has utilized this collaborative research network approach and has partnered in establishing, through direct funding of nearly $1 million annually, 15 elite MDA medical clinics (among its 200 hospital-affiliated clinics) to speed and support research focused on ALS (amyotrophic lateral sclerosis), Duchenne muscular dystrophy (DMD), and myotonic muscular dystrophy (DM).

MVP – Muscular Dystrophy Venture Philanthropy (MVP)

In the early 2000's, MDA launched its translational research program, now known as MVP, exclusively focused on funding the discovery and commercialization of treatments and cures for neuromuscular disease. Dedicated to building on our organizational strengths and the expertise of partners within the field, MVP makes selective investments in companies with promising paths to market; conducts professional diligence in evaluating investment opportunities; builds on MDA's investment since inception of more than $1 billion in science, manpower and infrastructure; and leverages investments at strategic points in the drug development process. Strengths of our program have included FDA consultation for clinical trial endpoints; a responsive physician network through MDA clinics; international scale registries with common core datasets; efficient clinical trial networks established with experienced clinicians for multicenter trials using standardized, validated endpoints; current natural history data; and access to world-class expertise in all disease areas. The program has helped move the field forward and has generated a number of successes where MDA's early investments were

leveraged into follow-on funding from a number of sources including industry and the NIH TRND program. One of our earliest successes through our translational research program funding mechanism includes:

- In 2005, MDA invested $1.5 million in a phase I and phase IIa study of Ataluren (formerly PTC 124) for Duchenne muscular dystrophy (CF Foundation also invested in this drug).
- In 2008, Genzyme and PTC Therapeutics signed a co-development deal worth up to $400 million to move the drug forward for four indications, including DMD and Cystic Fibrosis.
- Ataluren is now in phase III testing for DMD.

Hosting Conferences and Focused Symposia

MDA is committed to enhancing the communication of new research findings and information relating to the delivery of effective medical care across the various neuromuscular diseases. To achieve this goal, MDA hosts an annual conference series, with scientific and clinical conferences held in alternate years.

- MDA's most recent Clinical Conference was held March 16-19, 2014. The Clinical Conference focuses on bringing together health care professionals who are dedicated to diagnosing and caring for patients with neuromuscular diseases. Clinic teams share critical updates on the diagnosis and medical, rehabilitative and psychosocial management of neuromuscular disorders, with the goal of promoting an effective team approach to providing optimal patient care across the 200 hospital-affiliated clinical care centers funded by MDA.

- MDA's most recent Scientific Conference was held April 21-24, 2013. The sold-old event attracted more than 500 participants from around the world, focused on therapeutic strategies for neuromuscular diseases, with sessions highlighting different aspects of therapy development. Some 70 platform presentations and 200 poster presentations were included. The conference agenda focused on neuromuscular research strategies and cross-cutting themes — rather than individual diseases — including novel drug targets, biomarkers, therapeutic modalities and new animal models.

In 2012, MDA initiated a series of focused symposia, where a small group of experts discuss specific issues in neuromuscular disease research. These symposia have included:

- MDA/AFM joint evening symposium on gene therapy at the ASGCT annual meeting;
- Glial cells in amyotrophic lateral sclerosis;
- Translating academic research into drugs; and
- Newborn screening for Duchenne muscular dystrophy.

How can Congress incentivize, coordinate and accelerate basic research for diseases we know relatively little about?

The clinical and research community is in great need of robust financial support of clinical centers of excellence, cooperative clinical trial networks, basic science in muscle disease and removal of hurdles in the implementation of therapeutic approaches. Optimizing NIH funding of neuromuscular and motor neuron disease research and renewal of the Paul D. Wellstone Muscular Dystrophy Community Assistance, Research, and Education Amendments Act (MD-CARE Act) are essential components of providing resources to expedite lifesaving therapeutic development. Furthermore, as more and more therapeutics are anticipated to begin to move into human clinical trials, there is an urgency for clinical sites to become clinical trial-ready which requires additional funding resources, specialized personnel, and coordination within and among national trial sites.

MDA's clinical and research community has voiced their need for support to go to the most productive research groups and to develop oversight bodies with subspecialist evaluation to determine funding of projects (i.e. neuromuscular specialists evaluate research proposals). Others have suggested providing tax incentives and grants to companies who devote significant resources to neuromuscular and rare disease therapeutic development.

Furthermore, researchers have expressed concern regarding the incredible cost to conduct clinical trials, with little incentive or reward to the developers in disease populations that are small. Clinical trial participation continues to be expensive (with participation being cost-prohibitive to some families) and time-consuming to both participate in and implement.

Significant resources are necessary to increase our understanding of clinical trial design and to incentivize pursuing this in rare disease, including funding travel for trial participants, expanding the number of clinical-trial ready sites and increasing the number of people trained to administer clinical research.

How can we work together to better translate advances in science into safe and effective new therapies for patients?

Developing strategic partnerships, increasing research funding streams, and raising awareness of clinical trial participation are all necessary to translate advances in science into therapies for patients.

Currently, there are basic barriers to obtaining an accurate diagnosis for neuromuscular diseases, as the vast majority of testing is processed by commercial laboratories at a high price to insurers and families. Insurance companies frequently deny authorization for genetic testing for neuromuscular diseases in which there are no treatments and it will not significantly alter the course of medical intervention; however, knowing the specific mutation of a patient is necessary to conduct clinical trials. A family then faces the decision of whether to pay hundreds of dollars, or even thousands in some cases, out-of-pocket to obtain an accurate diagnosis or live with a more "general" diagnosis which would preclude

them from participating in clinical trials. The barriers to therapeutic development exist from the moment of diagnosis, to great detriment to the clinical, scientific and patient communities.

Furthermore, this genetic testing often can be performed prenatally or at birth, allowing any potential treatments to begin as soon as possible (even an experimental treatment, with parental consent), before the disease has done irreversible damage to muscles. Early diagnosis also could inform parents' future reproductive choices, and eliminate the long and frustrating "diagnostic odyssey" (search for a diagnosis) that many families undergo. Families can spend years seeking a correct diagnosis for their or their child's symptoms. Yet, newborn screening has only been currently approved for one neuromuscular disease in a select few states – the fatal childhood onset Pompe disease, for which enzyme replacement therapies are effective. Having newborn screening in place for diseases such as Duchenne muscular dystrophy and spinal muscular atrophy could allow clinical trial participation of infants prior to experiencing irreversible muscle damage that comes with age and disease progression.

As therapy development in rare diseases such as neuromuscular disease continue, genetic testing will become increasingly important. Innovative therapies may increasingly rely upon hitting the appropriate drug target, which may be a very specific segment of a particular gene. Personalized medicine relies upon matching the appropriate therapy to the appropriate patient. Failing to do so results in increased cost for inappropriately targeted treatment, missed opportunities to evaluate the therapy, and potentially precluding a patient from participating in a clinical trial that would be appropriate for that specific patient and his or her mechanism of disease. With limited "shots on goal" in a small, rare disease population, we cannot slow down the drug development pipeline and must ensure we are maximizing success in enrolling clinical trials and bringing treatments to patients.

How do you coordinate your research and outreach with other patients?

For most of the 40 diseases MDA fights, there exists at least one disease-specific patient advocacy organization or family foundation. For some of the diseases, there are dozens of disease-specific organizations. MDA strives to maintain open communication with each organization to reduce duplication and foster collaboration whenever possible. There exist some examples where these partnerships have yielded great outcomes such as the collaborative effort around the MD-CARE Act during the past decade and the facilitation of the FDA ALS subpart 15 Hearing.

Equally as important have been collaborations and the exchange of best practices with organizations outside of the neuromuscular space. MDA serves in both leadership and active participatory roles in dozens of patient coalitions through groups where cross-over between communities allows for great exchange. These groups include the patient coalitions associated with the various institutes of the National Institutes of Health (NIAMS Coalition, Friends of NICHD, ORDR CPAG, etc), the Centers for Disease Control, the Food and Drug Administration, as well as organizations that exist to convene groups (BIO, Genetic Alliance, Faster Cures, NORD).

MDA has worked closely with the American Academy of Neurology and the CDC to develop and test standards of care for several of the neuromuscular diseases. The MDA U.S. Neuromuscular Disease Registry was, in part, developed to learn more about adherence to standards of care and how those interventions impact health outcomes.

The Muscular Dystrophy Coordinating Committee (MDCC) also provides an excellent forum to coordinate research and exchange ideas. Originally established by the MD-CARE Act, the MDCC consists of inter-federal agency representatives as well as muscular dystrophy patient advocacy organizations, including MDA. The MDCC has worked to eliminate duplication and maximize opportunities for collaboration with government and private partners. The MDCC developed the MD Action Plan in 2005 and is in the process of updating that Action plan.

What is the role of government in your work, including any barriers to achieving your goals and advancing breakthroughs?

For many decades, MDA led and funded treatment and cure-driven research efforts without formalized collaborations with federal partners. Since the passage of critical legislation such as the MD-CARE Act and the ALS Registry Act, funding into neuromuscular disease research academic and clinical entities throughout the nation has increased substantially. Our federal agency partners have begun to have the funding traction needed to move the needle for improving health outcomes for the hundreds of thousands of Americans who are living with these progressive and fatal diseases. Particularly as exemplified by the results of the MD-CARE Act, government has provided the focus and coordination, allowing organizations such as MDA to supplement and act as force multipliers in particular research areas. This exemplary model of public-private partnership has helped to draw biotech and pharmaceutical partners, and the neuromuscular landscape now contains opportunities that would have likely not existed without the involvement of the federal government's funding and infrastructure resources. We must keep these collaborations and funding sources robust for our therapeutic pipelines to reach their full potential.

Some in the neuromuscular clinical community have expressed their concern that the current uncertain funding environment, characterized as "tenuous", may provide the biggest barriers to advancing breakthroughs. One clinician describes it as follows:

"The funding environment in the U.S. makes it very difficult to take on a project that might not pan out in the next few years. I have several promising projects that are currently on the shelf; they are too risky to put resources into because other projects are more likely to provide the data I need for the next grant."

-Submission to MDA Clinical and Research Community Survey on Congressional 21st Century Cures Initiative, June 2014

Others have commented that their local regulatory steps are "sluggish" and that resources are needed locally by clinical researchers to expedite human subjects review.

How should regulators evaluate benefit-risk? How do you work with regulators regarding benefit-risk? Can this process be improved?

In February of 2013, the Food and Drug Administration (FDA) sponsored a subpart 15 Hearing focused on ALS to assess how to accelerate therapy development in ALS and consider the benefit-risk equation in a disease where the risk of doing nothing outweighs the side effects of many trial therapies. MDA worked closely with the FDA to ensure that the Federal Register notice was widely disseminated to the patient, provider and research community; that a broad and representative demographic was represented in both docket submissions and day-of hearing testimony; and that the hearing itself was accessible to the targeted patient community.

Researchers and families have expressed the view that the severity and progression of the disease should enter into the discussion of the risk-benefit ratio. Any benefit may be worthwhile in these situations without causing overt harm due to the progressive nature of these diseases. The risk-benefit analysis is experienced differently for families who have a loved one with a rare and life-shortening disease. As one member of MDA's clinical community states:

> "Drug screening and safety are important, but it must be recognized that patients with uniformly fatal neuromuscular disease may be willing to endure side effects of an effective drug that may be unacceptable for a healthier patient population. I think that combining the safety and efficacy trials may help move promising drugs through the pipeline."
> -submission to MDA Patient Community Survey on Congressional 21st Century Cures Initiative, June 2014

In 2012, FDA initiated its Patient-Focused Drug Development (PFDD) program to obtain the patient perspective on certain diseases and their treatments. The FDA convened a series of very constructive public meetings to outline how it would proceed and to ensure that it had captured the patient voice for its PFDD meetings planned for Fiscal Years 2013-2015. During these meetings, MDA joined other leaders within the rare disease community as we worked through a number of benefit-risk issues that require special focus and attention, such as understanding the unique patient and parent perspective with serious or fatal pediatric onset diseases. These issues cut across specific diseases and raised important issues for regulators to consider. MDA supports such an approach for future FDA meetings, where categories or common issues are evaluated, rather than solely considering disease-specific issues. Focusing on common mechanisms of disease or recurrent issues not only ensures the best use of limited federal resources, it provides a foundation for FDA to draw upon in regulation and, more broadly, it ensures that all stakeholders benefit from one another's experiences and expertise. For instance, it might be appropriate to focus on pediatric-onset neuromuscular diseases, or to consider categories of therapeutic options, such as exon-skipping which may be used in multiple diseases, or to consider the mental health effects of various forms of treatment on pediatric populations and their caregivers.

Are there success stories the committee can highlight and best practices we can leverage in other areas?

The Muscular Dystrophy Community Assistance, Research and Education Amendments (MD-CARE Act), originally enacted in 2001 and updated in 2008, represents a tremendous success in public-private partnership as incentivized by congressional leadership. In the last 14 years, this legislation has helped change the muscular dystrophy landscape by coordinating and focusing federal research on all nine forms of muscular dystrophy, studying epidemiologic data, and developing and disseminating patient care guidelines -- all of which have made a significant impact on the quality of life and life expectancy of children and adults diagnosed with muscular dystrophy.

NIH's research through the Senator Paul Wellstone Muscular Dystrophy Cooperative Research Centers, has impacted many of the scientific breakthroughs across the muscular dystrophies, and has led to the expansion and intensification of MD research, including the leveraging of significant non-federal sources of funding. Since 2001, there have been 67 clinical trials of drugs or therapies for muscular dystrophy and there are currently more than 40 human clinical trials underway. A number of the potential therapies now in clinical investigation can be traced to the basic research efforts sponsored by the Centers. The impact of the investment has extended beyond muscular dystrophies and the neuromuscular community, with discoveries within Wellstone Centers forming the basis of new conceptual models that have potential impacts on therapy development for the muscular dystrophies and beyond neuromuscular diseases. Specifically:

- In 2010, through combined Wellstone Center research funding and support from nonprofit patient advocacy groups, after years of not understanding the underlying cause of facioscapulohumeral muscular dystrophy (FSH), researchers showed that abnormal production of a specific protein was the major molecular cause of FSH. In 2012, researchers identified the first ever therapeutic target in FSH, and the research field exploded with all new routes of investigation and discovery and clinical trials. Commenting about this 2010 discovery, Dr. Francis Collins, Director of the NIH stated: "If we were thinking of a collection of the genome's greatest hits, this would go on the list." *Kolata, Gina "Reanimated 'Junk' DNA Is Found to Cause Disease". The New York Times. August 29, 2010.*

What is the financial burden of your disease? How would better treatments and cures help save money for your family and the federal government?

As part of our initiative to understand the economic burden of several neuromuscular diseases, in 2010 MDA commissioned The Lewin Group to estimate the economic impact on the United States of ALS, DMD, myotonic muscular dystrophy (DM) and spinal muscular atrophy (SMA). The study considered the direct, indirect and, ultimately, the total national economic burden associated with these diseases in 2010. It utilized commercial and Medicare claims data to estimate direct medical costs and a national survey of a random sampling of families living with each of the neuromuscular disorders to estimate indirect costs.

Using the moderate prevalence estimate, we estimated that the total economic cost of the diseases above was approximately $3.2 billion in 2010. We also estimated that the total national burden is in the range of $1.2 to $4.8 billion/annually (using the low and high prevalence estimates respectively).

When using the moderate prevalence estimates, among the diseases studied, ALS is associated with the highest annual national economic burden ($1.03 billion), followed by SMA ($957 million), DMD ($791 million) and MMD ($450 million). It should be noted that, due to low sample sizes of the populations, there is a large margin of error for the estimate for SMA. (Larkindale J, Yang W, Hogan P, Simon C, Zhang Y, Jain A, Habeeb-Louks E, Kennedy A, Cwik V. Cost of illness for neuromuscular diseases in the United States. *Muscle & Nerve*. 2014;49(3):431-438.)

In June of 2014, MDA modified the questions posed by Congress in the request for comment related to the 21st Century Cures Initiative and distributed two nationwide electronic surveys: one survey tailored to families registered with our organization and another tailored to clinicians and researchers within our neuromuscular community. **We found that close to 70 percent of families with a neuromuscular disease experience financial problems as a result of their neuromuscular disease, and that this is consistent across diseases without respect to severity or life-threatening nature of the disease.** These costs include not only co-pays, deductibles and other medical expenses, but also the expenses related to home modifications, the purchase of accessible transportation and in-home caregiving support.

The middle class is particularly hit with out-of-pocket costs as they often don't qualify for income-related means-tested programs for health insurance and community-based support. The financial strain for families includes the loss of personal work productivity, family members leaving the workforce to care for the person with neuromuscular disease, the compounding financial strain of multiple family members being diagnosed with a genetic condition, and paying out-of-pocket to see neuromuscular specialists if the family's insurance refuses to authorize the visit. One family we work with reports, "We actually declared bankruptcy and lost our house due to medical bills about 2 years ago." We have heard from many families who barely make due, have lost their homes, or have had to declare bankruptcy as a result of their neuromuscular disease.

Many families surveyed also state that Congress must "consider other cost reductions that are recouped through decreased dependency on programs such as Medicaid, Social Security, and Medicare that would result from increased funding of therapy development." -Submissions to MDA Patient Community Survey on Congressional 21st Century Cures Initiative, June 2014

How can Congress help?

The 21st Century Cures Initiative is precisely how Congress can help most. Developing and delivering cures is a highly complex endeavor that requires involvement and input from a variety of different interests. As exemplified through Congress' unique ability and recent successes within our neuromuscular community to leverage resources and facilitate public-private collaborations among a variety of stakeholder groups, Congress' role within the pipeline is critical. For instance, are there collaborations that could be furthered between the NIH and the FDA, to ensure that the FDA benefits from the vast knowledge and experience gained in the NIH? In our experience, the two agencies are working very well on behalf of patients, but are there further efforts that might help facilitate the transfer of research knowledge to the regulators?

Models such as the Muscular Dystrophy Coordinating Committee, funding approaches such as those seen within the Wellstone Centers, and continued commitment to biomedical funding and innovation are critical. But they are not enough.

For families living with neuromuscular diseases, there are few treatments and no cures.

And while Congress must continue to seek incentives to attract and keep biotech and pharmaceutical industry partners in our disease spaces, much congressional impact can be made further downstream such as increasing appropriations and funding to state public health laboratories and the federal agencies that support them so that we can apply life-saving drug therapies to all patient communities at the earliest moment possible (newborn screening) to achieve maximum treatment effect.

We must ensure that our processes maintain scientific rigor, while becoming more streamlined. Examples of such streamlining would include incentivizing universities to utilize centralized institutional review boards (IRBs) and looking to innovative clinical trial models such as those created by the National Institute of Health National Institute of Neurological Disorders and Stroke's (NINDS) Neuro NEXT program.

In 2014, we as a nation have made great strides in therapeutic development and clinical innovation. And while we have begun to change the natural history of some of our neuromuscular diseases, we have not changed the outlook for people who are being diagnosed in physician's offices throughout America every day. But we are so close. MDA is working tirelessly to change this picture by funding worldwide research to develop treatments and cures; by providing comprehensive health care services and support to MDA families nationwide; and by rallying communities to fight back through advocacy, fundraising and local engagement.

While our therapeutic pipeline continues to move more promising therapies into late phase II and III clinical trials, families anxiously await the ability to access critical treatments. **We want nothing more than for safe and effective therapies to be delivered to patient families at the earliest moment possible.** We applaud the House of Representatives and the United States Congress for devoting attention and resources to ensuring this pathway exists and to expediting cures and treatments. MDA is eager to partner with you to achieve this goal we've been working towards for more than six decades.

NCCS
NATIONAL COALITION FOR CANCER SURVIVORSHIP
The power of survivorship. The promise of quality care.

June 13, 2014

The Honorable Fred Upton
Chairman
Energy & Commerce Committee
House of Representatives
Washington, D.C. 20515

The Honorable Henry Waxman
Ranking Member
Energy & Commerce Committee
House of Representatives
Washington, D.C. 20515

The Honorable Diana DeGette
Energy & Commerce Committee
House of Representatives
Washington, D.C. 20515

Dear Chairman Upton, Representative Waxman, and Representative DeGette:

The National Coalition for Cancer Survivorship (NCCS) represents survivors of all forms of cancer in public policy advocacy aimed at improving the quality of cancer care. We appreciate the opportunity to comment on the 21st Century Cures initiative undertaken by the Energy & Commerce Committee. NCCS is dedicated to providing every cancer patient the tools and opportunity to make informed decisions about his or her care and to removing obstacles to delivery of high-quality, evidence-based cancer care.

The 21st Century Cures effort provides an important opportunity to reflect on significant recent advances in cancer treatment and to assess barriers to development of new cancer treatments and failures in providing care for those who live with cancer as a chronic disease. In our comments below, we address the Call to Action and the questions that were posed to patient organizations as part of the 21st Century Cures fact-finding effort.

NCCS does not directly fund cancer research but instead focuses its efforts on creating the optimal environment for research, development, and approval of new cancer therapies and ensuring patient access to quality care.

Developing Cures While Enhancing Care

We applaud the ambitious goals of the 21st Century Cures initiative. As the committee seeks advice about creating a research and development climate that fosters bold treatment advances and cures, we urge that the needs of those who are living with and managing cancer as a chronic disease not be forgotten.

Research and development advances of the last several decades have turned cancer into a chronic disease for many, a welcome and important accomplishment. Cancer is in fact many different diseases, and most of them have humbled researchers because of their complexity and ability to adapt in the face of new treatments.

Pursuing cancer cures is an important aspiration. However, this pursuit should not be at odds with the development of cancer therapies that are transforming some forms of cancer into manageable chronic diseases.

The complexity of cancer and the difficulty of curing all cancers have implications for your effort and for the way in which the National Institutes of Health (NIH) and Food and Drug Administration (FDA) approach their cancer related responsibilities. While NIH investments should be made in ambitious research and development to cure cancer, there must also be an emphasis on developing treatments that are accompanied by fewer side effects and that help cancer survivors maintain a high quality of life with cancer as a chronic condition. In addition, greater investments should be made in understanding the late and long-term effects of cancer treatment. Those who might be "cured" of cancer are often at high risk of long-term side effects of treatment, including second cancers. We urge that the 21st Century Cures effort take a comprehensive and long-term approach to the concept of cancer treatment and cure.

Reconsidering the concept of treatment and cure will also have implications for FDA. Although we agree that FDA reviewers must be prepared for the development and review of targeted and personalized therapies (as we discuss below), so should they be prepared for evaluation of drugs that permit chronic management of cancer and that may be accompanied by significant late and long-term effects.

Achievements of the Office of Hematology and Oncology Office within the Center for Drug Evaluation and Research

The "Call to Action" document asks a number of important questions about the role of FDA in therapeutic development. For example, the white paper asks, "Is FDA structured and managed to enable the agency to rapidly incorporate innovative new approaches and technologies into its review processes? How can Congress ensure that the regulatory science keeps pace with advances in personalized medicine, including diagnostics?"

We direct the committee's attention to the record of the Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research, as we think the office's work might serve as a model for other review offices. The achievements of the office are many: 1) approval of a number of new agents according to accelerated approval standards, followed by careful monitoring to assure completion of post-approval confirmatory trials; 2) utilization of the breakthrough therapy designation authorized by the Food and Drug Administration Safety and Innovation Act (FDASIA) as a means of creating an open and less bureaucratic review process; 3) communication with researchers, patients, and sponsors to evaluate surrogate endpoints that might support accelerated approval; 4) publication of peer-reviewed articles and agency guidance documents outlining new pathways for development and review of cancer treatments, including a guidance on pathologic complete response as an endpoint for neoadjuvant breast cancer treatments, 5) aggressive management of adverse effects of effective cancer treatments, to ensure the continued use of products when warranted, and 6) an culture of open communication and collaboration with patients, researchers, and sponsors.

The achievements of the Office of Hematology and Oncology Products could be replicated in other therapeutic areas, but not without direct action to foster such efforts. A conscious effort to foster efforts parallel and complementary to those of the Office of Hematology and Oncology Products would also provide benefits to the office itself. More flexibility in hiring at FDA is warranted. For example, approaches that would permit hiring of clinicians and clinical researchers who split their time between NIH and FDA would help to ensure that FDA has the scientific and clinical experience it needs in an age of targeted therapies. In addition, those who are on staff at FDA should be permitted to maintain the professional and scientific relationships that are critical to their professional development and to their ability to review cutting edge products. Fostering a climate for intellectual and professional development may require a reconsideration of conflict of interest policies and also the appropriation of funds to permit travel and attendance at professional meetings. These are the settings in

which cutting edge science is discussed, but it is increasingly difficult for FDA officials to attend, as they may be thwarted by lack of travel funds or unnecessarily restrictive conflict of interest policies.

Many of the answers to improving the performance of FDA exist within FDA. We encourage the committee to evaluate and replicate successful performance at the agency.

Rewarding Innovation while Ensuring Access to New Therapies

In its materials defining the 21st Century Cures effort, the committee poses questions about the adequacy of rewards for innovation by biotechnology and pharmaceutical sponsors. These are difficult questions, and to date American society has been reluctant to see the health care system or the political system set standards for appropriate rewards for innovation. We have instead preferred to see the rewards for innovation set by market forces.

Health care consumers are increasingly confronting difficulties obtaining access to life-saving therapies. The obstacles are many: consumers may not be able to afford the cost-sharing responsibilities that accompany expensive but potentially life-saving new therapies or patients' insurance companies may impose coverage standards that block a patient's access to a new therapy. In the background is the question of whether the prices of new therapies necessarily reflect their benefits.

A movement is developing to strengthen the communication to patients about the cost of their treatment. As an organization that supports frank communication about cancer care options, we would include communication of cost of care in that effort. However, the patient who is making a treatment decision is not in a position to make determinations about the value or overall cost of his or her care. Patients should not be put in the position of making political judgments about the value of the treatments they are considering. We urge a broader consideration of this issue outside the patient-doctor communication. We specifically urge the committee to accompany any consideration of appropriate reward to innovators with consideration of the manageable cost of care for consumers, including their cost-sharing responsibilities. Cures will not be realized if consumers cannot afford them.

We appreciate the opportunity to comment on the 21st Century Cures initiative. We will continue to monitor the work of the committee and comment on additional questions and issues you pose for public comment.

Sincerely,

Shelley Fuld Nasso
Chief Executive Officer

cc: The Honorable Joe Pitts
The Honorable Frank Pallone