



Down Syndrome: Research Promises & Clinical Advances

Testimony prepared for
Down Syndrome Congressional Caucus

February 26, 2009

Brian G. Skotko, M.D., M.P.P.

Chair, Clinical Advisory Board, National Down Syndrome Society
Professional Advisory Council, National Down Syndrome Congress
Vice Chair, Board of Directors, Massachusetts Down Syndrome Congress
Board of Directors, Band of Angels Foundation
Physician, Children's Hospital Boston & Boston Medical Center

The time has never been so promising for people with Down syndrome. Advances in medical technology have changed their average lifespan from 25 years in 1983 to nearly 60 years now.¹⁻² According to some reports, approximately 14 out of 100 adults with Down syndrome will even live to 68 years old,³ although disparities have been noted in different racial groups.⁴ Success stories are now appreciated across the lifespan: children with Down syndrome are achieving new academic milestones in inclusive classrooms across the country; adolescents are attending post-secondary programs in colleges and universities and are proving to be reliable and effective workers in our marketplaces; and some adults are now moving out of their families' homes and into independent and semi-independent places of their own.

¹ Day SM, Strauss DJ, Shavelle RM, Reynolds RJ (2005). Mortality and causes of death in persons with Down syndrome in California. *Developmental Medicine & Child Neurology*, 47:171-176.

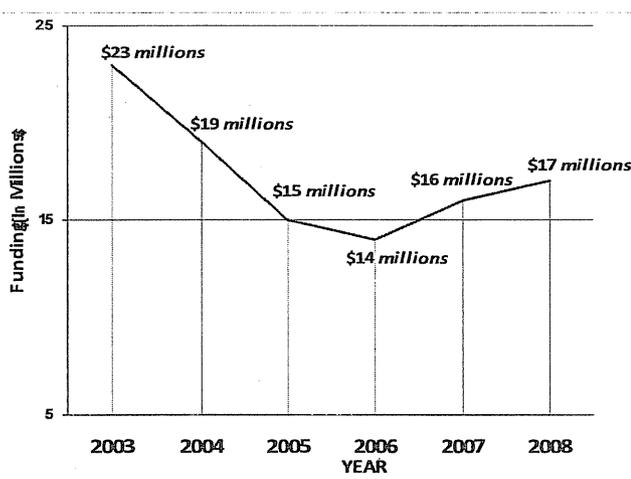
² Glasson EJ, Sullivan SG, Hussain R, Petterson BA, Montgomery PD, Bittles AH (2002). The changing survival profile of people with Down's syndrome: implications for genetic counseling. *Clinical Genetics* 62:390-393.

³ Baird PA, Sadovnick AD (1988). Life expectancy in Down syndrome adults. *The Lancet*, 2, 1354-1356.

⁴ Yang Q, Rasmussen SA, Friedman JM (2002). Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. *The Lancet*, 359:1019-25.

Amid these triumphs, however, lie several obstacles which impede the acceleration to a nation where all people with Down syndrome can maximize their full potential. At the core of these challenges are delays in research and clinical care. The following four issues urgently need to be addressed by Congress:

(1) Landmark breakthroughs for people with Down syndrome are possible with more research. The National Institutes of Health (NIH) funding for research related to Down syndrome has decreased from \$23 million in 2003 to \$17 million in 2008. With nearly 400,000 people with Down syndrome living in the United States today, this means that only \$40 is being committed in research dollars for each person with Down syndrome (Exhibit A). By contrast, \$3,000 in research money is being



CONDITION	US POPULATION (est.)	2008 NIH FUNDING Millions \$	2008 NIH \$ per CAPITA AMOUNT
Cystic Fibrosis	30,000	90	3,000
Parkinson's	1,500,000	152	101
ALS	30,000	43	1,433
Huntington's	30,000	51	1,700
Multiple Sclerosis	400,000	169	422
Crohn's Disease	400,000	51	128
DOWN SYNDROME	400,000	17	40
Fragile X	17,000	26	1,529
Autism	560,000	118	211
Duchenne MD	45,350	22	485

Exhibit A: (Left) NIH allocation of research money to Down syndrome; (Right) Comparison of NIH funding for various medical conditions, including Down syndrome. Tables and graphic adapted from data provided by M.M. Harpold, Down Syndrome Research and Treatment Foundation (DSRTF) as adapted from and based on 2009 NIH data, <http://report.nih.gov/rcdc/categories/>.

allocated to each person with cystic fibrosis, and about \$1,500 toward persons with Fragile X syndrome, both far less common medical conditions in comparison to Down syndrome. Since Down syndrome occurs in people of all different races and origins, the lack of funding for research on Down syndrome further contributes to health care disparities.

Further, while research money on the treatment for Down syndrome has been decreasing, the federal dollars dedicated to developing more advanced prenatal testing for Down syndrome have been nearly matched—if not larger. In 2005, as an example, approximately \$13 million was granted by the NIH and the National Institute of Child Health and Human Development (NICHD) to a single study conducted by Columbia University Medical Center for the discovery of a first-trimester Down syndrome prenatal

screen.⁵ Estimates on how much federal research money has been dedicated to prenatal testing in recent years remains unknown but is likely larger based on the increasing number of studies that are being published on the topic.

This shortfall in research dollars dedicated toward research and clinical aspects of Down syndrome comes at a time when new scientific breakthroughs are being discovered for people with Down syndrome. Now that a number of mouse models have been developed for Down syndrome, researchers are unlocking important clues on how the brain works in this chromosomal condition.

We know that there are three genetic variations of Down syndrome. About 95% of people have “trisomy 21,” with three copies of their 21st chromosome in each cell, where normally there would be two. Another 4% have “translocation Down syndrome,” where each cell has two copies of the 21st chromosome and an additional combination of chromosome 21 with another chromosome. The last 1% has “mosaic Down syndrome,” where some cells in the body—but not all—have three copies of the 21st chromosome.

Scientists are trying to unravel the mystery of what causes Down syndrome to occur in the first place. Further, they are beginning to discover potential treatments that could increase the learning and memory in people with Down syndrome. Conceptually, researchers should one day be able to treat most conditions associated with Down syndrome by modifying or reducing the action of the chromosome 21 genes that are triplicated.

People with Down syndrome might also hold the answers to so many other conditions that millions of Americans have. Seizure disorders, Alzheimer’s disease, congenital heart disease, leukemia, diabetes, celiac disease, and hypothyroidism are just a few of the medical conditions that more commonly occur in people with Down syndrome. By finding research solutions for people with Down syndrome, millions of Americans without Down syndrome benefit, as well. Further, adults with Down syndrome are less likely to develop breast cancer, lung cancer, and mouth cancers in comparison to people who do not have Down syndrome. Discovering why this is so might unlock the mysteries to many adult cancers.



The future is not far off when large-scale clinical trials will be needed to test potential treatments. However, the research has been slowed, and, in some cases, halted, because of lack of research funding. For decades now disability advocates have pointed out that the almost 200 federal programs and the 23 agencies of government serving individuals with disabilities are flawed in two essential ways: first, the legislation underpinning these programs is based on outdated premises about the competencies and potential of these individuals; second, there is no federal strategy to integrate disability policy and programs. The mission, goals, and outcomes of these programs are poorly aligned, if at all. The small amount of data that is collected has limited usefulness in

⁵ “New Prenatal Test Proves Earlier, More Accurate Predictor for Down Syndrome.” November 9, 2005. <http://nyp.org/news/hospital/906.html>

large part because the definitions of disability are inconsistent. An effort to coordinate disability programs is long overdue and, as a Government Accounting Office study indicated in June 4, 2008⁶, will require the creation of a coordination entity that will focus on developing consistent evaluation measures, data and outcomes for these programs. Congress could change this by doing the following:

Suggested Action: Support language in the fiscal year 2010 appropriations bill for the National Institutes of Health (NIH) urging the NIH Director to devote sufficient resources to meet the short- and long-term objectives of the agency's strategic plan for Down syndrome. In January, 2008, after consultation with the scientific research community and national organizations that focus on Down syndrome, and taking into account various congressional directives, the NIH Down Syndrome Working Group developed the "NIH Research Plan for Down Syndrome." This Plan is available at http://www.nichd.nih.gov/publications/pubs/upload/NIH_Downsyntaxrome_plan.pdf and is summarized in Exhibit B.

Suggested Action: Support language in the fiscal year 2010 appropriations bill for the Centers for Disease Control and Prevention (CDC) urging the CDC Director to devote sufficient resources to meet the objectives of the agency's strategic plan for Down syndrome. In November, 2007, the National Center on Birth Defects of the CDC and the National Down Syndrome Society convened experts on Down syndrome to establish a "Public Health Research Agenda on Down Syndrome." This Agenda prioritizes the urgent public health research needs for people with Down syndrome and is available in the *American Journal on Medical Genetics*.⁷

Suggested Action: With these two research agendas—one from the NIH and another from the CDC—Congress should encourage the two government entities to work together, once appropriations have been allocated. To achieve these collaborations, and avoid duplication, Congress should consider establishing an interagency, cross-governmental task force on Down syndrome. This "Interagency Down Syndrome Coordinating Committee" should prepare for the Secretary of Health and Human Services an annual report summarizing the advances in Down syndrome research in addition to reviewing the strategic plans for the conduct and support of such research.

⁶ US Government Accountability Office, June 4, 2008, "Federal Disability Programs; Coordination Could Facilitate Better Data Collection to Assess the Status of People with Disabilities." Testimony before the Subcommittee on Information Policy, Census, and National Archives Committee on Oversight and Government Reform, House of Representatives.

⁷ Rasmussen SA, Whitehead N, Collier SA, Frias JL. (2008). Setting a public health research agenda for Down syndrome: Summary of a meeting sponsored by the Centers for Disease Control and Prevention and the National Down Syndrome Society. *American Journal of Medical Genetics* 146A:2998-3010.

Down Syndrome Research Area	Short-term Objective (0 to 3 Years)	Medium-term Objective (4 to 6 Years)	Long-term Objective (7 to 10 Years)
<i>Pathophysiology of Down Syndrome and Disease Progression</i>	Continue testing cognitive and synaptic function in Down syndrome model mice.	Study whether the impact of aging on certain processes is greater than on others.	Explore genetic and environmental determinants of cognitive function in Down syndrome throughout the lifespan.
<i>Diagnosis, Screening, and Functional Measures</i>	Identify the cognitive phenotype of Down syndrome in a cohort throughout the lifespan.	Link human and mouse cognitive studies relating to Down syndrome.	Develop better measures of hippocampal and cognitive function.
<i>Treatment and Management</i>	Increase research on comorbid psychiatric and medical conditions throughout the lifespan.	Continue learning from the Alzheimer disease research community regarding the best therapeutics.	Investigate the impact of early intervention on psychomotor and cognitive development.
<i>Living with Down Syndrome</i>	Develop a more complete demographic knowledge base.	Study real-world outcomes for Down syndrome families.	Explore new intervention research, especially during transitional stages.
<i>Research Infrastructure</i>	Improve and expand availability of animal models.	Discuss the best mechanisms to use in fostering cross-disciplinary research.	Include cohorts of people with Down syndrome in longitudinal studies.

Exhibit B: Executive Summary Matrix of the NIH Research Plan on Down Syndrome.

(2) A national registry of people with Down syndrome is needed to provide for breakthrough research. Many pressing clinical questions remain unanswered about Down syndrome. To best help the nearly 400,000 persons with Down syndrome in the United States, health care professionals need the results of critical research on the etiology of congenital heart disease, thyroid conditions and the origin of autoimmunity, dual diagnoses with autism, supportive therapy for mental health conditions, screening guidelines for celiac and atlantoaxial joint instability, maintaining cognitive function, and the best interventions to control obesity, among many others. For interventional trials, statistical power is critically dependent on sample size, which is often difficult to attain in a single center.

In order to supply these answers, clinical researchers need a research infrastructure. The first step in this infrastructure is to develop a national registry of people with Down syndrome. This registry would provide a dual purpose: (1) an observational cohort in which to answer epidemiological questions about the type and frequency of secondary health concerns of people of all ages who have Down syndrome, and (2) a working database from which potential research participants can be identified to conduct multicenter clinical trials designed to address treatment issues.

Unfortunately, a database of confidential information about individuals with Down syndrome does not exist. Currently, researchers like me need to work through parents support groups, classrooms, or other ad-hoc groupings of families. For example, when I recently conducted a large-scale survey project, I needed to assemble my surveys, mail them to various Down syndrome support groups around the country, who then attached labels and mailed them to their families. Not only is this process time-intensive, inefficient, and expensive for the researcher and the support groups, this style of research is subject to many biases that skew the data. Only those families who are part of support groups get sampled. But, what about the families who have children with Down syndrome those are not part of support groups? In particular, what about all of the children from social and ethnic diversities who are typically not part of support group mailing lists? Until a population-based national registry is established, researchers will be forever limited in the conclusions that can be drawn from the current ad-hoc system.

There is precedence for developing national registries. As just one example, the Cystic Fibrosis Foundation organized such a registry which led to improved clinical services and research for people who have cystic fibrosis. This organization now has clinical centers of excellence throughout the U.S. that provide evidence-based medical care coupled with clinical research for this condition. The data is safe and the confidentiality of the patients is maintained at all time. Similar registries have been created for patients with Muscular Dystrophy, neurofibromatosis, Fabry disease, and congenital cytomegalovirus (CMV) disease). Congress could make this same change for the Down syndrome community by doing the following:

Suggested Action: Support a \$1 million appropriation to the CDC so that grants can be distributed for the establishment of a national Down syndrome registry. The CDC will distribute funding to hospital and non-profit organizations to develop a national, computerized listing of individuals with Down syndrome and their families who are interested in participating in research. Additionally, associated hospitals will begin to collect valuable data on disease management and standards of care for people with Down syndrome.

(3) Many medical conditions in people with Down syndrome can be better treated with the establishment of specialized clinics. Children with Down syndrome are at risk for a host of medical problems including congenital heart defects, cervical spine instability (potentially leading to spinal cord compression and paralysis), hearing impairment, obstructive sleep apnea (potentially leading to heart failure or to problems with behavior or growth), obesity, autism, and depression. These medical conditions can have significant deleterious effects on quality of life for children affected by them. These conditions occur across the population of individuals with Down syndrome. However, some children with DS have none of these problems and most have one or two concurrently. Fortunately, with appropriate screening and early initiation of appropriate treatments, the negative impact of many of these conditions can be greatly lessened or even completely eliminated.

The American Academy of Pediatrics (AAP)⁸ and the Down Syndrome Medical Interest Group (DSMIG)⁹ have established age-specific recommendations (e.g., screening for celiac disease at the age of 2, cervical spine X-rays at the age of 3, and yearly audiologic evaluations). However, families have indicated that many community healthcare providers do not actually follow these guidelines. As a result, Down Syndrome Centers of Excellence have been emerging at hospitals around the country as a way to ensure that all people with Down syndrome receive top quality health care.

Approximately 40 Down Syndrome Centers of Excellence currently exist in around the country (full database from the National Down Syndrome Society: http://www.ndss.org/index.php?option=com_content&view=article&id=74&Itemid=94&limitstart=2). However, many Centers are not able to provide a physician with specialized knowledge in Down syndrome, and these 40 clinics can only serve a very small portion of the more than 400,000 people with Down syndrome living in the United States. The National Down Syndrome Society's Clinical Advisory Board—a team of Down syndrome clinical specialists around the country—has defined the following ideal characteristics for “Down Syndrome Centers of Excellence”:

- Provides tertiary care dedicated solely to the condition of Down syndrome
- Collaborates with or works as the patient's primary care physician
- Has a licensed physician meet with each patient with Down syndrome during each visit
- Incorporates a multidisciplinary approach to Down syndrome, involving an identified person in each of the following specialties: nutrition, physical therapy, occupational therapy, speech therapy, audiology, ophthalmology, psychology, psychiatry, cardiology, sexual health, and education
- Integrates with the local Down syndrome support groups and other community resources
- Provides culturally sensitive care to all populations, including access to appropriate health literacy and communications
- Provides a continuity of care for people with Down syndrome of all ages, including the health concerns associated with the transition to adulthood
- Conducts patient-oriented, translational research on Down syndrome that has been approved by the institution's IRB
- Participates in a national registry for Down syndrome and associated multicenter collaborative efforts
- Has a part-time or full-time research coordinator associated with the Center

⁸ Committee on Genetics, American Academy of Pediatrics (2001). Health Supervision for Children with Down Syndrome. *Pediatrics*, 107(2): 442-449

⁹ Van Cleve SN, Cohen WI (2006). Part I: Clinical Practice Guidelines for Children with Down Syndrome From Birth to 12 Years. *Journal of Pediatric Health Care*, 20:47-54.

Congress could take leadership on the quality of health of people with Down syndrome by the following action:

Suggested Action: Support national legislation which would significantly expand the number of Down Syndrome Clinical Centers of Excellence around the country. By appropriating money through the NIH and CDC, these Centers of Excellence can serve the multidisciplinary health needs of people with Down syndrome while also providing an infrastructure to implement a national patient registry for Down syndrome and other translational research efforts.

(4) The quality and availability of information about Down syndrome must be improved. On October 8, 2008, President Bush signed into law S. 1820, the *Prenatally and Postnatally Diagnosed Conditions Awareness Act*, which was sponsored by Senator Edward Kennedy (D-MA) and Senator Sam Brownback (R-KS). This law seeks to ensure that new and expectant parents who learn of a diagnosis of Down syndrome are provided with up-to-date, scientific information about life expectancy, clinical course, and intellectual development. The law offers referrals to support services such as hotlines, Web sites, information clearinghouses, adoption registries, and parent support networks and programs specific to Down syndrome and other prenatally diagnosed conditions. The goal is to create a sensitive and coherent process for delivering information about the diagnosis across the variety of medical professionals who often provide conflicting and inaccurate information.

The American College of Obstetrics and Gynecology (ACOG) and the American College of Medical Genetics (ACMG) now recommend that all pregnant women be offered prenatal testing for Down syndrome. Typically, although not necessarily, mothers will begin with a prenatal screening test like the triple screen, quadruple screen, or the newest combination of two maternal serum markers and ultrasonographic findings. With a 5 percent false-positive rate, 69 percent of fetuses with Down syndrome are correctly detected with triple screening, 81 percent with quadruple screening, and 87 percent with the recent first-trimester screening involving 2 maternal serum protein markers and ultrasonographic findings. For a definitive prenatal diagnosis, mothers have one of two options: chorionic villus sampling (CVS), typically between the 8th – 12th weeks of pregnancy or amniocentesis, typically after the 15th week of pregnancy. Neither procedure, however, is without risk; both typically carry less than a 1 percent additional chance of causing a spontaneous miscarriage.

The *Prenatally and Postnatally Diagnosed Conditions Awareness Act* was informed by my research, and I was happy to provide testimony at its first hearing sponsored by Senators Kennedy and Brownback. In my study published in 2005 in the medical journal *American Journal of Obstetrics and Gynecology*,¹⁰ I found that

¹⁰ Skotko BG. (2005). Prenatally diagnosed Down syndrome: mothers who continued their pregnancies evaluate their health care providers. *American Journal of Obstetrics and Gynecology* 192:670-7.

obstetricians and genetic counselors provide too little information when it comes to delivering a prenatal diagnosis of Down syndrome to pregnant women.

Mothers who have children with Down syndrome, diagnosed prenatally, reported that doctors did not tell them about the positive potential of people with Down syndrome nor did they feel like they received enough up-to-date information or contact information for parent support groups. Further, the mothers reported that all of these shortcomings were happening at an emotional time when women have to decide whether or not to continue their pregnancies. This study remains the largest and most comprehensive study on prenatally diagnosed Down syndrome. Mothers in my research study offered the following seven recommendations for communicating a diagnosis of Down syndrome prenatally:

- Results from the prenatal screening should be clearly explained as a risk assessment, not as a “positive” or “negative” result.
- Results from the amniocentesis or CVS should, whenever possible, be delivered in person, with both parents present.
- Sensitive language should be used when delivering a diagnosis of Down syndrome.
- If obstetricians rely on genetic counselors or other specialists to explain Down syndrome, sensitive, accurate, and consistent messages must be conveyed.
- Physicians should discuss all reasons for prenatal diagnosis including reassurance, advance awareness before delivery of the diagnosis of Down syndrome, adoption, as well as pregnancy termination.
- Up-to-date information on Down syndrome should be available.
- Contact with local Down syndrome support groups should be offered, if desired.

I also published additional research in 2005 in the medical journal *Pediatrics*,¹¹ which summarized responses from women who received the Down syndrome diagnosis postnatally. Mothers indicated that physicians remain overwhelmingly negative in communicating the diagnosis of Down syndrome postnatally. Mothers reported that the majority of physicians were uninformed about the positive potential for children with Down syndrome and rarely provided an adequate, up-to-date description of children, printed information, or telephone numbers of other parents. Mothers in this study offered the following ten recommendations for communicating a diagnosis of Down syndrome postnatally:

- The person to communicate the Down syndrome diagnosis should be a physician.
- Obstetricians, neonatologists and pediatricians should coordinate their messages.

¹¹ Skotko, B. (2005). Mothers of children with Down syndrome reflect on their postnatal support. *Pediatrics*. 115:64-77.

- The diagnosis should be delivered as soon as a physician suspects the diagnosis, but only after the mother is settled.
- Parents should receive the news together, in a private setting.
- The physician should first congratulate the parents on the birth of their child and not forget to talk about the positive aspects of Down syndrome. They should not begin the conversation by saying, “I’m sorry.”
- Health care professionals should keep their personal opinions to themselves.
- Mothers should be provided with up-to-date printed materials – at a minimum, a bibliography listing the most current resources for new parents.
- Parents should be put in touch with other families who have children with Down syndrome.
- After the diagnosis or suspicion is shared, parents should be offered a private hospital room.
- All physicians should educate themselves about the educational and social potentials of children with Down syndrome.

Last year, Congress took an important first step in ensuring that all new and expectant parents receive accurate, up-to-date information by passing the *Prenatally and Postnatally Diagnosed Conditions Awareness Act*. Without funding, however, this Act has no impact. Congress can complete this good effort with the following action:

Suggested Action: Support a \$5 million appropriation, per year, over 5 years to implement fully the *Prenatally and Postnatally Diagnosed Conditions Awareness Act*.

Approximately 400,000 Americans with Down syndrome and their family members are depending on Congress to take these important and urgent steps. Their futures are in your hands.

I would like to thank Madeleine Will, Vincent Randazzo, Sara Weir, Barry Zuckerman, M.D., Robert Vinci, M.D., Leonard Rappaport, M.D., Ira Lott, M.D., George Capone, M.D., Pat Winders, PT, Michael Harpold, Ph.D., Emily Davidson, M.D., Cynthia Kidder, Mark Leach, and Amy Judge for their help in reviewing and preparing this testimony.