ACCELERATING TOWARDS A CURE

2019 HCU Network America Conference | Indianapolis, IN

Contents – Outline of Report

A copy of the conference program, recording of the speaker conferences and panels, conference handouts, pictures from the conference, as well as, interviews can be found on our conference website: https://hcunetworkamerica.org/2019-conference

Introduction

Individuals with homocystinuria and related disorders have a tremendous need for enhanced awareness, education, networking opportunities, reassurance of management approaches available today and hope for even better therapies in the future.

Accelerating Towards a Cure, HCU Network America's patient/family conference took place in Indianapolis, Indiana on October 19-20, 2019. Our second conference was organized specifically for individuals with homocystinuria and associated disorders and their families. The main objective of the conference was disseminating sound information regarding best practices and research to effectively manage Homocystinuria. This was achieved through patients and caregivers sharing their experiences, healthcare professional's presentations, breakout sessions led by healthcare professionals, and HCU Network America and industry sharing information on research underway for new therapies in the future.

The second goal of our conference was to strengthen the dialogue between patients, caregivers and family members. Providing an opportunity for them to socialize, share information and best practices and realize they are not alone in this journey is a very important part of the process.

Accelerating Towards a Cure for HCU brought together 19 industry leaders and vendors, 4 medical professionals and over 80 patients, caregivers and relatives from all over the country.

This report presents an overview of the conference and provides a brief synopsis of the information each speaker or panel provided.

Participants

Speakers, Panelist and Breakout Leaders

Speakers:

Marcia Sellos-Moura: Senior Vice President, Orphan Technologies
Dr. Kimberly Chapman: Metabolic Clinician, Children's National Hospital, Washington DC
Katie Sapp: Genetic Counselor, Indiana University Health Physicians | Riley Children's Hospital
Margie McGlynn: President, HCU Network America

Panel:

Moderator: Mark Lewis, Director, HCU Network America
Metabolic Clinician: Dr. Kimberly Chapman, Children's National Hospital, Washington DC
Genetic Counselor: Katie Sapp: Indiana University Health Physicians at Riley Children's Hospital
Dietitian: Abby Hall: Indiana University Health Physicians at Riley Children's Hospital
Parent: Rachel Skeens
Patient: Benjamin Lewis

Breakout Leaders:

Birth through Age 4: Dr. Kimberly Chapman, Children's National Hospital, Washington DC
Elementary: Abby Hall, Indiana University Health Physicians at Riley Children's Hospital

High School: Danielle Drake, Indiana University Health Physicians at Riley Children's Hospital
College and Beyond: Katie Sapp, Indiana University Health Physicians at Riley Children's Hospital

Key Organizers:

Danae' Bartke: Conference Organizer, Executive Director of HCU Network America
Amber Gibson: Food and Beverage Organizer and low protein chef

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Conference Outline

The two day conference commenced with a casual dinner meet-up on Friday evening. The intention of the meet-up was to allow conference goers the opportunity to connect and get to now each other before the conference began.

The first day of the conference was designed to help attendees better understand how homocystinuria affects patients and how to better manage the diagnosis. The speakers we selected provided the audience with information on The Natural History Study, Best Practices in Treatment of HCU and Screening Family Members for Homocystinuria and Family Planning. The breakout session allowed families and patients to take a further look into aspects on homocystinuria by age group and learn how to better manage some of the specific issues that come with each age group. The content shared on the first day was meant to paint a better understanding of the possible effects of homocystinuria and the best practices in how to prevent any clinical issues.

The second day of the conference focused on research and development that is currently underway for homocystinuria. The speakers selected were able to provide the most up-to-date information on the therapies in the pipeline by giving us an overview of Therapies on the Horizon, and a more in-depth look at OT-58 and AEB4104. Also, on day two, we awarded the second HCU Hero Award posthumously to Dr. Jan Kraus for his commitment and contributions to the HCU Community. We made particular note that because of Dr. Kraus's work, OT-58 is not just a dream, but a reality! The day was then closed with an Ask The Expert Panel where audience members could ask patient, parent and medical professionals crucial questions they still may have.

The sessions were recorded with the intent of archiving them to serve as educational resources for the overall homocystinuria community. In addition to the recorded sessions, we interviewed 4 patients from the HCU Community. By sharing their stories, we are reminded of the shared humanity which helps strengthen our bonds and build understanding and awareness. You can find these recordings on the 2019 conference page on our website, as well as, our YouTube Channel.

Summary of Presentations

Day 1: Homocystinuria Effects and Management

Natural History Study Update – Marcia Moura-Sellos

In 2016, Orphan Technologies initiated the first comprehensive longitudinal, prospective natural history study for classical homocystinuria. The study provides novel insights into the clinical course of patients with classical homocystinuria on current therapy.

Marcia briefly walked us through the biochemical pathway of classical homocystinuria and an overview of the systems affected by homocystinuria to help lay the groundwork for her presentation. She then touched on the original natural history study led by Dr. Harvey Mudd, noting there has been significant progress since the study had been published in 1985. Orphan Technologies initiated the current natural history study (NHS) to understand how the current treatments and

therapies of Homocystinuria affect patient outcomes, with the hope to persuade regulatory bodies that patients need better options for therapies.

The Natural History Study has 58 patients from 8 different sites in 3 countries, with the majority of the patients living in the US. Patients in the study undergo several tests every 6 months, with the initial visit serving as a baseline. The Natural History Study looks in detail at patients' medial history, liver function, inflammation, sulfur amino acids, cardiovascular and osteoporosis biomarkers, bone density, executive function, eye health and growth and development. It is believed that the majority of patients in the study make every effort to follow their prescribed treatment, despite it's difficulty.

The initial data indicates that significantly less patients are having their lenses dislocate than in the 1985 study, but many still suffer from Myopia. Like the original study, the majority of patients still have significantly elevated homocysteine and methionine levels. Through DEXA scans, which is a bone density test, the study also showed that patients had skeletal fragility. The patients are also subjected to the NIH Toolkit to measure cognition, which shows that patients with lower methionine and total homycsteine levels have better cognition. Patients with higher levels struggled with the ability to focus and control impulses– which presents as ADHD like symptoms.

Marcia admits that the data is biased towards the patients who are most engaged and trying to follow diet, but the data still proves that patients need better therapy options based upon the initial study outcomes.

Best Practices in Treatment of HCU – Kimberly Chapman

Dr. Kimberly Chapman is a Metabolic Geneticist at Children's National Hospital, DC and a board member for HCU Network America. She was a member of the E-HOD Guidelines Committee and was responsible for gathering the data from a review of scientific literature that led to the Guidelines for Diagnosis and Management of Cystathionine Beta-Synthase (CBS) Deficiency that was published in the 2017 Journal of Inherited Metabolic Disease.

Dr. Chapman started with a brief explanation of E-HOD (European Network and Registry for Homocystinurias and Methylation Defects), and their goal to find the best clinical practices by assessing the current data. She noted the best paper in their review of over 1,000 papers was Dr. Mudd's paper from 1985 and she believes there still isn't much known about Homocystinuria. Dr. Chapman then briefly walked us through the biochemical pathways of the homocystinurias, what homocystinuria is and then focused on a type of homocystinuria called Cystathionine Beta-Synthase (CBS) Deficiency, or classical Homocystinuria. She then went into detail about the affected systems, total homocysteine v. free homocysteine, and the total homocysteine goal for pyridoxine responsive and non-pyridoxine responsive patients. After defining the goal, she then explained the process of how your doctor will determine if you are pyridoxine responsive, and based on that assessment, what medications you would need and what the diet looks like. She then explained that prevention is key to avoid cognitive delays, psychiatry disorders and thrombosis. She also talked about the importance of taking the necessary preventative steps when planning surgery or pregnancy. She closed by talking about what your clinic visit should look like.

Screening Family Members and Family Planning – Katie Sapp

For the past 10 years, Katie Sapp has worked as a genetic counselor at Indiana Univeristy Health Phyiscians and Riley Children's Hospital in Indianapolis. She has provided genetic counseling services as part of the multidisplinary clinic with all types of inborn errors of metabolism, including those with positive newborn screens.

She started her presentation with a breif explanation of what Newborn Screening is and how states decide what is on the list of diseases they check for. She noted, that the primary goal of newborn screening is to identify children with treatable conditions before they are pre-symptomatic. With that goal in mind, she pointed out that newborn screening takes place between 24-48 hours after the baby is born, ideally before the mother and child are discharged from the hospital. She noted that homocystinuria newborn screening does not look at homocysteine levels, but rather methionine and that is due to technical issues measuring homocysteine. This approach also creates issues because methionine levels don't always rise fast enough for that 24-48 hour time window. Newborn screening labs should be adjusting their methionine cut off's to maximize the validity of the test.

Katie then reviewed basic genetics, reminded us that everyone should have a complete set of 46 chromosones, with 23 pairs – the last pair of chromosones determing sex, either XX (Female), or XY (Male). The CBS gene is located on chromosone 21. She explained that Homocystinuria is an autosomal recessive disorder, which means the child has received one copy from mom and one copy from dad that is changed or defective so they can't produce normal CBS enzyme. Each time that 2 parents who are carriers have a child, there is a 25 % chance of that child having homocystinuria, a 50% chance there are a carrier and a 25% change they have 2 normal genes.

"She then discussed the recurrence risk of homocystinuria in family members and who should be screened if there is a known case of homocystinuria. For full siblings of patients that were diagnosed later, not through newborn screening, she says they should be screened with a simple homocysteine test. If the homocysteine test comes back elevated, then they proceed with a genetic test to confirm diagnosis. For siblings of those diagnosed through NBS, it may not be "medically necessary" to screen them if they were tested in the same state with the same technology, since If one sibling is picked up by NBS, we would expect the others to be as well. However, many parents may want to test other siblings for confirmation. Parents and extended relatives who don't exhibit symptoms do not need to be screened – they have a greater risk to be a carrier, which has an incidence rate of 1 in 250. Siblings of the parents who plan to have children should also undergo carrier testing. If they come back as a positive carrier, then their partner should also be screened so they understand the probability of having a child with HCU."

Katie then closed by speaking about the various forms of carrier testing and their pros and cons and what the test means for extended family. She spoke about known mutation testing (looking for a specific mutation that a family member has), gene sequencing (looking for any mutatation that may be on a speicif gene), and expanded carrier panel testing (looking for carrier status for several genetic defects). She noted that expanded carrier panel testing is great because it includes a large variety of genes and is very cost effective, though if you are looking for a specific mutation due to a family history then you need to make sure that mutation is on the panel. To decide if carrier testing is right for you, schedule an appointment with a genetic counselor – they can also help assist in getting the test ordered and helping you understand your results.

Breakout Sessions: By age group

Patients, parents and other relatives had the opportunity to attend breakout sessions by age group. The first group was 0-4 years old, which was led by Metabolic Clinician, Dr. Kimberly Chapman. The next group was for 5-12 year olds and was led by Metabolic Dietitian, Abby Hall. The last 2 groups, 13-18 year olds and College and beyond combined together for a joint session. The joint session was led by Metabolic Dieitian Daniel Drake (Indiana Univeristy Health Physican's at Riley Children's Hospital) and Genetic Counselor, Katie Sapp.

In these sessions, patients and families were able to discuss specific issues that related to their age group and the medical professionals (along with other patients/families in attendance) were able to offer support and advice to better understand and tackle the issues. This time allowed families to gain a better understanding and helped give peace of mind with their diagnosis and treatment.

Therapies on the Horizon – Margie McGlynn

Margaret (Margie) McGlynn is the President of HCU Network America, a patient advocacy organization she co-founded to provide support for patients and families affected by homocystinuria. She is also the President of the Hempling Foundation for Homocystinuria Research, a fund she established to support research on new therapies for HCU in honor of her late sisters, Judy and Susie Hempling.

Margie opened up with a quick reminder of where the error in the Cystathionine Beta-Synthase (CBS) pathway can be found. This reminder was the groundwork for her to be able to then share 5 novel approaches for HCU that are underway that affect different aspects of the cyle: Enzyme Replacement Therapy, Gene Therapy, Alternative Enzymes, CBS activation/stabilization and Metabolic Pathway Modification. Margie showed a slide demonstrating how those therapeutic approaches fit in with the pathway. She then described each of the various approaches, the companies and researchers sponsoring them, their current status and estimated timeline. She again showed the pathway, with the specific potential products inserted into the chart.

Margie then talked about the Global Research Grants Process that is implemented in partnership with HCU Network Australia, and the Scientific Advisory Board whoch was established to helps guide key priorities for future research and patient advocacy and review specific grant proposals. The key priorities the committee has outlined are optimize current therapy, improved CBS detection and advance new treatment modalities. With those priorities in mind, HCU Network America in conjunction with HCU Network Australia implemented the first grant cycle and awarded their first grant in 2018 to Dr. Kenneth Maclean at the University of Colorado (with additional funding from the Will Hummel Foundation). A second call was issued in April 2019, and two full proposals are being reviewed by the Global Scientific Advisory Board (SAB). Margie then closed by discussing next steps, asking the committee and the community to fundraise and help support our efforts, so that we may expand our research map over time and include other causes of HCU.

> As part of the Therapies on the Horizon session, HCU Network America asked Orphan Technologies, Marcia Sellos-Moura and Aeglea BioTherapeutics, Chris Daige to provide an overview of their potential therapies and an update on their progress.

OT-58 Update:
Marcia reminded us that the Natural History Study showed us that even with the current treatments available, Homocystinuria patients still struggle to maintain low homocysteine levels. Marcia noted that Dr. Kraus spent his life aware of this issue and was dedicated to finding a solution to ease the burden for patients and their families. It was Dr. Kraus's tireless dedication that has evolved into what we now know as OT-58.

She shared that OT-58 reverses the HCU-related problems in the mouse model of HCU. Not only does it reduce plasma and tissue level of Homocysteine, but also improved eye health, prevented osteoporosis, improved learning, and improved vascular function in HCU mice. Additionally, it also gave the mice the ability to eat a regular – non-low-protein diet.

Marcia then gave a quick overview of the drug development process pathway, noting how complex it is. She explained they are undertaking a Phase 1/2 clinical trial. Phase 1 is usually done to determine a drug's safety in people. In Phase 2 they continue to look at safety, but also whether the drug achieves the efficacy goals they have set for therapy as well as what dose level and frequency of administration is needed. For OT-58, a combined Phase 1/2 study is underway to address all of these needs. Placebos have to be part of the study to compare the drug in patients against those who are only on conventional therapy to see the added benefits or risks of the drug. Marcia explained that a Phase III pivotal trial will not to be conducted once the Phase 1/2 results are available in order to gain regulatory approval and be able to market the drug for patient use.

AEB4104 Update:
Chris started his talk with background about Aeglea, noting they grew out of the George Georgiou Lab at University of Austin. Their mission is to develop next generation human enzymes. Their most developed therapy currently is for another rare disease, Arginase 1 Deficiency.

AEB4104, takes already existing human enzyme and mutates it to have different activity. The enzyme they are using is Cystathionine Gamma Lyase (CBL). This mutated enzyme has the unique ability to modulate activity to metabolize homocysteine. Once the enzyme is introduced, it is expected to metabolize homocysteine and keep the homocysteine levels down for an extended period of time. At the time of their presentation, they were undergoing toxicology evaluation in preparation for entering Clinical Trials, with a phase 1 trial expected to begin the second quarter of 2020.

Panel: Ask the Expert
A panel discussion was then held with a patient, a caregiver and healthcare experts. These experts included an active metabolic clinician, metabolic dietitian and genetic counselor who works with homocystinuria patients, as well as other inborn errors of metabolism, and 2 patients: a mother of a child with HCU and an adult male HCU patient, both of whom have excelled at managing the disease while having their own unique backgrounds when it came to diagnosis.

The moderator, Mark Lewis, HCU NA board member and parent of 2 HCU patients, opened with introductions of each of the panel members. He started the discussion by asking Dr. Chapman "You are sitting in front of a patient, what is the most important thing you can try to convey to your patient?" Dr. Chapman spoke about how she wants them to really focus on getting their levels below 100 and communicate honestly with her and the medical team. She points out that you can't properly treat patients if they aren't honest about their formula, diet and medicine intake. He then asked Katie Sapp, genetic

counselor, "…is there some advice that the clinic gives along the way for a sibling that tests positive for a carrier status, is there anything that that sibling should do for their lifestyle or dietary needs?" Katie replied that those who test positive for carrier status do not have to change anything about their health or medical management. Dr. Chapman noted that at this point in time, we don't believe that being a carrier increases your risk of having things happen as you get older (i.e. thrombosis or vision imapirment etc.). The only time that information comes into play is when that invidiual is planning a family of their own. She noted that when it comes to family planning, that it's not just about the individual, but their partner's carrier status as well. Mark then moved on to Abby Hall, metabolic dietitian, asking her what tools do you provide when talking to patients about their dietary needs. Abby noted that the advice she gives depends upon the stage and age of the family and patient. She echoed some of the same sentiments as Dr. Chapman, that establishing that trusting and honest relationship is important to provide the best care and using that to establish a plan that works for each individual.

Then Mark questioned the patients and caregivers. Mark asked Rachel Skeens, mother of a 12 year old boy, Landon, who was diagnosed at 4, to "what kind of advice do you have for someone who is managing through a diagnosis on managing overall metabolic health." Rachel walked us through Landon's journey, noting he was never a happy baby, and not meeting any milestones. Starting at 9 months old Landon started a program in his state called Birth to Three, which offered speech, occupational and phyiscal therapy. Even with these programs, Landon was not meeting the targets. Concerned, Rachel pushed and sought consult from multiple pediatricians, with each one saying that they were wasting their time. It was their 7th pediatrician who told them that "your child is going to die and you needed to leave the state." It was then that they went to Cinncinatti Children's. She came to their appointment with records in hand, and once again was told "you are wasting your time". Feeling frustrtated, Rachel said she told them "we drove 5 ½ hours, we have no money, my son can't move his left side, can you please just look at him?". The pediatrician agreed and gave Landon an MRI. The neurologist then came in and told them their son had Metachromatic leukodystrophy and that he had 2 weeks to live. They then went home and prepared to lose Landon. Then a week later, they got a phone call that Landon did not have Metachromatic leukodystrophy, but instead, Homocystinuria, and it was treatable! They were overjoyed – it was treatable. About 6 months after he began medication and diet, he gained strength, started to talk and began to relearn all the things he had lost as a result of misdiagnosis. He is now a normal happy, healthy 12 year old. Her advice "If you feel something about your child in your gut, it's more than likely accurate. Never stop questioning your doctor, don't be intimidated by the no's or their level of intellegence, because we are parents, we know them better than anyone else". Before Mark moved on, he echoed how important advoacy is across the board when managing homocystinuria.

Mark then questioned his son Ben, an adult male patient who has successfully navigated high school and college, and just completed his MBA program. Mark asked Ben to "pick a point in your life in one of those major transitions and how you managed to balance those transitions and mange your HCU"? Ben chose to touch on his experince in college. He said adherence to diet and treatment was hard and it varied. It was his first real experince having his family support network away from him on an everyday basis. His Freshman year was tough, as it was a trial and error experince with the protocal they had put in place to allow him to be a healthy HCU patient. The program didn't work because his special dietary restrictions didn't match the average student with their needs. He then echoed Mark and Rachel's point, that advocacy is important and going back to the drawing board to find a plan that works. The next three years Ben was assigned a personal chef to help assist in meal planning and preparation, but he had to be flexible and not picky with the foods provided.

Feedback From the Community

The survey feedback from our conference is critical to shaping future events around the unique needs and perspectives of our community. Last year, the community asked for more time between speakers and more time to network and get to know one another. We responded by giving longer vendor breaks, providing a networking lunch vs. a working lunch and bringing back the Saturday evening reception. Last year survey responders also asked for breakout sessions. We added a breakout session at the end of day one based upon patient age groups. This time was important in helping families understand and navigate the unique obstacles and situtions they may be facing or have faced. The time that we gave was highlighy reflected in our conference feedback this year – everyone was so thankful to have the time to network, socialize and learn from eachother!

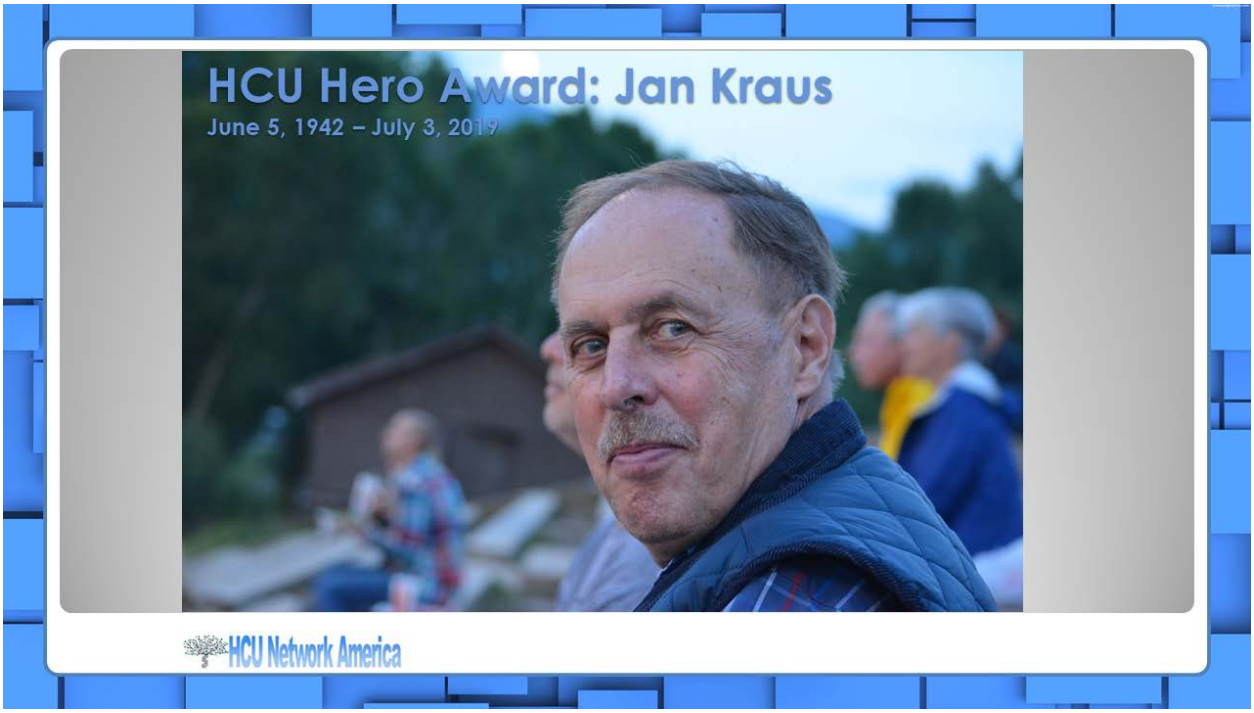
> "I will say that the extended break time between sessions was fantastic because it allowed the opportunity just to talk and connect to people! I also would love to continue with the breakout sessions based on age because the conversations can be tailored more specifically."

100% of those who took the post conference survey agreed that the meeting helped imporoved their understanding of homocystinuria and they would be sharing what they learned with someone else who was not at the conference. All the sessions were well received, but for the past two years the highest ranked keynote speakers were Margie McGlynn, for her presentation on Therapies on the Horizon, and Dr. Kimberly Chapman for her presentation on CBS treatment. Their presentations provided further understanding in how to manage their homocystinuria, the chemical process and provided hope for their or their childs future!

> "I was very interested in the studies that are taking place and ways that we might provide a better future for our loved ones with HCU"

When asked what attendees would like to see at the next conference they all agreed they would like research updates and to hear about the status of the therapies Margie presented. In addition to research and therapy updates, most attendee's would like to see more breakout sessions added with the option of a cooking class or demonstration. We will take this feedback and find a way to incorporate it into our next conference.

HCU Hero Award: Dr. Jan Kraus



The second HCU Hero Award was presented posthumously in memory of Dr. Jan Kraus. We are hoping to share a video of the award presentation along with the award with his wife Eva Kraus and some of Jan's close collegues in the Spring of 2020.

Jan Kraus was a Professor in Pediatric Clinical Genetics and Metabolism at the University of Colorado. Jan, considered by many as the "Father of Homoycstinuria", dedicated his life's work to the understanding and diagnosis and treatment of Homocystinuria (HCU) and Proprionic Acidemia (PA). Since the 1960's Jan authored and co-authored over 160 publications regarding HCU and PA. Jan's career highlights include building a database of all the genetic mutations associated with Homocystinuria, as well as being the inventor of the OT-58 product (a pegylated version of the CBS enzyme) that is in human trials for Classical Homocystinuria patients. The community will never forget Jan and his commitment to patients and families suffering from these diseases, and we send our sincere condolences to his wife Eva and family.