

## **Cerebral Palsy Research Funding from the National Institutes of Health, 2001 – 2013**

Yvonne W. Wu, MD MPH<sup>1</sup>, Alison S. Mehravari, BA<sup>2</sup>, Adam L. Numis, MD<sup>3</sup>, Paul Gross, BA<sup>4</sup>

1. Departments of Neurology and Pediatrics, University of California, San Francisco, CA
2. Program in Neuroscience, University of Washington, Seattle, WA
3. Departments of Neurology and Pediatrics, University of California, Los Angeles, CA
4. Hydrocephalus Association, Bethesda, MD

**Short title:** Cerebral palsy NIH funding

### **Corresponding Author:**

Yvonne Wu, MD, MPH  
UCSF Child Neurology  
675 Nelson Rising Lane Ste 411  
San Francisco, CA 94158-0663  
email: wuy@ucsf.edu  
Phone: (415) 502-7417

**Abstract** word count: 196 words (<200)  
**Manuscript** word count: 2757 words (<3000)  
**Tables:** 1  
**Figures:** 3

### **Abbreviations**

CP cerebral palsy  
NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases  
NIH National Institutes of Health  
NIBIB National Institute of Biomedical Imaging and Bioengineering  
NICHD National Institute of Child Health and Human Development  
NIDCD National Institute of Deafness and Other Communication Disorders  
NINDS National Institute of Neurological Disorders and Stroke  
NINR National Institute of Nursing Research

**Keywords:** cerebral palsy, research funding

**Funding Source:** This study was funded by Paul and Lori Gross, Cerebral Palsy International Research Foundation, CP Daily Living, and Let's Cure CP.

**Conflict of Interest Statements:** Dr. Wu has provided expert witness consultation on medicolegal cases related to cerebral palsy. Paul Gross who provided partial funding for this project also participated in the design of the study, data analysis and interpretation, and drafting of the final manuscript.

### **What This Study Adds**

- The NIH spent \$30 million per year on research related to CP.
- Overall, NIH funding for CP research increased over the study period.
- NIH funding for clinical intervention studies has declined.

## Abstract

**Aim:** Cerebral palsy (CP) is a poorly understood disorder with no cure. We determined the landscape of NIH funding for CP-related research.

**Method:** We searched NIH databases Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER), and Research, Condition, and Disease Categorization (RCDC) for keywords “cerebral palsy” among all NIH funded studies, 2001-2013. We classified grants by type and area of study.

**Results:** NIH funding, averaging \$30 million per year, supported clinical (\$215 million), basic (\$187 million) and translational (\$26.3 million) CP-related research. Clinical intervention studies comprised 19% of funding, and focused on treatments (\$60.3 million), early parent intervention (\$2.7 million) and CP prevention (\$2.5 million). Among grants that specified gestational age, more funds were devoted to preterm (\$166 million) than term infants (\$15 million). CP in adulthood was the main focus of 4% of all funding. Annual NIH funding for CP increased steadily over the study period from \$3.6 to \$66.7 million. However, funding for clinical intervention studies peaked in 2008, and has since decreased.

**Interpretation:** Additional research funds are needed to improve the treatment and prevention of CP. Topics that have been relatively underfunded include clinical interventions, prevention, term infants and adults with CP.

Short title: NIH funding for CP research

## Introduction

Cerebral palsy (CP) is the most common motor disability of childhood. The population prevalence of CP in the U.S. is 2-3.6 per 1000 births<sup>1,2</sup>, and about 12,000 newborns each year will develop CP. In addition to debilitating motor and postural abnormalities, many patients also experience cognitive deficits, epilepsy, visual and other developmental impairments.<sup>3</sup> CP is a heterogeneous and poorly understood disorder with no cure. Medical costs for individuals with CP are estimated at \$1.2 million per person over a lifespan (2012 US currency).<sup>4</sup> Each year, new cases of CP together introduce an economic burden of \$1.9 billion lifetime costs in the U.S. Additional research is urgently needed to prevent and reduce suffering from this lifelong disorder.

The amount of public funding spent on CP research in the US is not well described. There have been no NIH Program Announcements or Requests for Applications that contain the words “cerebral palsy” in their title.<sup>5</sup> In 2014, the NIH held a “State-of-the-Science and Treatment Decisions in Cerebral Palsy Workshop” to discuss gaps in CP research. To further inform discussions about research priorities, we set out to determine the landscape of NIH funding for CP research over a recent 12-year period.

## Methods

Using the online NIH search engine RePORTER (Research Portfolio Online Reporting Tools Expenditures and Results), we identified all grants funded by the NIH between January 1 2001 and May 31, 2013 that contained the keyword “cerebral palsy” within the grant title, abstract and/or project terms. A study investigator (AM) reviewed each grant abstract identified in the electronic search to determine if the research was indeed related to CP pathogenesis, prevention, treatment or symptomatology. Grants that were considered unrelated to CP by two investigators (AM and YW) were excluded from further analyses, as were grants that were funded by the Food and Drug administration (FDA) or the Centers for Disease Control (CDC). Grant entries with identical serial numbers and topics of study were considered a single individual grant. We added all years of funding for any individual grant to determine the total funding allocated to that grant.

Since 2009, The NIH “Research, Condition, and Disease Categorization” (RCDC) classification system has categorized all grants into 233 reported diseases and research areas, including CP. For years 2009-2013, we reviewed all grant abstracts that were linked to the RCDC category of “cerebral palsy”, to identify additional grants that may have been missed by the RePORT keyword search.

Research grants were classified into one or more of 4 major categories: 1) basic research, 2) clinical research, 3) translational research, and/or 4) pre-clinical development of new technologies. Translational research refers to research in which findings are moved from the researcher’s bench to the patient’s bedside and community.<sup>6</sup> Based on published consensus definitions, we defined 3 types of translational research: 1) basic to clinical = research that applies discoveries generated in the laboratory in preclinical studies, to the development of trials and studies in humans; 2) clinical to community practice = research that enhances the adoption of best practices in the community; and 3) cost effectiveness of prevention and treatment strategies.”<sup>6</sup>

We further classified each CP research grant into one or more of the following general areas of study: central nervous system development, muscle, cellular mechanisms of injury,

neuroimaging, genomics, biomarkers, risk factors for CP, speech/communication, research network or core facility, stem cells, quality of life, bone, and other.

We classified clinical intervention studies as being either an observational study or a clinical trial. Clinical trials were further categorized into phase I, II or III trials, based on available information within the grant title and abstract. The type of intervention was categorized as follows: medications, orthopedic surgery, neurosurgery, cognitive/behavioral, rehabilitation, early parent intervention, neuromuscular stimulation, feeding/nutrition, prevention of CP, or other.

For each CP grant, we classified the target gestational age as preterm (<36 weeks gestation); term ( $\geq 36$  weeks gestation); all gestational ages; unclear; or not applicable. When human subjects were involved in the research, we categorized the patient population as follows: age < 6 years; 6-12 years; 13-20 years;  $\geq 21$  years; children of unclear age; all ages; pregnant mothers; or unknown.

We determined inter-rater reliability of data abstraction by calculating Kappa values from two independent reviewers (AM and AN) who each abstracted data from 50 individual grants. The following categories revealed *good to excellent* ( $K > 0.6$ ) inter-observer reliability: basic research ( $K = 1.0$ ), medication intervention ( $K = 1.0$ ), rehabilitation ( $K = 1.0$ ), intervention study/clinical trial ( $K = 0.96$ ), neuroimaging ( $K = 0.87$ ), muscle ( $K = 0.79$ ), bone ( $K = 0.81$ ), development of new technology ( $K = 0.79$ ), biomarkers ( $K = 0.73$ ), clinical research ( $K = 0.70$ ), genomics ( $K = 0.66$ ), cognitive/behavioral ( $K = 0.65$ ), and intracellular mechanisms ( $K = 0.65$ ). Variables with only *moderate* agreement included nervous system development/regeneration ( $K = 0.43$ ) and translational research ( $K = 0.37$ ). We eliminated variables with only *poor to fair* inter-observer agreement (i.e.,  $K < 0.35$ ) from further study: epidemiologic study, long-term outcomes, and causal pathway category. After reviewing and clarifying discrepancies with a child neurologist (YW), a single investigator (AM) then completed the data abstraction for remaining grants. A child neurologist (YW) re-reviewed all nervous system development/regeneration and translational research grants (i.e., categories that demonstrated only moderate inter-rater reliability), and all clinical trials to determine phase of clinical testing.

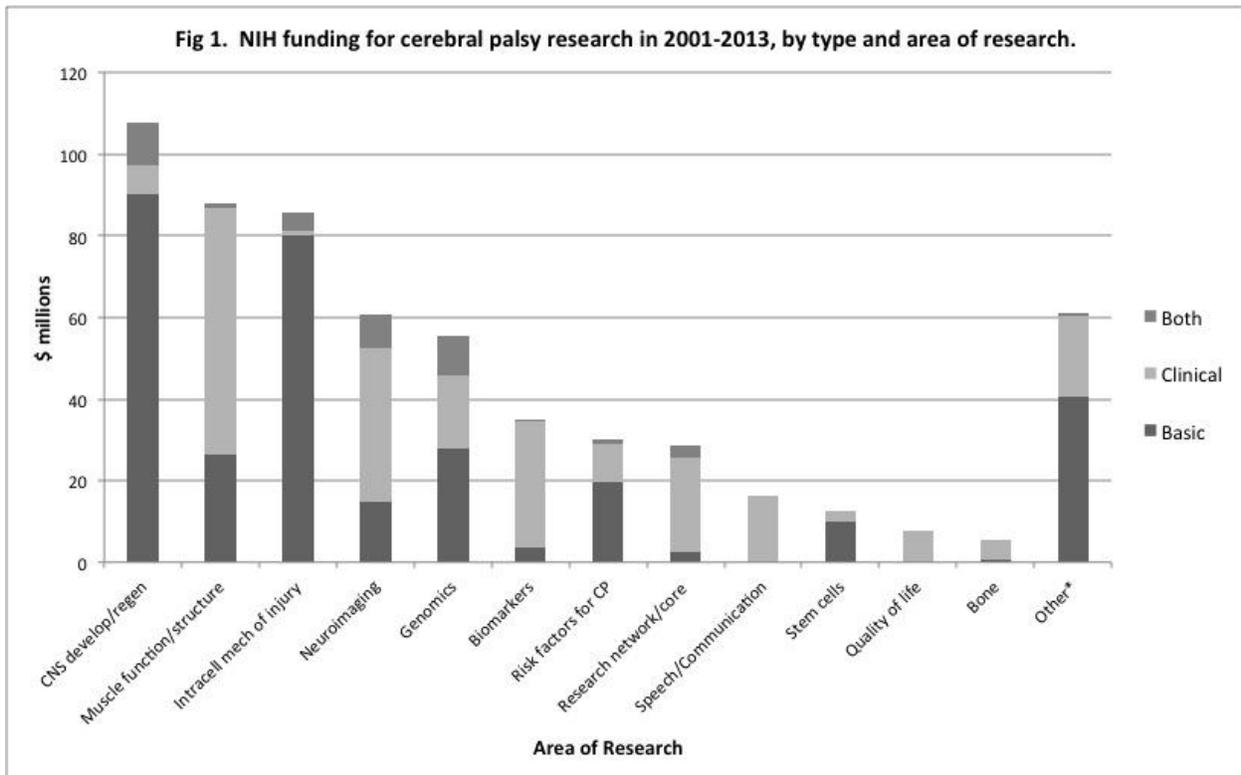
## Results

We identified 489 individual NIH-funded grants from the RePORTER electronic “cerebral palsy” keyword search, and an additional 18 grants from the NIH Research, Condition, and Disease Categorization (RCDC) search for grants related to CP. Of these 507 grants, 40 (7.9%) were found upon further review to be unrelated to cerebral palsy, and 12 (2.4%) grants were funded by agencies outside of the NIH. The remaining 455 grants represent a total of \$392.8 million in NIH-sponsored CP research funding. These grants span 188 organizations across 43 U.S. states, and are led by 369 individual principal investigators.

Based on data provided in RePORTER, the majority of CP funding was devoted to traditional research grants, i.e, research projects (75%), intramural research (9%) or other research (8%), while smaller amounts of funding supported Small Business Innovative Research and Technology Transfer Research (3%), research centers (3%) and training grants (1%). Specific grant mechanisms included “R” research grants (\$259 million, 65%), “U” consortium grants (\$44 million, 11%), “P” or “M” program project or center grants (\$27 million, 7%), “K” or “F” training grants (\$21 million, 5%), and other grants (\$44 million, 11%).

Twenty different NIH institutes provided funding for grants relating to CP during the study period. The NICHD (\$160 million) and NINDS (\$137 million) together accounted for 76% of all CP research funding. Four other institutes each allocated over \$5 million towards CP research: NIBIB (\$17.5 million), NIDCD (\$13.9 million), NIAMS (\$9.5 million) and NINR (\$5.3 million). The relative contribution of funding from other institutes was relatively minor.

After removing \$1.4 million of funding spent on 80 scientific meetings, the remaining funds were categorized into one or more of the following non-exclusive research categories: clinical research (\$215 million, 55%); basic research (\$187 million, 48%); pre-clinical development of new technologies (\$45 million, 11%); and translational research (\$26.3 million, 7%). All translational research funds involved basic to clinical translation. We identified no CP grants that involved clinical to community translation, and no cost effectiveness studies related to CP.



The majority of basic science research funds supported studies of central nervous system development and cellular mechanisms of injury (Figure 1). The majority of clinical research funding was spent on studies of muscle structure and function, neuroimaging, biomarkers and genomics. Studies of risk factors for CP received a relatively small amount of funding compared to other types of CP research.

Studies that evaluated a clinical intervention received \$73.3 million, or 19% of all CP research funding. The following 4 interventions received over three-quarters of the funds (Table):

Table. NIH funding for cerebral palsy research

Involving a clinical intervention, 2001-2013.

Type of intervention studied	\$ millions
------------------------------	-------------

Medication	37.0
Rehabilitation	15.3
Neurosurgical	4.8
Orthopedic	3.2
Early parent/ home	2.7
Prevention of CP	2.5
Feeding of nutrition	1.8
Neuromuscular stimulation	1.7
Cognitive or behavioral	0.3
Other*	3.6

\*Other inventions include robotics, sexual health, pre-operative

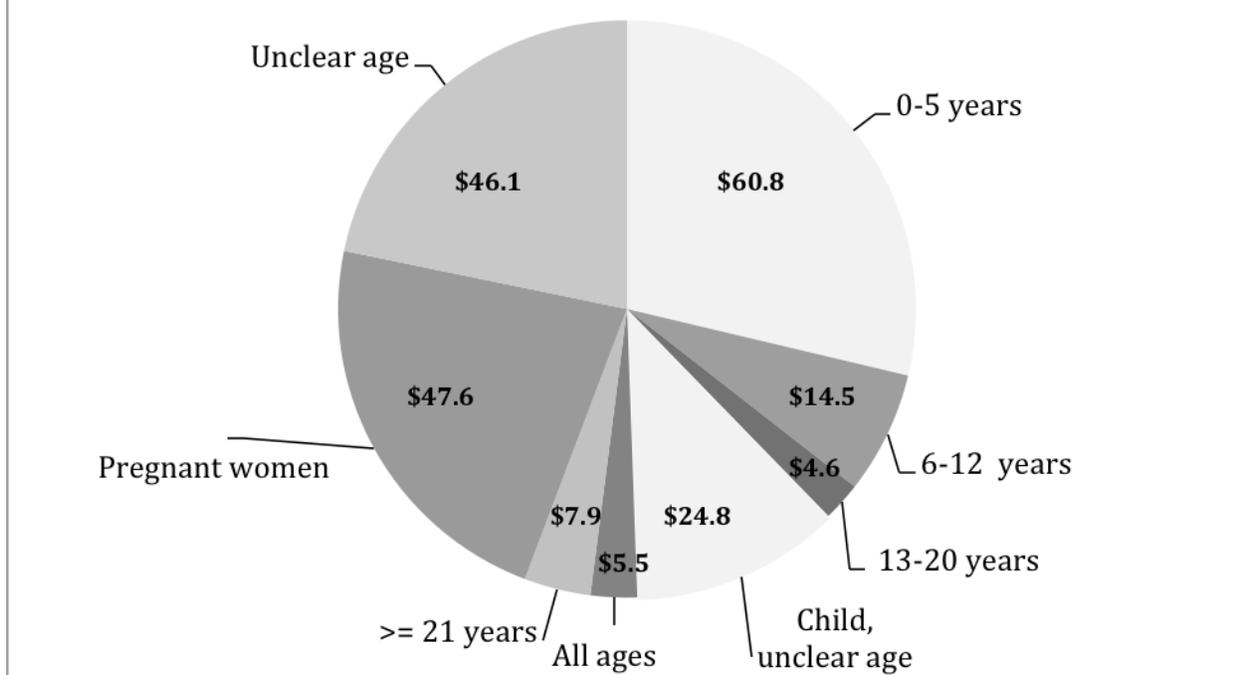
gait analysis, vibration, virtual reality, wellness coaching.

medications (\$37.0 million), rehabilitation (\$15.3 million), neurosurgery (\$4.8 million), and orthopedics (\$3.2 million). Studies of interventions designed to prevent CP received a relatively low amount of funding (\$2.5 million), as did studies of cognitive and behavioral interventions.

Clinical interventions were evaluated in observational studies (\$38.3 million) or in clinical trials (\$35.0 million). More funding was allocated to phase I (\$11.3 million) and II clinical trials (\$17.6 million), than to phase III trials (\$6.1 million). We identified the following phase III clinical trials: prevention trials evaluating hypothermia, magnesium sulfate, and Indocin + delayed cord clamping, and treatment trials evaluating home-based early intervention, constraint-induced movement therapy, and family-centered therapy. An additional \$29.3 million was spent on clinical trial infrastructure and to train investigators to perform clinical trials relating to CP.

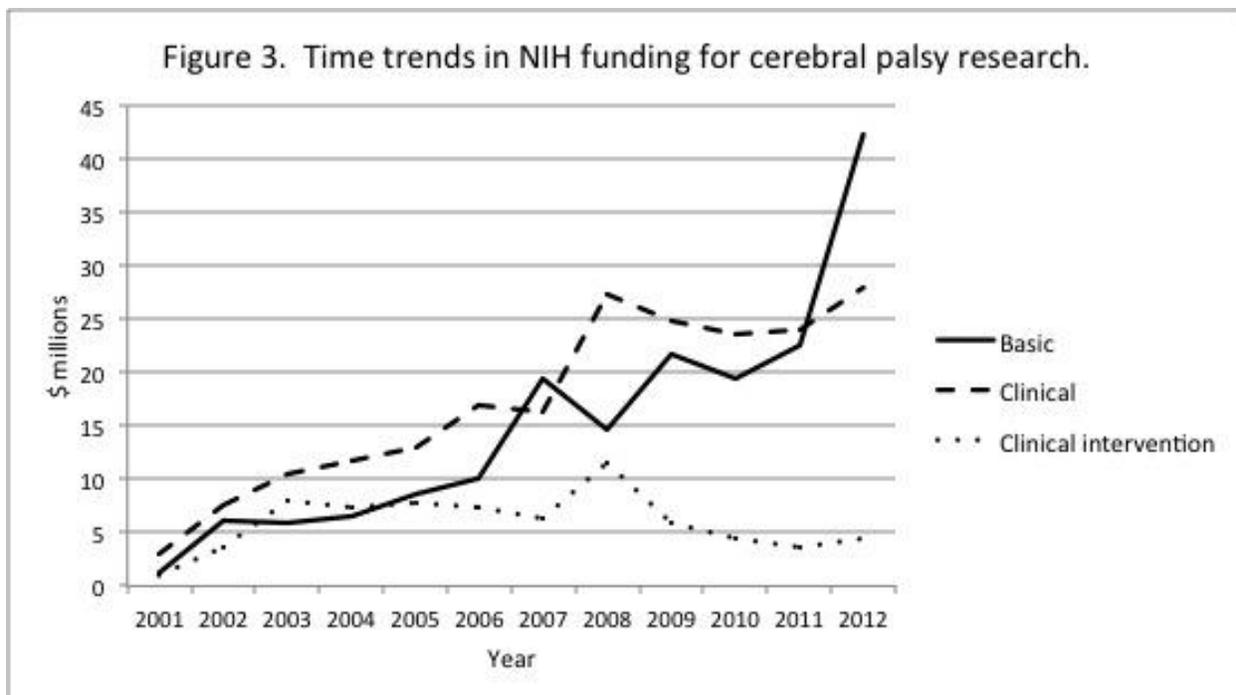
The majority of funds (\$205 million, 52%) devoted to CP research did not have a clear gestational age focus that could be determined from the study abstract. Among grants that specified a gestational age focus, more funding was devoted to studies of the preterm brain (\$166 million, 42%), than studies of the term brain (\$15.3 million, 4%), or to studies of CP affecting all gestational ages (\$6.5 million, 2%).

**Figure 2. Age groups targeted by NIH funded studies of clinical cerebral palsy research.**



By definition, clinical studies involved human participants. About half (\$110.2 million, 51%) of all clinical research funding was spent on studies that enrolled children (participants under 21 years of age.) Children under age 6 received the largest proportion of research funds, while studies focusing on adults with CP received a relatively small amount of funding (\$8 million, 4%, Figure 2).

NIH provided on average \$30 million a year of funding for CP research. The annual funding amount rose steadily from \$3.6 to \$66.7 million during 2001-2012, the years when full data were available. Increases in research funding were seen for both basic science and clinical research grants. However, studies of clinical interventions have received decreasing amounts of funding since 2008 (Figure 3).



Starting in 2009, NIH began classifying grants using the NIH Research, Condition, and Disease Categorization (RCDC). In the years 2009-2013, we identified more CP-related grants using the RePORTER keyword search than by searching RCDC. Among 267 CP grants that were funded during these years, 140 (52%) were identified both within RePORTER and RCDC; 109 (41%) were identified only by RePORTER keyword search; and 18 (7%) were identified in RCDC but not in RePORTER. Similarly 68% of the \$218 million in NIH funding devoted to CP in 2009-2013 was categorized by RCDC as relating to CP.

## Discussion

Continued research efforts and funding are needed to develop effective strategies to prevent and treat CP. Although overall NIH funding for CP research has increased steadily since 2001, funding for studies that evaluate clinical interventions has dropped in recent years. Based on our data, specific areas of study that have been relatively underfunded include studies of clinical interventions including clinical trials, and studies of prevention of CP. Clinical to community translation studies were non-existent. Patient populations that have been relatively underfunded include term infants and adults with CP.

Our study has several limitations. Our findings are subject to incomplete ascertainment, since only grants that included the words "cerebral palsy" were reviewed. For instance, our search did not identify all NIH-sponsored hypothermia neuroprotection trials, since the original grant proposals for these studies did not include the words cerebral palsy. However, among the grants we did review, all studies that could lead to information impacting prevention or treatment of CP were considered to be related to CP, even when CP may not have been the primary focus, and we identified 40% more grants that related to CP than would have been revealed by a search of the NIH RCDC categorization alone. The publically available grant abstracts may not provide sufficient detail to allow accurate categorization of grants. We addressed this issue by having 2 independent observers review a subset of grant abstracts, and eliminating all variables with poor inter-rater reliability.

Cerebral palsy occurs in 2-4 children per 1000 live births. In the U.S., the prevalence of CP increased from 1.7 to 2.0 per 1000 live births between the mid-1970s and late 1980s<sup>2</sup>, and was as high as 3.6 per 1000 8-year-old children in 2002.<sup>1</sup> Based on these numbers, approximately 12,000 children with CP are born annually in the US.

In the U.S as well as in other developed countries, there is generally more research funding available for conditions that affect adults than children. Even among childhood disorders, funding for CP research lags behind other conditions. For instance, in 2010, an estimated \$21 million of NIH funding went to grants targeting cerebral palsy, based on the NIH RCDC categorization system. A similar RCDC analysis of NIH funding for cystic fibrosis research in 2010 revealed a total of \$99 million in funding. The annual incidence of CP in the United States is about 3 per 1000 births, while cystic fibrosis occurs in 0.3 per 1000 births. Based on these numbers, the federal government spent \$1,750 research dollars on every new case of cerebral palsy, compared to \$82,500 for every new case of cystic fibrosis in 2010. Similar differences are seen when NIH funding for CP is compared with autism, which received \$218 million of NIH funding in 2010. The annual incidence of autistic spectrum disorder is 11 per 1000 births<sup>7</sup>; thus, \$4,950 NIH research dollars were spent on every new case of autism.

Beyond NIH, private research foundations and patient advocacy groups also play important roles in supporting CP research. However, the amount of funding available outside the NIH for CP research also lags behind support for other childhood disorders. For instance, the Cerebral Palsy International Research Foundation, the only foundation in the US entirely devoted to researching prevention and treatment of CP, had a research budget of \$1.6 million in 2009. In contrast, the US Cystic Fibrosis Foundation and the Juvenile Diabetes Foundation provide about \$85 million and \$156 million annually in research support. Of note, private foundations promoting CP research have typically focused functional therapies rather than prevention and cure.

Why has there been relatively less funding for CP? The misguided emphasis on labor and delivery complications as the primary cause of CP is one potential reason that there have not been many comprehensive etiologic studies. Furthermore, the diagnosis of CP is often confusing to clinicians, researchers and patients alike. Cerebral palsy is a heterogeneous group of syndromes of motor dysfunction resulting from a wide range of brain disorders<sup>8,9</sup>, including brain injury of prematurity, global hypoxic-ischemic brain injury, focal arterial and venous infarctions, brain malformations, genetic abnormalities, intrauterine infection and more. Evidence shows that with the current state of knowledge, we are unable to prevent cerebral palsy in the vast majority of cases.<sup>10</sup> The underlying causal pathways that lead to each of these types of brain injuries are complex, often intersect, and remain incompletely understood. Several groups have published causal diagrams and roadmaps to CP research, that belie the complexities involved in understanding this heterogeneous disorder.<sup>11,12</sup>

The term "Early Developmental Brain Injury/Interference (EDBI)", which focuses on the brain impairment rather than the motor deficits of CP, has been proposed as an alternative framework and approach to CP.<sup>13</sup> An intended advantage of using this term is to align the CP research community with on-going efforts of the U.S. national BRAIN Initiative ([www.nih.gov/science/brain](http://www.nih.gov/science/brain)). That is, "formally and clearly calling CP a brain condition, rather than highlighting the motoric disturbances, places it where it belongs, next to the robustly supported traumatic brain injury community already in the foreground of the public's attention."<sup>13</sup>

Recent efforts to increase public awareness and to boost CP research funding have begun to make positive changes. The work of patient advocacy groups has led to the inclusion of the a new statement by the 2015 U.S. Senate Appropriations Committee: “a 5-year strategic plan for Cerebral Palsy prevention, treatment, and cure through the lifespan with the goal of reducing the number of people impacted by CP overall, as well as improving the opportunity for recovery of those already diagnosed.”<sup>14</sup> Whether there will be adequate funding to support this initiative remains unclear. The Cerebral Palsy Alliance Research Foundation held several research summit meetings which led to the formation of an international multidisciplinary research network called IMPACT for CP.<sup>15</sup> In 2014, the NIH hosted a State-of-the-Science and Treatment Decisions in Cerebral Palsy Workshop, bringing together leaders in research, patient care and patient advocacy. This workshop has led to renewed efforts to organize multicenter efforts to further CP research within the U.S. and beyond, and should lead to new opportunities for improving neurological function for children and adults with CP. Thus, momentum is gaining both in the international and U.S. communities to address the serious gaps in our understanding of the treatment and prevention of CP.

### **Acknowledgements**

The authors would like to thank Cara Long for her assistance with interpreting NIH variables in RePORT, Emma Anderson for her assistance with calculations of kappa values, and Rebecca Webb for her assistance with creating the figures in the manuscript.

**REFERENCES (Max 25)**

1. YeARGIN-AllSopp M, Van Naarden Braun K, Doernberg NS, Benedict RE, Kirby RS, Durkin MS. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: a multisite collaboration. *Pediatrics*. Mar 2008;121(3):547-554.
2. Winter S, Autry A, Boyle C, YeARGIN-AllSopp M. Trends in the prevalence of cerebral palsy in a population-based study. *Pediatrics*. Dec 2002;110(6):1220-1225.
3. Bax M, Goldstein M, Rosenbaum P, et al. Proposed definition and classification of cerebral palsy, April 2005. *Dev Med Child Neurol*. Aug 2005;47(8):571-576.
4. Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment--United States, 2003. *MMWR Morb Mortal Wkly Rep*. Jan 30 2004;53(3):57-59.
5. [http://grants.nih.gov/grants/guide/search\\_guide.htm](http://grants.nih.gov/grants/guide/search_guide.htm). Accessed January 9, 2015.
6. Rubio DM, Schoenbaum EE, Lee LS, et al. Defining translational research: implications for training. *Acad Med*. Mar 2010;85(3):470-475.
7. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. *MMWR Surveill Summ*. Mar 30 2012;61(3):1-19.
8. McIntyre S, Blair E, Badawi N, Keogh J, Nelson KB. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. *Obstet Gynecol*. Oct 2013;122(4):869-877.
9. Wu YW, Croen LA, Shah SJ, Newman TB, Najjar DV. Cerebral palsy in a term population: risk factors and neuroimaging findings. *Pediatrics*. Aug 2006;118(2):690-697.
10. Nelson KB. Can we prevent cerebral palsy? *N Engl J Med*. Oct 30 2003;349(18):1765-1769.
11. <http://impact.cerebralpalsy.org.au/activities/research-summits/2011-summit-report/>. Accessed January 8, 2015.
12. ACOG, ed *Neonatal Encephalopathy and Neurologic Outcome*. 2nd ed. Washington DC2014.
13. Shusterman M. Introducing the term 'early developmental brain injury/interference' and a new framework for discussing cerebral palsy. *Dev Med Child Neurol*. Nov 22 2014.
14. Department of Health and Human Services Senate Appropriations Subcommittee. Washington DC2015:In press (Feb 2, 2015).
15. <http://impact.cerebralpalsy.org.au/>. Accessed January 8, 2015.

Table. NIH funding for cerebral palsy research

Involving a clinical intervention, 2001-2013.

Type of intervention studied	\$ millions
Medication	37.0
Rehabilitation	15.3
Neurosurgical	4.8
Orthopedic	3.2
Early parent/ home	2.7
Prevention of CP	2.5
Feeding of nutrition	1.8
Neuromuscular stimulation	1.7
Cognitive or behavioral	0.3
Other*	3.6

\*Other inventions include robotics, sexual health, pre-operative

gait analysis, vibration, virtual reality, wellness coaching.

## Figure Legends

### **Figure 1**

*Title:* NIH funding for cerebral palsy research in 2001-2013, by type and area of research.

*Legend:* Other areas of CP research include proteomics, sleep, portion control, palliative care, pain, disaster preparedness, CP classification, aging, oral health, pain, and self-injurious behavior.

### **Figure 2**

*Title:*

*Legend:* none

### **Figure 3**

*Title:* Time trends in NIH funding for cerebral palsy research

*Legend:* The large increase in basic research funding in 2012 can be attributed to the award of a single \$21 million grant, evaluating the role of subclinical infection and cytokines in animal models of preterm delivery. Clinical intervention research is a subset of clinical research.