**FEATURE ARTICLE**

By Tim McClean, Clinical Operation Manager of EHDN, West Linton, UK

**EHDN Clinical Trials Update**

A primary objective of the European Huntington’s Disease Network (EHDN) is to provide the infrastructure for high-quality, definitive clinical trials of potential therapeutics for Huntington’s disease (HD). With the successful completion of two trials, EHDN has succeeded in establishing the resources and experience required to fulfill this function.

This article gives a brief overview of clinical trials conducted by EHDN sites, including those recently completed, those currently enrolling patients, as well as those in the start-up phase (see Table). This overview provides an introduction to a regular article in the EHDN News that will report updates on clinical trial developments and summaries of results.

I. Recently completed clinical trials

**Horizon**

The clinical trial results most recently announced, and perhaps most eagerly awaited, were those of the Horizon trial, in which the efficacy and safety of the drug Dimebon (generic name: latrepirdine) were tested in patients with manifest HD. A total of 403 HD patients with some degree of cognitive impairment were recruited at 64 sites across eight countries in Europe, North America and Australia. Patients received either 60 mg Dimebon or placebo daily for 26 weeks. The results, which were announced in April of this year, showed that there were no statistically significant improvements.
for the Dimebon group relative to the placebo group on either of the co-primary endpoints, Mini-Mental State Examination (MMSE) and the Clinician’s Interview-Based Impression of Change, plus caregiver input (CIBIC-plus).

Unfortunately these results were unequivocal and therefore, no future research into Dimebon as a treatment for HD is planned. Clearly this is a disappointing outcome for the HD community as well as for the co-sponsors of the study. Indeed, Medivation is withdrawing from HD research, although Pfizer has not ruled out further HD-related research activities.

Despite the disappointing outcome, there were a number of positive aspects to the study, including the successful delivery of quality data within agreed timelines by 64 HD centres and 403 HD patients, many of whom were convinced of the benefits gained from their clinical trial participation. Further analyses of the results will tease out any factors that should be taken into account when designing future HD clinical trials. Full results will be reported at the HD World Congress in September 2011.

**MermaiHD**

Positive results are being reported for the dopamine stabiliser drug Huntexil® (also known as ACR-16 or pridopidine) by the company NeuroSearch. You may recall the promising results from the European Phase III study (MermaiHD) reported in the June 2010 edition of EHDN News. In brief, the results showed a trend toward an improvement in the modified UHDRS motor scale (m-UHDRS1-M) after 26 weeks of treatment with the highest dose of Huntexil® (90 mg/day), although this was not statistically significant. Improvements in the secondary endpoints (total UHDRS-M score, dystonia and eye movements) did however reach statistical significance. These results were later confirmed by the North American HART study, a dose range-finding Phase IIb study in which patients were randomly allocated to one of three doses of Huntexil® (22.5, 45 or 90 mg/day) for only 13 weeks. The results were similar to the European study, showing a trend towards a dose-related improvement in the m-UHDRS-M score, although, once again, this did not reach statistical significance.

Following recent advice from the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA), NeuroSearch is planning a further Phase III confirmatory clinical trial. This is likely to be a large multinational study with Total Motor Score (TMS) as the primary endpoint. Additional supportive measures of clinical relevance will also be included to characterise the overall benefit/risk assessment. The timing of this study will be announced later this summer.

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1 Unified Huntington’s Disease Rating Scale
II. Ongoing Clinical Trials

AFQ056
As a potential treatment for chorea, the mGluR5 receptor antagonist AFQ056 is currently being tested in a Phase II randomised double-blind, placebo-controlled, dose titration proof-of-concept study sponsored by Novartis Pharmaceuticals. HD patients are being recruited at eight EHDN centres across Germany and the UK. Primary outcome measures are the efficacy of AFQ056 on the severity of chorea as measured by the UHDRS maximal chorea score.

III. Clinical Trials currently in set-up phase

SEN0014196
Preparatory work is ongoing for a Phase II study of SEN0014196, a selective inhibitor of the deacetylase Sirtuin 1 with potential HD modulating activity. This is primarily a safety and tolerability study but will also include cognitive, motor and behavioural assessments of efficacy. The sponsor, Siena Biotech SPA, is working with the support of EHDN to set up this study in 18 sites across Germany, Italy and the UK, whereby 140 patients will be recruited into one of three treatment groups. An update on status and timelines will be included in the next issue of EHDN News.

Elontril
Also in the set-up phase is the investigator-led Phase II study of the selective dopamine and norepinephrine reuptake inhibitor Elontril (generic name: bupropion).

This drug is to be assessed for the treatment of the symptoms of apathy in HD patients. Forty patients at four German sites will be recruited into one of two groups receiving either bupropion at a dose escalated to 300 mg per day or placebo. After 10 weeks of treatment and a short washout period, all patients will cross over into the other group for a further 10 weeks of treatment. The primary objective will be to assess the effect of active treatment compared with placebo using the Apathy Evaluation Scale – Informant (AES-I). Secondary objectives include an assessment of the change of ventral striatal and ventromedial prefrontal activation in response to a reward paradigm as quantified by functional magnetic resonance imaging (fMRI). The study is scheduled to start recruitment this summer.

More information on these, and any future EHDN-endorsed clinical trials, will be included in a regular EHDN Clinical Trials Update in subsequent editions of EHDN News.

Successful Launch of REGISTRY version 3

REGISTRY version 3 (R3) was successfully launched on 23 June 2011. To learn more about R3, attend one of the webinars that are being offered from June to September 2011 or contact your Language Area Coordinator. A catalogue of frequently asked questions (FAQs) about R3 is provided at https://www.euro-hd.net/html/registry/docs/r3_faq. More information on case report forms and how to enrol participants into R3 can be found at https://www.euro-hd.net/html/registry. You may also send any queries about R3 to info@euro-hd.net.
PLoS Currents: Huntington disease – a new platform for rapidly sharing data
Gillian Bates (King’s College London, UK) and Patrick Reilly (Publications Manager, Public Library of Science, UK)

PLoS Currents – rapid publication of new research
The publication of scientific studies in conventional journals can be a long process. PLoS Currents aims to reduce the time from submission to publication from months to days. The first section, ‘PLoS Currents: Influenza’, was launched in 2009 in response to the influenza pandemic. Three more PLoS Currents sections were launched in 2010, including PLoS Currents: Huntington disease (HD). Articles published in PLoS Currents are:
- Peer-reviewed by experts
- Citable and assigned a DOI
- Archived in PubMed central
- Included in PubMed
- Open access

Why PLoS Currents: Huntington Disease?
The scientific and clinical HD research communities generate a large amount of data that is not in the public domain because the hurdle to publication is too high. To accelerate the search for disease-modifying treatments, there is a clear need for a platform through which these data can be rapidly shared. PLoS Currents: HD aims to remove the barriers to publication of such data.

Types of articles and criteria for acceptance
Submissions may include:
- Research findings including those reporting negative results or outcomes
- Short reports presenting results or observations of interest
- Pilot studies/small scale analyses
- Results that confirm/contradict published studies
- Data sets e.g. transcriptional arrays
- Other categories as suggested by HD community

All scientifically sound manuscripts will be published, and emphasis should be placed on data presentation rather than interpretation. PLoS Currents: HD does not publish review articles.

Submission and review process
Authors submit to PLoS Currents: HD through Google knol (http://currents.plos.org/hd). It is possible to include videos. The Editors (Gill Bates, Mike Levine and Sarah Tabrizi) establish that the submission is within the scientific scope, and then select members of the Review Board to evaluate the work. If the review process identifies scientific flaws, these must be fixed or the paper will be rejected and, similarly, inaccuracies or inconsistencies must be corrected. The reviewers will not ask for more experiments to be performed, although they may suggest improvements, the implementation of which is at the discretion of the authors. Once a revised version has been accepted, the article is immediately published in PLoS Currents, transferred to PubMed Central and PubMed, and given a stable identifier for citation purposes. The process is simple and therefore, there are no publication charges to authors.

PLoS Currents articles can also be updated. Revised versions are submitted and reviewed as before and then published alongside the original version. Comments can be posted on the articles by the scientific community after publication.

Call to action
The Editors and Review Board are committed to maintaining a rapid review process and encourage you to submit new findings. For more information, please contact Patrick Reilly (preilly@plos.org).

July 2011 · Issue 14
Strategic Scientific Plan – the onset of a new cycle

Joaquim Ferreira, Science Director of EHDN, Lisbon, Portugal

Scope
In December 2010, the Executive Committee of the European Huntington’s Disease Network (EHDN) proposed the development of a Strategic Scientific Plan for the period 2011-15. Hence, an Advisory Committee chaired by Joaquim Ferreira was established. This initiative comes at a time when EHDN is becoming a well-consolidated European organisation able to offer a network of clinical centres for HD patients, as well as to design and conduct high-quality preclinical and clinical research. At an international level, EHDN is in the privileged position of becoming a leader in HD research able to define the scientific and regulatory standards that will shape the development of HD therapeutics.

Objectives
The Strategic Scientific Plan aims to improve the quality and efficiency of research activities within EHDN and to re-focus them on the main mission of EHDN. In practice, this represents an explicit move from the initially adopted ‘bottom-up’ strategy to a ‘top-down’ approach.

Process
The research activities and achievements of EHDN (2004-2010) were reviewed. This was followed by open discussions with the Lead Facilitators of EHDN Working Groups (WGs), members of the Scientific and Bioethics Advisory Committee and Principal Investigators of REGISTRY. A planning meeting took place in London in March 2011, during which it was decided that (1) the development of this Strategic Plan should be in accordance with the EHDN mission and (2) the current EHDN structure should be appropriate to support a set of realistic actions and activities. All WGs have been requested to define concrete goals and initiatives for the next five years.

Preliminary proposals
The priority objectives for the period 2011-15 will focus on the improvement of health outcomes for HD patients and the design and conduct of good-quality clinical trials. Specific strategies with explicit timelines will be defined. A Scientific Planning Committee and a Clinical Trials Task Force will be established. Strategies for funding research within EHDN were discussed. These include the continuation of seed funding to facilitate innovative pilot studies as well as other proposals for funding specific WG activities. As a new venture, EHDN should strive for a pioneering role in innovative areas of research which could benefit from the structure and type of data gathered via EHDN, for example mathematical biosciences. The Strategic Plan will also address research training and communication, as well as develop mechanisms for improving scientific governance. In particular, EHDN aims to improve the scientific output of the network (science managing, science writing, editing, biostatistical support, etc.).

Conclusions
The implementation of this Strategic Scientific Plan will realign old objectives and define new directions for EHDN, embedded in the dedicated commitment of its active members. The Plan is still under discussion. All inputs are welcome and should be sent to Joaquim Ferreira (joaquimjferreira@net.sapo.pt).

1 The committee is composed of Joaquim Ferreira, Bernhard Landwehrmeyer, Jean-Marc Burgunder, Raymund Roos, Ralf Reinmann, Sarah Tabrizi, Anne-Catherine Bachoud-Lévi and Michael Orth.
REGISTRY 3.0 and lifestyle factors in Huntington’s disease

By Susana Pro Koivisto, Associate REGISTRY Project Manager, Oslo, Norway

Background

Studies using Huntington’s disease (HD) mouse models as well as findings from other neurodegenerative disorders (Alzheimer’s disease and Parkinson’s disease) have shown that an active lifestyle and enriched environment can delay the onset of symptoms in these diseases. Similarly, a study conducted in Australia and New Zealand showed that avoiding a passive lifestyle may delay the onset of HD symptoms by several years.

Lifestyle Sub-Study

Prof Martin Delatycki and Dr Kaye Trembath from the Murdoch Children’s Research Institute, Melbourne, Australia, are the lead facilitators of the EHDN Environmental Modifiers Working Group and have proposed and developed the Lifestyle Sub-Study that has been incorporated into REGISTRY version 3.0. The aim of this retrospective study is to assess the impact of lifestyle factors on age at onset in early-stage HD patients. It will also determine whether the outcomes of the study carried out in Australia and New Zealand can be replicated in a culturally and ethnically different European cohort.

The assessment protocol consists of (1) the Lifestyle Activity questionnaire, (2) the DUREL (Duke University Religion Index) self-report questionnaire, (3) the UHDRS Motor assessment, (4) measurement of the length of the CAG repeat and (5) general and clinical characteristics of the participant. The data will be collected via a single interview of eligible HD participants in stage I (TMS1 > 5; TFC2 = 11–13) or stage II (TMS > 5; TFC = 7–10). The cohort that will be monitored consists of 200 participants from selected sites across the UK, German-speaking countries and Italy. Contributing sites will be automatically informed of potential REGISTRY participants via the EHDN IT system.

Lifestyle Activity Questionnaire

This questionnaire collects information about lifestyle factors such as education, occupation and employment, interests and activities, as well as home duties and related activities. The Lifestyle Activity Questionnaire takes approximately 20-25 minutes to administer. Assistance from family members and/or carers is appreciated in order to ensure that the information collected is as accurate as possible. Training for interviewers will be provided through guidelines, a training video and WG training sessions. The Environmental Modifiers WG held a training session for those involved in the Lifestyle Sub-Study in London in May 2011.

The Lifestyle Sub-Study will be administered as part of REGISTRY version 3.0 from July to December 2011 at 14 different sites. The information collected will be used to develop a cross-sectional prospective study of lifestyle factors with the aim of providing individuals who are ‘at risk of HD’ and in the ‘premanifest’ phase with lifestyle strategies that may delay the onset of symptoms by several years.

Sub-study coordinators, Marleen van Walsem, marleen.walsem@euro-hd.net and Joaquim Ferreira, joaquimferreira@net.sapo.pt

1 TMS = total motor score
2 TFC = total functional capacity
What is the impact of education on Huntington’s disease?

Education does not delay the onset of Huntington’s disease, but ameliorates the impact of symptoms in motor, cognitive and behavioural domains.

Background
The length of the expanded CAG repeat in the HTT gene is the most important factor in determining age at onset and disease severity in Huntington’s disease (HD). However, there are other contributing factors that act as both genetic and environmental modifiers. Environmental enrichment has been shown to delay disease onset and slow progression in mouse models of HD. In Alzheimer’s disease, the level of education early in life plays a crucial role in cognitive deterioration late in life. Furthermore, the prevalence of Alzheimer’s disease is lower in highly educated people. Such a correlation has not yet been studied in HD. This study investigated the relationship between years of education and both the age at onset and the severity of symptoms in HD patients.

Subjects and methods
The authors used multiple linear regression analysis to examine the impact of education on both the age at onset and disease severity in 891 manifest HD patients participating in REGISTRY. Patients were recruited at 66 EHDN study sites from 13 European countries. Subjects were divided into two groups: those with ≥ 10 years of education and those with < 10 years, which represents the end of obligatory secondary school education in Europe. The age at onset was estimated retrospectively by experienced clinicians. Disease severity was rated using four components of the UHDRS\(^1\), assessing motor performance, cognition, behaviour and functional capacity. The model was adjusted for CAG repeat length and age at the time of assessment.

Results
The group with ≥ 10 years of education had an earlier age at onset than the group with lower education (mean of 2.7 years earlier; \(p < 0.001\)). Surprisingly, patients without a family history of HD had an age at onset of 7.2 and 9.1 years later than those with a recognised affected mother or father respectively, despite small differences in the CAG repeat length.

After adjusting for age at assessment and number of CAG repeats, patients with ≥ 10 years of education had:
- better motor performance (-3.6 in UHDRS-motor; \(p = 0.006\))
- better cognitive function (+27.0 points in UHDRS-cognitive; \(p < 0.001\))
- better behavioural status (-3.0 in UHRDS-behavioral; \(p < 0.001\))
- better functional capacity (+1.1 points in UHRDS-functional capacity; \(p < 0.001\)).

The beneficial effects of education on the clinical scores of the four subscales persisted in all four quartiles of the disease, indicating that they were not diminished by disease severity (see figure).

Conclusions
These findings suggest that education may be an environmental modifier in HD. The earlier estimated age at onset in patients with higher education may result from an earlier recognition of the first symptoms in this patient group. Importantly, education improved the clinical scores in all domains independently from CAG repeat length and age.

\(^1\) Unified Huntington’s Disease Rating Scale
Early changes in the hypothalamic region in prodromal Huntington disease revealed by MRI analysis

Charlotte Soneson et al., Neurobiology of Disease (2010), 40: 531-543

Alterations in grey matter content in the hypothalamic region occur at least a decade before clinical diagnosis in Huntington’s disease.

Background

In addition to the apparent motor, cognitive and behavioural symptoms that are characteristic of Huntington’s disease (HD), other subtle changes occur both in premanifest and manifest HD. They include changes in body functions that are regulated by the hypothalamus, a region of the brain that releases specific neurohormones and regulates certain physiological processes, such as sleep, circadian cycles, appetite and energy metabolism.

Recent studies have shown that there is atrophy of the hypothalamus in early-stage HD patients as well as in transgenic HD mice. Several other signs of hypothalamic dysfunction in early HD have also been described in the literature. The authors of the present study hypothesised that changes in the hypothalamus could be detected prior to disease onset in premanifest HD gene mutation carriers, and that the changes would correlate with different estimated times to clinical diagnosis.

Subjects and methods

Participants were recruited from PREDICT-HD, a multinational study of predictors of HD onset. A total of 220 premanifest HD mutation carriers were stratified by the predicted time to clinical diagnosis into three groups: preHD<sub>near</sub> (<9 years), preHD<sub>mid</sub> (9-15 years) and preHD<sub>far</sub> (>15 years). Control subjects were selected from the same cohort and matched for age and gender. All subjects had 1.5 tesla MRI scans. Images were analysed by voxel-based morphometry (an automated technique for statistical comparisons of tissue composition between groups) and logistic regression models.

Results

Significant changes in local grey matter content were detected in different brain regions in all preHD groups compared to the control group. In particular, changes were seen in the caudate nucleus, insula and hypothalamus, and to a lesser extent in the cerebral cortex and cerebellum. Most of these changes reflected grey matter atrophy (see figure).

The preHD<sub>near</sub> and the preHD<sub>mid</sub> groups were well discriminated from the control group for all brain regions studied as well as for comparisons of whole-brain volume. By contrast, only measures of the hypothalamus, caudate nucleus and whole brain were able to distinguish between the preHD<sub>far</sub> and the control group. This suggests that changes in the hypothalamus and caudate nucleus are part of the very early pathological events in HD. Notably, the caudate nucleus, hypothalamus and insula were the best regions by which the preHD groups could be distinguished from each other, suggesting that disease progression could be tracked using structural MRI of these areas. A combination of all five regions yielded a better classification accuracy (except for the comparison preHD<sub>far</sub> vs. preHD<sub>near</sub>, where caudate nucleus alone was superior).

Conclusions

This is the first study to show that changes in grey matter content in the hypothalamic region occur in premanifest HD as early as 16 years before clinical diagnosis. These findings may explain some of the non-motor symptoms observed in HD. They may also provide a useful source of imaging biomarkers for future clinical trials.

<sup>1</sup> Magnetic Resonance Imaging
An antisense CAG repeat transcript at the \textit{JPH3} locus mediates expanded polyglutamine protein toxicity in Huntington’s disease-like 2 mice

Brian Wilburn et al., Neuron (2011) 70: 427-440

A new transgenic mouse model reveals common pathogenic mechanisms between Huntington’s disease and Huntington’s disease-like 2.

Background

Huntington’s disease-like 2 (HDL2) has a broad phenotypic overlap with Huntington’s disease (HD), including adult onset of similar symptoms (chorea, dystonia, rigidity, bradykinesia, psychiatric symptoms and dementia) and the presence of nuclear inclusions (NIs) in brain tissue. However, HDL2 is caused by a CTG/CAG repeat expansion in the alternatively spliced exon 2A of the \textit{Junctophilin-3 (JPH3)} locus on chromosome 16. On the sense strand, three alternatively spliced variants place the CTG expansion into either a polyleucine or polyalanine open reading frame, or into a 3’ untranslated region. Foci containing the \textit{JPH3} mRNA carrying CUG repeats are also found in the brain of HDL2 patients. Hence, until now, the reason for the clinical similarity between both diseases has been unclear.

Results

The authors generated mice transgenic for a bacterial artificial chromosome (BAC) carrying the human \textit{JPH3} locus with an expansion of 120 CTG repeats. Following genetic, neuropathological and behavioural characterisation of the BAC-HDL2 mice in comparison to wild-type and other transgenic lines, they found that

• BAC-HDL2 mice showed motor deficits in the rotarod assay that were age-dependent and increased over time
• BAC-HDL2 mice developed a selective forebrain atrophy
• NIs were present in the brain of BAC-HDL2 mice with a distribution similar to that found in HDL2 patients
• the formation of NIs was progressive and their size increased with time
• CUG RNA foci were found in the cortex of BAC-HDL2 mice.

Surprisingly, the NIs were immunostained with two different polyQ-specific antibodies, indicating that they contained expanded polyQ proteins. Disease pathogenesis was dependent on the CTG repeat expansion. The polyQ protein found in NIs was made from a CAG repeat-containing transcript emanating from the antisense strand of the CTG repeat of \textit{JPH3}, with its expression driven by a promoter located upstream of the CAG repeat. However, polyQ pathogenesis was independent of the production of the \textit{JPH3} protein and the CUG transcripts that are both encoded by the sense strand. Therefore, expression of the antisense CAG transcripts alone was sufficient to elicit disease pathogenesis.

A model for pathogenic mechanisms in HDL2. Mutant HDL2-CAG protein made from the antisense expanded CAG transcript is transported into the nucleus to form NIs consisting of polyQ protein, ubiquitin and, at a later time point, CBP.
As well as polyQ protein, the NIs contained the transcriptional factor CBP\(^1\), which aggregated in a time-dependent manner after the formation of the ubiquitin/polyQ aggregates. Furthermore, transcription of *Bdnf*\(^2\) was reduced in the cortex of BAC-HDL2 mice due to a selective reduction in the amount of CBP bound to *Bdnf* promoter IV. A decrease in histone H4 acetylation (a marker of transcriptional activation) was also detected.

\(^{1}\) CREB Binding Protein  
\(^{2}\) Brain-Derived Neurotrophic Factor

**Conclusions**

The expression of an expanded polyQ protein encoded by the antisense strand of *JPH3* is involved in HDL2 pathogenesis, thus unveiling common pathogenic mechanisms between HD and an HD-like disorder. Transcriptional dysregulation due to sequestration of CBP into polyQ aggregates is likely to be another common feature between HD and HDL2 (see figure). This provides evidence that therapeutics targeted at reducing polyQ toxicity could ameliorate both diseases.

**Upcoming Meetings 2011/2012**

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<td><strong>2011</strong></td>
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<td>Sept 24</td>
<td>Russian EHDN Site Investigators Meeting, venue to be confirmed</td>
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<td>Oct 9-14</td>
<td>14th European Congress of Neurosurgery, Rome, Italy</td>
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<td>Oct 20-23</td>
<td>7th International Congress on Vascular Dementia, Riga, Latvia</td>
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<td>Nov 3</td>
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| **2012**   |                                                                       |                                                  |
| Nov 12-17  | 20th World Congress of Neurology, Marrakesh, Morocco                   | [http://www2.kenes.com/wcn/Pages/Home.aspx](http://www2.kenes.com/wcn/Pages/Home.aspx) |
| Dec 11-14  | XIX World Federation of Neurology World Congress on Parkinson’s Disease and Related Disorders, Shanghai, China | [http://www2.kenes.com/parkinson/Pages/Home.aspx](http://www2.kenes.com/parkinson/Pages/Home.aspx) |
| Feb 22-23  | 8th Annual Update Symposium on Clinical Neurology and Neurophysiology, Tel Aviv, Israel | [http://www.isas.co.il/neurophysiology2012](http://www.isas.co.il/neurophysiology2012) |
| June 9-12  | 22nd Meeting of the European Neurological Society, Prague, Czech Republic | [http://www.congrex.ch/ens2012](http://www.congrex.ch/ens2012) |
| Sept 14-16 | EHDN 2012, 7th EHDN Plenary Meeting, Stockholm, Sweden                |                                                  |
| Nov 6-10   | 62nd Annual Meeting of the American Society of Human Genetics, San Francisco, CA, USA | [http://www.ashg.org/2012meeting/](http://www.ashg.org/2012meeting/) |