Down Syndrome: Update on the State of the Science &

Potential for Discoveries Across Other Major Diseases

TESTIMONY

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Dear Members of the Committee,

Thank you Chairman Cole and Ranking Member DeLauro and all distinguished members of the subcommittee for convening today's hearing and inviting me to testify.

I am here today to share with you my understanding of what I believe is one of the most remarkable developments in the history of medicine and biomedical research.

I know you are well aware that one in every four Americans will die of cancer. This coming December, it will be 46 years since President Nixon, with bipartisan support from Congress, declared the War on Cancer. Despite a massive investment in cancer research during the past half century, cancer will kill more Americans in 2018 than in 2017. And even more in 2019.

I know that you also know the impact of Alzheimer's disease in our society is reaching epic proportions. Today, more than five million Americans live with this disease, and this number is expected to triple by 2050. One in three of our senior citizens dies with Alzheimer's or another dementia. In 2017, Alzheimer's and other dementias will cost the nation $259 billion, and this number is expected to quadruple by 2050.

Clearly, our nation, and the world at large, could use new ideas and resources to address these massive medical problems.

Now, what if I told you that there is a special group of American citizens for whom these statistics do not apply? What if a told you that, due to a small difference in their genetic make up,

these Americans are naturally protected from most cancers? What if I told you that these same individuals are also the largest population with a genetic predisposition to early onset Alzheimer's disease, whereby virtually all of them will develop the brain pathology of Alzheimer's at an early age? Wouldn't you agree that this special population would deserve our attention?

Of course, I am referring here to people with Down syndrome.

People with Down syndrome are very special. Unlike typical people, whose DNA comes packaged into 46 chromosomes, people with Down syndrome have 47 chromosomes. They have an extra copy of chromosome 21 - three copies instead of the usual two - and this is why the condition is also known as trisomy 21. This small extra piece of DNA, which carries less than one percent of the genetic information in the genome, causes a different 'disease spectrum' in the population with Down syndrome, whereby they are naturally protected from developing some major medical conditions, but highly predisposed to others. The aforementioned examples of cancer and Alzheimer's are just the tip of the iceberg. For instance, it is extremely rare to hear of a person with Down syndrome dying of a heart attack. For unknown reasons, they rarely suffer from hypertension, atherosclerosis or myocardial infarction. On the other hand, they are highly predisposed to develop autoimmune disorders, such as autoimmune hypothyroidism, celiac disease, rheumatoid arthritis, type 1 diabetes, and various autoimmune skin conditions. Intriguingly, although they are strongly protected from most cancers of 'solid tissues', such as breast cancer and prostate cancer, they have a much higher risk of developing leukemia.

I hope you would agree that these fascinating observations are worthy of much scientific research. Unfortunately, Down syndrome is one of the least understood genetic conditions, and one that is not receiving its due share of resources from the biomedical research enterprise, either

by government agencies like the National Institute of Health or by the private sector. How could this be? I believe this is most likely due to a historical delay in our collective awareness of the value of people with Down syndrome, as well as some profound societal misperceptions.

First, the epidemiological observations that I shared with you are fairly recent, mostly from the last 15 years, because until not too long ago, people with Down syndrome didn't live long enough for researchers to be able to gather these data. The life expectancy for people with Down syndrome has more than doubled since the 1980's, and a baby born today with Down syndrome is expected to live well into her 60's. Because of this steady increase in life expectancy, there are four times more American citizens with Down syndrome today than in the 1950's. Their total number in the U.S.A. is well above 200,000, possibly as many as 400,000, and around six million worldwide. Thanks to these large numbers, we are now able to document with unequivocal data that they have a different disease spectrum.

Second, I believe the lack of interest in Down syndrome research is due in good measure to two societal misperceptions. One is that the population with Down syndrome would eventually disappear due to early pre-natal screening and elective terminations. This is obviously not supported by the data. In the U.S.A., the rate of live births with Down syndrome has actually increased over the last three decades, currently being at around 1 in 700. Simply put, people with Down syndrome are here to stay. Another misperception is that Down syndrome is too complex of a condition, and that there is little that can be done to reverse the deleterious impacts of the extra chromosome. This is also false. Thanks to proper medical care with standard interventions, such as heart surgery for those babies with Down syndrome born with a congenital heart defect, or hormonal management for those with hypothyroidism, people with Down syndrome are living longer, better lives, and achieving things that would have been unthinkable a few decades ago.

Take for example my friend Connor Long, a self-advocate who recently earned an Emmy award for his role as a news reporter working at a TV channel in Denver. I am convinced that, with the proper investment in specialized research, the life expectancy and quality of life of people with Down syndrome will continue to increase to unprecedented levels. In fact, research at the Crnic Institute indicates that Down syndrome could be driven by strong dysregulation of the immune system, which opens up novel opportunities to test immunotherapies for this condition.

Regardless of the reasons for our current collective ignorance about Down syndrome, the truth remains that this population continues to be severely underserved by the biomedical research enterprise, as illustrated by Michelle Sie Whitten's testimony. Down syndrome is a multi-system, multi-organ condition affecting human biology in myriad ways, with well-established impacts on diverse neurological, immunological, cardiovascular, developmental, and metabolic processes. Consequently, research on Down syndrome could not possibly fit within the scope of a single Institute or Center within the National Institute of Health. However, historically, research on Down syndrome has been largely restricted to the Eunice Kennedy Shriver National Institute on Child Health and Human Development (NICHD). Recently, the National Institute on Aging (NIA) has recognized the enormous potential that research on Down syndrome has to advance our understanding of Alzheimer's disease, leading to new research grants to study the connection between the two conditions. Because research on Down syndrome will also advance our understanding of many other diseases including cancer, leukemia, autoimmune disorders such as type I diabetes and rheumatoid arthritis, neurological conditions such as autism and epilepsy, as well as various heart and lung conditions, and because Down syndrome can no longer be considered solely a pediatric condition, there is an exciting opportunity to create a trans-NIH initiative to study this condition.

The concept of a trans-NIH initiative catalyzed by Congressional support to address an emergent biomedical problem is not new. In fact, such an orchestrated action by Congress and NIH played a key part in one of the biggest achievements in modern medicine. Back in 1988, having appreciated the threat of the incipient HIV/AIDS epidemics, Congress and NIH worked swiftly to create the Office of AIDS Research (OAR). The OAR was initially established by the Assistant Secretary of Health and then codified in the Health Omnibus Programs Extension (HOPE) of 1988. Since then, the OAR has planned and coordinated a large, trans-disciplinary HIV/AIDS research portfolio that crosses the boundaries of individual NIH Institutes and Centers. Today, the total number of new AIDS diagnoses in the U.S.A. continues to decline every year, and the number of annual deaths caused by HIV is less than a third of what it was in the mid 90's. Clearly, the investment by the federal government in this area (currently at more than $3 billion per year), as well as the investment from the pharmaceutical industry, have paid off big dividends.

When Congress acted to create the OAR in 1988, the total cumulative number of AIDS diagnoses in the USA was less than 100,000. That same year, there were more than 150,000 people with Down syndrome in the U.S.A. How much longer should people with Down syndrome wait to receive the attention they deserve? How many more people with Down syndrome should there be to justify a trans-NIH initiative supported by Congress?

I believe the time is now. I believe there are already more than enough people with Down syndrome to justify a significant investment in specialized research for this condition. I also believe, as my mentor Dr. Tom Blumenthal would say, that people with Down syndrome are a gift, and that by studying their special nature we can benefit them and the rest of humankind.