

# Toward a CURE



A RESEARCH UPDATE

WINTER 2011

## WCHD Melbourne, Australia, September 2011

*As reported by Fred Taubman, HDSA Marketing and Communications Director*

If there was a theme to the recent World Congress on Huntington's disease (WCHD) in Melbourne, Australia it was "the spirit of cooperation," meaning that collaboration would be necessary, not only worldwide between scientists and private industry (pharmas, biotechs and academics), but also among all of these groups as well as clinicians, people with HD and their families, in order to bring therapies for HD to reality.

Even developing the therapies will require cooperation, as there was a great deal of discussion at the Congress, about the possibility that eventually several treatments (a cocktail) would be utilized to delay the onset of HD, and may eventually block the onset entirely.

Before the opening of the Congress, the International Huntington Association (IHA) held its bi-annual meeting, with representatives of 23 HD Family organizations. There was much discussion about improving inter-organization communication and sharing of resources, as well as the redesign of the IHA website, which would help accelerate the sharing of information and materials.

There was also discussion of the revision of the genetic testing guidelines, which had been developed in 1993. The IHA decided that it would promote further discussions on the topic before voting on the guidelines, as there was a determination made that all constituencies had not been given the opportunity to comment on the proposed changes.

Nancy Wexler, PhD and Charles Sabine were the keynote speakers for the IHA's Marjorie Guthrie Day. Martha Nance, MD from Hennepin County Medical Center, MN, presented a panel on youth and HD, and other workshops included discussions about relationships, career and family planning, coping strategies for caregivers, and multidisciplinary care for people with HD. The Board of the IHA (including new board member HDSA CEO Louise Vetter) promised to

promote international cooperation as a high priority in their future endeavors.

At the opening session on Monday morning, Congress organizers, Andrew Churchyard, Julie Stout and Nellie Georgiou-Karistianis welcomed the attendees and explained that to set the stage it was important to look back at how we had arrived at this moment in HD history, and where we stood in terms of therapeutic progress.

Sir Peter Harper, MD, Professor Emeritus at Cardiff University, reviewed key moments in the history of HD, and emphasized that the hallmarks of shared community, of researchers possessing a pioneering spirit, and the unusual spirit of cooperation are what have made the HD community so special historically. From George Huntington, born into a family of doctors who first identified the disease, through the formation of lay societies by Marjorie Guthrie and others, and the groundbreaking genetic and neurological discoveries by HD researchers, Huntington's has been a paradigmatic, or model, disease that has created a roadmap for groups focused on other chronic diseases. This continues to be true today.

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# From the Desk of Louise Vetter

## HDSA's Chief Executive Officer

Dear Friends,

HDSA recently hosted its inaugural Congressional Briefing on Capitol Hill for the health-focused staff of members of the U.S. House of Representatives and U.S. Senate. The session focused on genomics, the study of the genetic roadmap of an organism, and how advances in this relatively new field will affect healthcare and its delivery in the future. You may ask, what does genomics have to do with HD? How will it help me or my children?

We know that HD is caused by a genetic stutter or repeat in a single gene in our DNA. Those who inherit this stutter will develop HD at sometime in their life. Since the discovery of this gene 18 years ago, researchers have been diligently investigating ways to halt the progression or delay onset – in other words, to discover ways to intervene in the deadly progression of HD. This is genomics in action.

HD scientists and clinicians are currently at work developing biomarkers that will be used not only to identify and recognize the earliest signs of disease onset (studies like PREDICT-HD), but also which treatments could be most effective for an individual given that person's unique genetic makeup, i.e. personalized medicine. Biomarkers are also being developed for use in clinical trials in order to determine whether an investigatory drug is effective in people who are gene positive, but not yet symptomatic.

Discovering effective therapies that intervene in how the gene functions is key to improving the quality of life for a person with the HD gene. But as research advances, we must remain vigilant to undercurrents in healthcare that could create obstacles and barriers to quality care.

Legislation such as the Affordable Care Act, which was passed last year, contains provisions that mandate that states create health insurance exchanges where uninsured individuals can buy health insurance from different vendors. However, there are many questions about what each vendor will offer, how much health insurance purchased this way would cost and how much choice in coverage a person may have in his or her state. These issues pose challenges to the HD community – ensuring that these state run insurance exchanges provide coverage at an affordable price and with multiple options are vital to people with chronic conditions like HD.

This is just one issue where HDSA is working behind the scenes to positively impact legislation that will take effect in 2014. In the coming months we will be asking the HD community to lend its voice by writing letters, attending Town Hall sessions and even meeting with your state leaders. It's easy to get involved. Just contact Jane Kogan, HDSA's Advocacy and Programs Manager or go online to [www.hdsa.org/join](http://www.hdsa.org/join) and sign up to be an advocate today.

Educating elected officials about HD, and the science that is quickly changing the field, is vital to removing barriers to care and to making sure that important research continues. Your support over the years has made it possible for HDSA to lead these discussions, and now as we increase the dialog about affordable healthcare for people with HD and their families, we ask for your continued support. Please consider donating today to help HDSA's mission continue. Together, we can improve the lives of everyone affected by HD.

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The purpose of *Toward a Cure* is to provide information and opinion and to relay items of interest to individuals with Huntington's disease and their families, healthcare professionals and interested friends and supporters.

The appearance of advertising, or the mention of commercial articles available for sale in articles published in this newsletter, is not an HDSA guarantee or endorsement of the product or the claims made for the product by the manufacturer. Statements and opinions expressed in articles are not necessarily those of HDSA, Inc.

The Huntington's Disease Society of America (HDSA) is a national not-for-profit organization. The Society is dedicated to eradicating Huntington's disease by promoting and supporting HD research; to helping families cope with the problems presented by HD; and to educating the public and healthcare professionals about HD.

HDSA is a member of the National Health Council, the National Organization of Rare Disorders, the International Huntington Association, the Alliance for Genetic Support and the American Brain Coalition.

The Huntington's Disease Society of America meets all nine standards of the National Charities Information Bureau.



**Huntington's Disease  
Society of America**

Sarah Tabrizi, MD, from UCL Institute of Neurology, surveyed the current state of HD research, specifically the targeted approaches closest to clinical trials in the next few years. She talked about the excitement surrounding two approaches to “gene silencing,” utilizing Antisense Oligonucleotides (ASOs) and RNA interference (RNAi), and the issues in balancing the need to maintain normal huntingtin protein while lowering mutant huntingtin. Dr. Tabrizi also discussed post-translational modification to address issues such as autophagy with sirtuin (proteins involved in apoptosis, a cell death process) inhibition and kynurenine monooxygenase (KMO) inhibition. Approaches to modify mitochondrial function are moving through the pipeline with new CoQ10 and creatine analogs being developed. Dr. Tabrizi also cited work on HDAC-4 inhibition as a target that looks promising, and theorized that it would most likely be a combination of these approaches (or other ones) that will be used in the future to slow the onset of HD. She finished by stressing the importance of biomarker development, and how striatal shrinkage captured years before symptom onset (in TRACK-HD) is an example of the type of finding that could shorten clinical trials, and allow scientists to determine the efficacy of a potential therapy in pre-onset participants. Dr. Tabrizi finished her talk by leading the 450 attendees in a rousing chant of “Yes We Can” in response to the question of whether treatments will be found for HD.

The first science session focused on **clinical research**— and how the disease evolves. Jim Gusella, PhD from Harvard MGH, explained that while we know that mutant huntingtin causes HD, and CAG length is somewhat predictive of symptom onset, there are other genetic factors that affect the speed of onset. He described work being done to identify potential modifier genes – and how recent analytic methods have shown that some that were thought to be involved are actually not, so a full genomic study is necessary to identify legitimate modifiers that may be targeted to alter disease progression.

Elizabeth Aylward, PhD from the Center for Integrative Brain Research, Seattle Children's Research Institute, showed data from the PREDICT-HD imaging studies and their potential as biomarkers. Anthony Hannan, PhD (Florey Neurosciences Institute), offered evidence that environmental enrichment (sensory stimulation, cognitive activity and physical exercise) can delay disease onset in mice, while work being done to identify the molecular modulation caused by these environmental influences may be disrupting gene expression.

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## HDSA Burden of Care Poster included at World Congress on HD!

In November 2010, HDSA partnered with the EURO-HD Network on a burden of care survey. Using an online tool, HDSA collected surveys from 358 caregivers and 169 people with HD. Preliminary results were shared with EURO-HD and a poster was presented during the Congress.

This study is the first to assess the overall burden of HD in the US:

- Patients experience substantially reduced HRQoL (health-related quality of life) relating to the motor, psychological and social aspects of HD.
- Caregivers spent a substantial amount of time caring for patients and reported spending an average of 6 hours per day on this activity.
- Caregivers spent a mean of \$1,284.33 per year on caring for their patients.
- Generally, caregivers also had a diminished HRQoL, with 43% reporting that they were dissatisfied with their overall quality of life.
- Total costs from the Medicare perspective were evaluated to be \$5,906 per individual.
- Disability appears to be an important element of the disease burden and is associated with loss of autonomy.
- The cost to society, as well as out-of-pocket expenses and health insurance costs, are all high.
- Given the large burden for patients, their caregivers and society, HD should be considered as an important research area for public funding.

## RESEARCH OPPORTUNITIES

**Cognitive Assessment Battery:** This research study evaluates thinking abilities in people who have HD. This includes both people who have tested positive but are not yet symptomatic as well as people who have developed symptoms. The study is also recruiting people who do not carry the HD gene. The purpose of the study is to determine which tests are best at showing those changes in thinking that may occur in people who have the gene for HD.

The study will include about 100 control participants, 100 participants with the HD gene who have not yet been diagnosed, and 50 participants who have been diagnosed with HD. Participants should be between 25-55 and able to travel to a test site for 3 visits over a 6 week period.

If you are interested in this study, please contact the site closest to you or go to [www.HDTrials.org](http://www.HDTrials.org).

### **University of California, San Diego**

Jody Goldstein:  
858-622-5854 or email [jgoldstein@ucsd.edu](mailto:jgoldstein@ucsd.edu)

### **University of California, Los Angeles**

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### **Oregon Health and Science University, Portland, OR**

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# Enroll-HD Update

For the past 6 months, Enroll-HD working groups have been completing the preliminary tasks needed to move this groundbreaking international observational study forward. Setting up the data management and data sharing systems, drafting ethics guidelines, arranging for bio repository systems, and the development of the study protocol were among the major priorities of these committees.

The most important task, the creation of the Enroll-HD Protocol has been finalized after review and comments by members of different segments of the HD community. The finalized protocol is being distributed, and meetings are being held with COHORT Investigators (in the US and Canada) to begin the process of IRB approval and related issues.

The current goal is to have all clinical sites in North America and Australia that had formerly participated in COHORT, as well as new Latin American sites, up and running under the Enroll-HD protocol by Q1 2012. This will be a challenge to achieve given some of the IRB and contract review times, but the Enroll-HD team is working to have as many sites as possible engaged by that time. New clinical sites in North America and Australia that were not previously involved in COHORT will follow soon after.

Starting in October 2011, the Enroll-HD Study Team started conducting site assessment visits at Latin American sites recommended by the Red Latinoamericana de

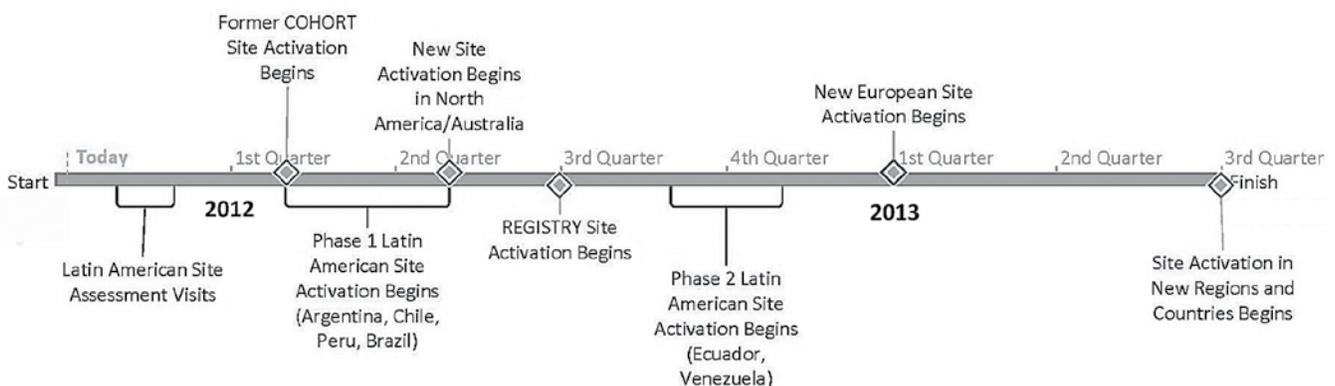


Huntington (RLAH), the new Latin American HD network, in order to evaluate the resources currently available to the sites and, where needed, offer support to enable successful conduct of the study. A preliminary survey identified the countries where there were interested and motivated professionals, and so far 13 clinical sites in Argentina, Brazil, Chile, Ecuador, Peru and Venezuela have joined the network.

One of the initial priorities of the RLAH was to establish a collective observational study to serve as a platform for clinical trials, so the development of the global Enroll-HD has been an invaluable foundation for the set-up of the network. REGISTRY (Europe) sites will begin to be transitioned to Enroll-HD in the middle of 2012, followed by sites in Asia and Australia in 2013.

To keep abreast of Enroll-HD, visit the HDSA website for regular updates or visit [enroll-hd.org](http://enroll-hd.org).

## Enroll-HD Timeline



## Amaryllis Season is here!

Amaryllis bulbs are among the easiest bulbs to grow indoors and the most rewarding. These premium Dutch bulbs need minimal attention but you will be rewarded with spectacular blooms to brighten up the dark winter days. Planting Amaryllis and watching them grow is a fun activity for the entire family.

Amaryllis are available in individual kits or cases of solid colors and assorted for gift giving.

The COMPLETE KIT will contain everything you need to have your own spectacular Amaryllis this winter including: one 26/28 cm Amaryllis Bulb, decorative pot, professional growing medium, planting and aftercare instructions.

Each kit costs only \$10.00 plus shipping and handling.

Amaryllis make the perfect gift that can be enjoyed for many weeks.

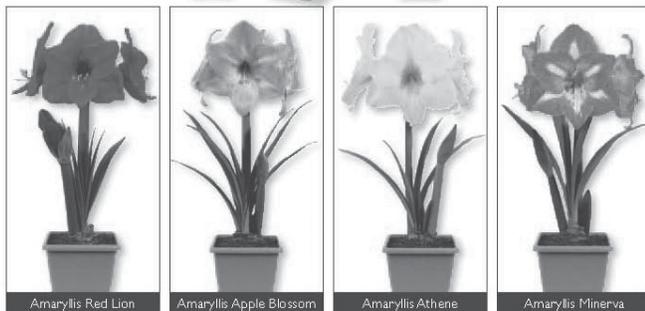
Some gift ideas include:

- Thanksgiving
- Christmas
- Chanukah
- Housewarming
- Get Well
- Birthday
- Gifts for friends, teachers, co-workers

When you purchase an Amaryllis plant, you support the fight against Huntington's disease in your community and across America, and allow HDSA programs of research, care, education and advocacy continue to grow.

Amaryllis can be purchased from your local chapter or on line at [www.hdsa.org/amalyllis](http://www.hdsa.org/amalyllis).

## Fall Amaryllis Sale!



# Many Ways

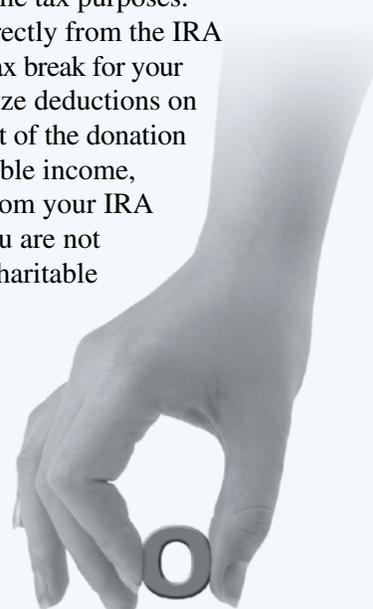
## Year End Giving Suggestion

Thinking about making a year end donation to support the Huntington's Disease Society of America's efforts to support and influence research to find the answers to HD and to provide programs and services to meet the needs of all those who are affected by HD? Please consider a gift of appreciated stock or a donation from your IRA.

A donation of appreciated stock will enable you to help HDSA fulfill our mission – to improve the lives of people with Huntington's disease and their families – while receiving a charitable tax deduction for the full fair market value of the stock at the time of the donation and simultaneously lowering your capital gains taxes.

If you are 70 ½ years old or older, an important window of the Tax Relief Act of 2010 has remained open through December 31, 2011 – you can make a tax free direct charitable distribution from your Traditional or Roth IRA to HDSA of up to \$100,000 without having to count the distribution as income for federal income tax purposes. Transferring the money directly from the IRA to HDSA is a way to get a tax break for your donation if you don't itemize deductions on your tax return. The amount of the donation is excluded from your taxable income, provided it goes directly from your IRA provider to HDSA, but, you are not entitled to an income tax charitable deduction for your gift.

For more information on making a gift of stock or a donation from your IRA to HDSA please call **1-800-345-HDSA (4372)**, extension 235.



SUPP RT

# to Give

There are many ways for you to make a contribution to help HDSA improve the lives of people with Huntington's disease and their families.

- **Make a one-time Donation or a Tribute/Memorial Gift to honor a friend or relative or the memory of a loved one:** Please visit our website, [www.hdsa.org](http://www.hdsa.org) and click on the “Donate” icon in the upper left hand corner of the page. This will take you to a secure page where you can make a **direct donation** to HDSA.

Or you can use the donation envelope located in this newsletter.

- **Donate Appreciated Stock and/or Mutual Funds:** Earn a charitable tax deduction for the full fair market value of the gift while you lower your capital gains taxes.
  - For information on how to make a stock or mutual fund donation please call 1-800-345-HDSA (4372), extension 235
- **Establish a Family Fund:** Join with friends and relatives and pool your resources to honor your family or remember a loved one and make your donated dollars work harder than you could individually.
  - For information on how to establish a Family Fund please call 1-800-345-HDSA (4372), extension 235
- **Make a Planned Gift: Join the HDSA Heritage Club:**
  - Remember HDSA in your Will or Estate Plans
  - Establish a HDSA **Charitable Remainder Annuity Trust, Charitable Lead Trust, Charitable Remainder Trust, Charitable Remainder Unitrust**
  - Name HDSA as a beneficiary of your retirement plan
  - Name HDSA as a beneficiary of your life insurance policy

For information on making a planned gift to HDSA please call 1-800-345-HDSA (4372), extension 235

- **Work Place Giving**

- **Matching Gifts:** Your employer or organization may be part of the HDSA Program, which can double your donation.
  - A list of participants is available on our website. If your employer is not part of this program, we would be happy to help enroll your company or organization.

- **United Way/Community Health Charities/ Combined Federal Campaign:** Giving at work through payroll deductions to support HDSA is simple and there are many convenient ways to contribute. Check to see if your employer participates in any of these workplace giving programs.

- **Become a Corporate Partner:** Businesses of all sizes can help bring us closer to the day when there will be the last generation with HD.
  - Give a cash or grant donation
  - **Join an event:** Participate or become a sponsor of the hundreds of HDSA events around the country, such as our Team Hope Walks or Celebration of Hope Galas.
  - **Workplace Giving:** Encourage employee giving through payroll deductions and show your employees that you support their philanthropic efforts by contributing a company match of their gift.

- **Donate your Vehicle:** Call toll free 888-HDSA-151/888-437-2151 or e-mail [donations@charitableautoresources.com](mailto:donations@charitableautoresources.com) to speak to an HDSA Vehicle Donation Representative. Our representative will schedule a pickup that's convenient for you, and provide you with confirmation of your donation.

Or visit our website, [www.hdsa.org](http://www.hdsa.org) and click on the “How You Can Help” icon to donate your vehicle online. Select the Vehicle donation page, which will take you to a secure page where you can choose to make an **online vehicle donation** to HDSA.

Please visit our website regularly and browse the **HDSA Marketplace**. Purchasing a Care2Cure Bracelet or Necklace, amaryllis plant, golf polo shirt and other merchandise makes a difference – and helps us build awareness at the same time.

# Novel Research Studies

Many HDSA Centers of Excellence are involved in novel clinical research that will improve the lives of people with HD. In this issue of *Toward a Cure*, we are pleased to share the results of five studies conducted at the HDSA Center of Excellence at the University of Iowa.

## Clinical predictors of driving

Driving a vehicle is one of the earliest reported areas of decline for people with HD, according to University of Iowa researchers Leigh Beglinger, PhD, and Luke Prest. People value the freedom of being able to drive, so when clinicians are faced with the difficult decision of whether or not to recommend that a person stop driving, they do not take this decision lightly. Because there hadn't been much research done involving HD and driving, Beglinger and Prest set out to determine what aspects of HD (cognitive and motor, for example) were associated with whether or not a person was still driving, and what aspects coincided with a clinician's recommendation to stop driving.

Seventy-four patients with HD were evaluated for cognitive, motor, psychiatric and functional status using a standardized battery during a research clinic visit. Researchers reviewed the data to identify significant clinical predictors of those driving compared to those not driving.

The results show that declining cognitive performance provided the best predictive indicator of when a person stopped driving or was told to stop driving. The cognitive tests that measured a person's learning and psychomotor speed/attention (for example, the ability to react to a car pulling out in front of you) were most strongly associated with whether or not a person was driving. For this reason, in an article (currently under review) reporting their results, Beglinger and Prest recommend that a cognitive assessment should be a routine part of clinical monitoring for people with HD who are still driving.

## Quality of life in HD: scale development

Quality of life is an important issue for people affected by HD. Understanding the disease's impact on quality of life can help people with HD and their family members plan care and develop realistic expectations for the future, say researchers Rebecca E. Ready, PhD, from the University of Massachusetts and Jane Paulsen, PhD, from the University of Iowa.

Quality of life measures can also be used to determine effectiveness of treatments in clinical trials. Currently, as Ready and Paulsen note, there are no quality of life measures specifically for HD. For the past four years, they have been gathering data about quality of life in HD to develop a measure that would be relevant to a wide range of persons affected by HD. After gathering input from persons at risk for HD, persons with HD, HD family members, and health care professionals, the measure was piloted with those who are at risk for HD, those prediagnosed, and those who have HD.

The Quality of Life in Huntington's Disease measure is a brief 18-item instrument that can be completed by persons affected by HD or a companion. In an article currently under review, Ready and Paulsen say the goal of future HD research will be to refine and improve the scale and to understand how HD affects life quality and to determine what HD symptoms most strongly predict life quality.

## Retrospective work supervisor study

Being able to work and earn a living is important to most people. The financial stress and a diminished sense of meaning and purpose often caused by unemployment can create psychological distress for people affected by HD. University of Iowa researcher Justin O'Rourke, PhD, and others, set out to identify what areas of work function are most affected by HD so that proactive steps can be taken to help people with HD continue to work for as long as possible.

With hopes of better understanding work performance changes in HD, O'Rourke and his colleagues are talking to supervisors of former workers who are gene positive. They are also talking to the former workers themselves, and their companions, to gain further insight.



Preliminary results from this ongoing study indicate that former workers affected by HD first showed declines in the ability to adapt to changes in the work environment and to creatively solve daily problems at work. Researchers hope that the results from this study will educate employers and employees about what changes to expect as a result of HD so that they do not mistakenly attribute performance changes to poor work ethic or incompetence. Additionally, results from this study can be used as a basis for developing accommodations that may help people with HD continue to do their job. In other words, if employers knew certain work declines were a result of HD, and they knew which accommodations could be implemented to support their employees, then it may be possible to prolong employment for those with HD. O'Rourke and his colleagues plan to have their full findings published in a medical journal once the study has concluded.

### **Couples' representation and coping in prodromal HD**

A recent study showed that people with prodromal (meaning prediagnosed) HD use positive coping methods as a way of dealing with HD.

University of Iowa researcher Nancy Downing, PhD, and others asked 23 participants and their companions from the PREDICT-HD study about how they cope with changes in their life, some of which the participants attribute to prodromal HD. Detailed in an article by Downing and others (currently under review), results showed that the couples used coping methods like acceptance, planning for the future and getting emotional support. They also used prescription drugs for certain issues, such as depression. They generally stayed away from negative coping methods like substance abuse, denial and disengaging from loved ones.

Downing and her coauthors say that these positive coping methods may help people in HD families cope with daily life. Additionally, couples may benefit from proactive HD counseling that emphasizes using active coping strategies and learning to accept certain changes in their life caused by prodromal HD. These findings may also be useful for couples facing other neurodegenerative conditions like Alzheimer's and Parkinson's diseases.

### **Achievement in HD study**

The decline in thinking ability for those who have been diagnosed with HD and even those with early HD has been shown in several studies. Now, University of Iowa researcher Peg Nopoulos, MD, wants to see if people who later develop HD had any academic difficulties that predate the onset of the disease.

She will be looking at academic achievement of adults who have HD by examining standardized test scores. The University of Iowa is lucky, Nopoulos said, to have in its Department of Education the developers of the Iowa Test of Basic Skills (ITBS), a well-validated test of academic achievement. This test is administered to school-aged children throughout several points in their school-aged years.

Since the test was developed at the University of Iowa, Iowa is the only state to have maintained records of all ITBS scores, and with participant consent, Nopoulos and colleagues can retrieve this data.

Nopoulos plans to obtain ITBS scores for adults with HD who agree to participate in the study from grades three, eight and 11. She says she will then group all of the HD participants together to look at mean test scores and compare them to normative scores from Iowa students to see if there are any differences.

**Save the Date!**

Join us for the  
27th Annual  
HDSA Convention

**June 8-10, 2012**

Red Rock Resort and Spa  
Las Vegas, NV

Details available on  
[www.hdsa.org](http://www.hdsa.org)  
beginning Jan 2012

## RESEARCH OPPORTUNITIES *(Continued from Page 4)*

### Join HDTrials.org.

If you are interested in being part of a clinical or observational trial but don't know where to go for information about what trials will soon be recruiting or where they will be located, then join **HDTrials.org**, an online alert system that uses your zip code and email address to notify registered users about upcoming trials and studies.

**HDTrials.org** is a collaborative web initiative of major Huntington organizations and volunteer groups that includes HDAdvocacyCenter, HDDrugworks, Huntington's Disease Society of America, Huntington Society of Canada and the HDLighthouse.

The **HDTrials.org** web site performs two functions: it provides quick notification to registered users about opportunities to participate in clinical trials and studies through a confidential email list thus speeding the time it takes to recruit participants, and it creates a separate list using only a zip code as an identifier which will help our scientists to identify locations where a large number of potential participants for a clinical trial are available.

Your privacy and confidentiality are protected. **HDTrials.org** is hosted on a separate server and HDSA has hired an administrator to create and manage the site who has no involvement with HDSA. In order to further secure your privacy, you may wish to create a new email address through gmail.com, hotmail.com, yahoo.com or another free web-based email provider. Your email address and your zip code will never be distributed to any outside party. For more information about **HDTrials.org**, please contact Fred Taubman at HDSA ([Ftaubman@hdsa.org](mailto:Ftaubman@hdsa.org)).

There can be no treatment advances in Huntington's disease without clinical trials. Just as it took the collaborative efforts of many Huntington families and scientists to find the gene more than a decade ago, it will take the sustained research efforts from all organizations and the HD community to move research to where it matters most: treatments for people. Every single clinical trial volunteer is a hero for this generation.

Please sign up today – and encourage your family members and friends in the HD community to do the same. Remember, that together we have the power to speed treatments for Huntington families.

### On Line Survey Opportunity

#### Telling the Children: Disclosure Challenges and Support Needs of Parents with Children At Risk for Huntington Disease

HDSA has been asked to share information about this study with you.

This research will study the challenges that parents face in telling their children about their own risk for HD, as well as identifying support resources used and found helpful for parents.

**Eligibility:** You have received a positive genetic test result for HD and you have at least one biological child under the age of 21 years old OR your current or former spouse/partner has received a positive genetic test result for HD and has at least one biological child 21 years of age or younger.

In this study, spouse/partner is defined as a current/previous spouse or common-law partner who shares children with a gene positive individual. As a spouse/partner, the children may be your biological children or they may not be your biological children but you play a parenting role.

If you are eligible, please complete the on line survey by going to <https://www.surveymonkey.com/s/TellingTheChildrenStudy>. This survey is anonymous and participation is completely voluntary. The survey will take about 20 minutes.

If you have any questions, please contact Jennifer Semotok at the University of Toronto ([jennifer.semotok@sickkids.ca](mailto:jennifer.semotok@sickkids.ca)) or Clare Gibbons at North York General Hospital ([clare.gibbons@nygh.ca](mailto:clare.gibbons@nygh.ca)).

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Colin Masters, MD, of the Mental Health Research Institute, spoke about oligomers (short single stranded DNA or RNA fragments) which seem to be both a biomarker and a therapeutic target in Alzheimer's, and suggested that they be looked at similarly in Huntington's. He also spoke about Prana's PBT2 which reduces copper aggregates in R6/2 mice. Prana (for which Dr. Masters is Chief Scientist) is moving forward with clinical trials in the US and Australia using PBT2, based on findings in Alzheimer's trials and animal models of HD. These trials are scheduled to begin in the U.S. in early 2012.

**Therapeutic strategies** was the focus of the next Science Session. Frank Bennett, PhD of Isis Pharmaceuticals outlined their work with ASOs, and how they can bind and target RNA to modify the production of mutant huntingtin. ASOs were able to reach their targets within key areas of the brain through injection into the spine. This method is being tested in ALS, and trials with HD mouse models have been successful in lowering the mutant huntingtin without any adverse affects.

Don Cleveland, PhD from UC San Diego went into more detail on the use of ASOs and how the effects of HD continued to be modified in mouse models after infusion of ASOs were stopped, suggesting that this approach might be used intermittently, allowing an "HD Holiday." Isis expects to start clinical trials in HD with ASOs sometime in the next few years.

Post-translational modification was the theme of Leslie Thompson's, PhD (UC Irvine) talk. These involved adding a molecule or protein to a target

protein, which would modify the action of the protein. Huntingtin is subject to a number of post-translational modifications including phosphorylation, SUMOylation, acetylation, caspase cleavage and histone modifications, making their enzymes potential therapeutic targets.

Xiao-Jiang Li, MD, PhD from Emory University, finished the session with an interesting analysis of how different transgenic HD animal models yield different information and neuropathological results. Therefore, it's important to utilize different types of models to truly understand the pathogenesis of HD and determine the potential of a possible therapeutic approach.

Day Two started with a focus on *clinical trials*. Karl Kiebertz, MD, University of Rochester Medical Center, explained how trials are designed – how the dosages and populations are determined and ways in which those methods can be improved. Robert Pacifici, PhD of CHDI stressed the need to understand failures, and that identifying a mechanism for a potential therapeutic is critical, as is determining whether and how a drug gets to its target, how it engages with its target and how to verify that it achieves the desired biochemical effect.



Joaquim Ferreira, MD, Institut de Medecina Molecular (Lisbon), took on the challenge of whether we are ready to conduct trials in pre-symptomatic gene carriers. He pointed out that there has been progress made in biomarker development, but that they need to be validated, and suggested that there are enough identifiable potential participants should a suitable

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substance be found by using sites in several countries. Recently, the FDA has said that it was open to utilizing validated biomarkers in the drug approval process, which would be a key factor in such a trial.

The second session of Day Two examined **biomarkers** for clinical research. Nellie Georgiou-Karistianis, PhD, Monash University, talked about the different technologies (MRI, DTI, functional MRI) that are being used, and the possibility that different neuroimaging measures may be sensitive to neurodegenerative change at different points in disease progression – and that



different parts of the brain may show changes at different times. Rachel Scahill, PhD, UCL Institute of Neurology, described the need to establish outcome measures utilizing imaging to assess the success of future therapeutics, and how these measures need to be sensitive to changes in premanifest as well as manifest participants over short and long term periods.

The need for more comprehensive cognitive assessment tools to measure clinical trial outcomes was the topic of Julie Stout's (PhD, Monash University) presentation. Ralf Reilman, MD, University of Meunster, presented his work on Q-motor (qualitative motor) assessments and how these functional improvements relate to imaging changes, and the role they will play in future clinical trials.

**Homeostasis**, the ability for an organism to regulate and stabilize its internal processes, was the topic of the second Science session of Day Two. Steve Finkbeiner, MD, PhD, Gladstone Institute (San Francisco), explained that the misfolding of proteins clearly stresses that process, resulting in neurodegeneration. To measure the changes caused by misfolding, he has

developed a robotic microscopy to examine changes in a neuron at the single cell level, which will offer insights into how this misfolding affects neuroprotection and what can be done to stabilize protein homeostasis in the face of mutant huntingtin. Danny Hatters, PhD, University of Melbourne, showed how the use of fluorescent sensors help track the oligomers being formed and the inclusions (static formations of material) they caused in cells. Disrupting this process could aid homeostasis. Advances in RNAi therapies were presented by Beverly Davidson, PhD, University of Iowa. At the present time, some RNAi can bind and regulate unintended mRNA (messenger RNA) targets, with negative results. Methods to avoid this mistargeting are being worked on through the design of new siRNAs.

Paul Muchowski, PhD, Gladstone Institute, presented a different approach to the modification of neurodegeneration in HD. HD patients have abnormalities in their immune system, and studies have shown that a manipulation of the peripheral immune system can affect neurodegeneration in mouse models of HD. By inhibiting the enzyme KMO (kynureneine, 3-mono-oxygenase) in blood cells, synapse loss and brain inflammation were decreased. More work on the relationship between blood cells and neurodegeneration in HD is underway. The attraction to this approach is that it negates the problems caused in delivering a therapy past the blood-brain barrier.

Juan Botas, PhD, Baylor College of Medicine, closed the session with a description of his work on screening potential genetic modifiers of huntingtin for neuronal dysfunction in *Drosophila* (fruit flies). These findings are compared to mouse and human genomes with the hope of identifying genetic targets for therapeutic intervention.

Session Three was themed around **systems and peripheral pathology** in HD. Maria Bjorkqvist, PhD, Lund University, Sweden, made the case that mutant huntingtin is found in every cell in the body, and that HD is clearly complicated by peripheral problems such as weight loss, osteoporosis, and gastrointestinal dysfunction. These issues should be investigated more closely to understand HD pathogenesis, and perhaps identify usable biomarkers of disease progression. Richard Faull, PhD, Dsc, University of Auckland, New Zealand presented data from his investigation of brains from people with HD, and how the evidence of stem cell proliferation correlates with cell death in the striatum

and the number of CAG repeats. The correlation between different symptoms and the pattern of cell death in the striatum and cerebral cortex suggests that neuronal stem cells may be valuable as part of a therapeutic strategy.

Normally brain neurons fire in synchrony, but in the R6/2 transgenic mouse, they don't. George Rebec, PhD, Indiana University, addressed the theory that this may be caused by glutamate transport dysfunction, through an overstimulation in the corticostriatal system. His lab has identified GLT1 as a target for upregulation (increased expression), which seems to stabilize the process and therefore could be neuroprotective. William Yang, MD, PhD, University of California, Los Angeles, showed new data using BAC transgenic mice that suggest that the first 17 amino acid domain of huntingtin may act as a molecular switch to regulate onset and disease progression.

The day ended with a wrap-up of several new HD initiatives including *HD Buzz* which is supported by HDSA (scientists writing for the lay HD audience); the Enroll-HD Study – a new international observational trial combining and updating COHORT (in the US/Canada/Australia) and Registry (in Europe) and adding a new Latin American association of sites; HD Insights, a new publication for HD researchers by the Huntington Study Group; the US NIH/NINDS Common Data Elements project, which will standardize language and other details for clinical trials and studies in the US; My-HD space, a new Australian based on-line resource for people with HD and their families, and the *Journal of Huntington's Disease*, a new peer-reviewed publication.

The final day of the 2011 World Congress on HD began with a fascinating presentation by Michael Hayden, MD, PhD, Centre for Molecular Medicine and Therapeutics, Vancouver on the **changing prevalence** of HD. New studies in Canada and the UK suggest that there are more people with HD than previously believed. Additionally, as people live longer, people with shorter CAG expansions (36-39) may become symptomatic at a later age – as suggested by the recent diagnoses of more people with very late in life onset. This could have wide ramifications on the nature of the HD population – in size and median age. Hayden also presented data on fathers with intermediate alleles passing on expanded CAG lengths to their offspring.

Mark Guttman, MD, Centre for Movement Disorders, Toronto spoke about the need to reconsider the stages

of HD and look at them as a spectrum of clinical manifestations rather than a pre-manifest/manifest paradigm. TRACK-HD and other studies identifying changes 15 years before symptom onset, and recognition that cognitive and psychological functions are often the earliest symptoms, as well as the growing belief that future treatments will begin before onset, lend credence to this thinking.

To close out the session, Elizabeth McCusker, MD, Westmead Hospital, Australia and Andrew Churchyard, MD, Cabrini Health, Australia took the assembled group through several case presentations to demonstrate the difficulties clinician's face.

Session Two began with Wayne Matson, PhD, Bedford VA Medical Center, Massachusetts, speaking on the use of **metabolomics** (the study of chemical processes involving metabolites – the products of metabolism). An individual's metabolome is a result of feedback among the genome, transcriptome (all RNAs), proteome (proteins expressed by the genome), gut microbiome (microbes in the gut) and the environment. Matson believes that by measuring these interactions, we may find valid biomarkers relating to mechanical dysfunctions such as oxidative stress, mitochondrial problems and protein aggregation.

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Blair Leavitt, MD, Centre for Molecular Medicine and Therapeutics, Vancouver talked about neuroinflammation in HD, as evidenced by the existence of activated microglia (the immune cells of the brain) seen in PET scans of the brains of people with HD – and the fact that the more severe the onset, the greater proliferation of activated microglia is seen. This suggests that targeting the microglial processes may be a valid therapeutic approach.

Current evidence shows that huntingtin affects gene expression in many genes involving many biological processes. Ruth Luthi-Carter, PhD, EPFL, Switzerland proposed that further evaluation of these relationships may lead to potential targets to detect which ones can be manipulated to improve the neuroprotective gene expression effects.

Chris Ross, MD, PhD, Johns Hopkins University, presented an overview of the work being done by the NIH/NINDS iPS (induced pluripotent stem cell) initiative. Skin biopsies of HD patients have been used to create cells that can be differentiated into neurons that very closely mimic the medium spiny neurons affected by HD. This work will greatly enhance our ability to model human HD in cell cultures and help define specific therapeutic targets, as well as the efficacy of potential therapies.

Lesley Jones, PhD, Cardiff University closed the session with a description of the differences in gene expression and behavior in different transgenic HD mouse models. Closer analyses have identified common pathways to neuronal function and intracellular signaling. Identifying the relationship between gene expression and behavior can help identify underlying molecular events in HD progression, which would yield both potential biomarkers and potential targets for treatment.

The last Science Session of the Congress featured “*late breaking*” developments. Jeff Carroll, PhD, Harvard, presented new data on metabolites in the striatum of people with HD. Bernhard Landwehrmeyer, MD, University Hospital of Ulm, Germany spoke about the failed Dimebon clinical trial, and the lessons to be learned, including the affect of the participant’s expectations on trial outcomes. Larry Marsh, PhD, University of California, Irvine, presented findings that suggest targeting chromatin (a fibrous complex of DNA and

proteins) may slow HDAC activity and therefore slow neurodegeneration. Clare Van Eyk, PhD, University of Adelaide, discussed her work in measuring the toxicity of different repeat-caused pathogenic agents in *Drosophila*, and how these may be potential biomarkers of disease progression. Jennifer Thompson, PhD, Salford Royal NHS Trust, spoke about her studies of the impact of neuropsychiatric symptoms on the quality of life in people with HD, and how these symptoms, including apathy, irritability and depression were prevalent in almost 100% of the HD population, and therefore may be a valid endpoint in future clinical trials.

Robi Blumenstein, of CHDI, closed the Congress with an impassioned plea that the role of people with HD and families must be better defined and recognized, as they are the essential element in the pursuit of therapies to delay the onset, negate symptoms and eventually cure Huntington’s disease. He called for continued work on the development of therapeutic agents and better designs for future clinical trials, but stressed that the historical developments cited by Peter Dunbar at the beginning of the Congress – the cooperation of scientists, clinicians, people with HD and families, was essential to the successful outcome of all of the efforts presented during the previous three days.

Most attendees left the Congress with a feeling of hope – that new approaches, such as research on the interaction between the autoimmune system and the brain; the expanding bank of potential biomarkers; increased international collaboration; the potential of gene silencing and the discussions regarding a “cocktail approach” to HD, all point to progress. While we don’t know as yet where the 2013 World Congress will be held, it is sure to be exciting as new developments are expected!

# HDSA Hosts Inaugural Congressional Briefing:

On Thursday, October 27, HDSA invited health staffers to our inaugural Capitol Hill Briefing, entitled “Our Genetic Future: The Congressional Role” which focused on the scientific, personal, and policy aspects of genomics, the study of the human genome.



*Hope Axelrod, Elena Keydel, Peggy Tighe, Dr. Christopher Ross, Eric Gascho and Louise Vetter*

The briefing was very successful and was attended by 86 Congressional Health staffers who work closely with members of Congress on the many health-related issues that touch the lives of their constituents every day. Offices represented spanned the nation and included Bachmann (MN), Casey (PA), Durbin (IL), Harkin (IA) and other members of the HELP (Health Education, Labor and Pensions) and Ways & Means Committees, which are two of the committees of jurisdiction for the Huntington’s Disease Parity Act.

Our champions in the House lent their support by providing staff assistance, spreading the word about the briefing and opening the session. Rep. Brian Bilbray welcomed all with an impassioned speech about the importance of investing in science and the need for the public and private sectors to work together. Elena Keydel, Chief Aide to Congressman Bob Filner, welcomed the group on behalf of the Congressmen and promoted the Huntington’s Disease Parity Act (H.R. 718). Louise Vetter, HDSA Chief Executive Officer, hosted the event and provided an overview of the milestones in the field of genomics that set the tone for subsequent speakers.

Eric Gascho from the National Health Council, an agency of which HDSA is a member and with whom we partner on issues concerning chronic diseases, spoke about the challenges and economic benefits in developing personalized medicine using biomarkers as an example; Dr. Christopher Ross, a clinician and researcher, as well as the co-director of the HDSA Center of Excellence at Johns Hopkins University then offered insight into the opportunities that advances in the world of genomics offer using HD as a model for other neurodegenerative diseases; Hope Axelrod, the HDSA Metro DC Chapter social worker, also used HD as an example of a genetic disease and spoke about the factors that influence the decision making process for at risk individuals; and Peggy Tighe, from Strategic Healthcare, reminded the staffers about the Congressional role in genomics, including oversight, funding, and legislation.

Our thanks to our lead sponsors, Reps. Filner and Bilbray in the House and Kirsten Gillibrand in the Senate for their support of this event and a special thank you to our advocates who wrote almost 1,000 e-vites to their Members of Congress.



*Rep. Brian Bilbray (R-CA)*



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