Patient Listening Session

Hypomyelination with Atrophy of Basal ganglia and Cerebellum (H-ABC)

Or TUBB4A associated leukodystrophy

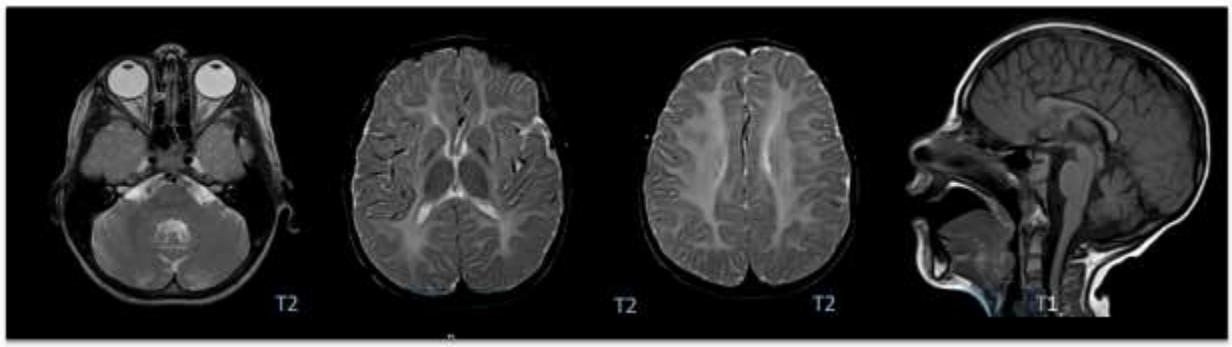
May 9, 2022

On May 9, 2022, six parents providing care for their children living with H-ABC, participated in a Patient Listening Session with the FDA. There is currently no cure for H-ABC and many doctors don't even know what it is. Life expectancy varies, to date we are aware of at least five children who have died from the side effects of H-ABC, likely many more.

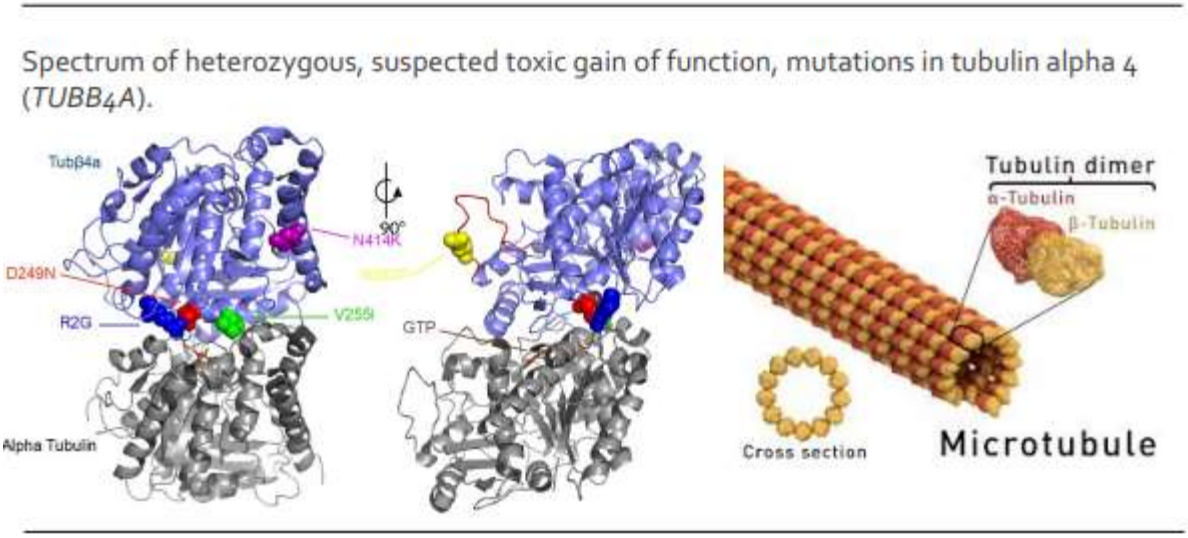
Below is a summary of the meeting. We thank the FDA for taking time out to listen in an effort to understand more about this rare disease and its impact on our children.

Clinical Summary (Dr. Vanderver, Children's Hospital of Philadelphia)

Hypomyelination with atrophy of basal ganglia and cerebellum (H-ABC) was first identified in 2002 (van der Knaap et al, AJNR Am J Neuroradiol. 2002 Oct). Initially diagnosed with typical MRI (hypomyelination with progressive atrophy of basal ganglia, in particular the putamen and to a lesser degree the caudate nucleus, while sparing the globus pallidus and thalamus, progressive atrophy of the cerebellum)



Typical onset in toddlers with hemidystonia and gait dysfunction. Gradual motor decline with extrapyramidal and pyramidal dysfunction, with cerebellar ataxia and dysarthria. Decline related to oromotor dysfunction, orthopedic and respiratory complications



True epidemiology is difficult to assess, but incidence may be as high as 1 in 7,663 live births (Bonkowsky et al, Neurology, 2010). TUBB4A associated leukodystrophy is the most common hypomyelinating leukodystrophy

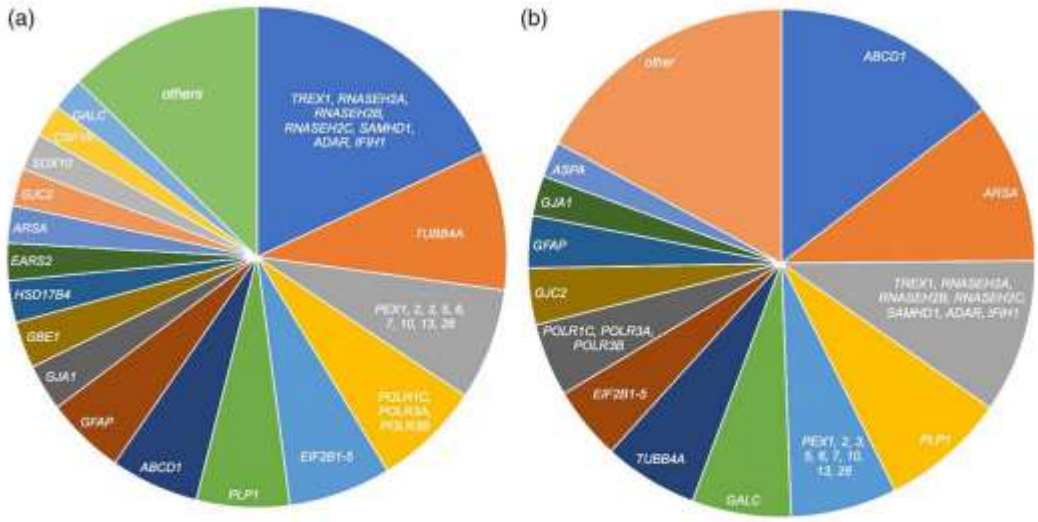


FIGURE 1 (a) Relative frequency of cases identified in exome sequencing cohorts. The remainder of the genes (*SLC17A5, CYP27A1, SUMF1, PSAP, DARS2, HEPACAM, MLC1, PSAP, RNASET2, ALDH3A2, ASPA, FUCA1, DARS, FAM126A, ACOX1, LMNB1, CLCN2, SCP2* in decreasing order of frequency) each represented less than 2% of the total population. (b) Relative frequency of cases identified in exome, gene panel and single gene sequencing cohorts. The remainder of the genes (*LMNB1, GBE1, HSD17B4, EARS2, CYP27A1, SUMF1, SOX10, CSF1R, SLC17A5, HEPACAM, DARS2, MLC1, ALDH3A2, PSAP, FUCA1, FAM126A, PSAP, RNASET2, DARS, ACOX1, CLCN2, SCP2* in decreasing order of frequency) each represented less than 2% of the total population [Color figure can be viewed at wileyonlinelibrary.com]

Amongst >50,000 trio exomes from major US testing laboratories (A) and exome plus available biochemical and single gene testing (B), the relative frequency of different disorders is different than historical conceptions of frequency (Schmidt et al. Am J Med Genet A. 2020 Jun 23)

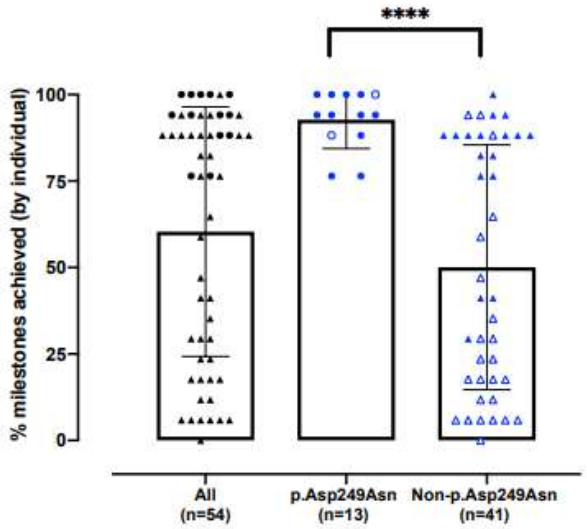
p.Asp249Asn remains the most common mutation (41/186 or ~20%) frequency in other mutations are appearing as more patients are diagnosed. Specific mutation often has a good correlation with motor outcomes in TUBB4A associated leukodystrophy

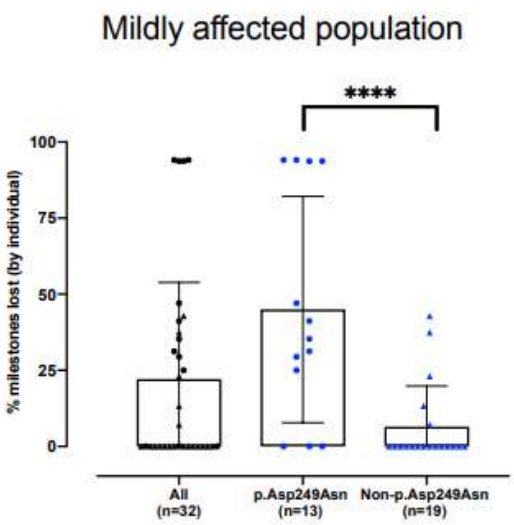
In a study of 186 individuals with confirmed TUBB4A Associated Leukodystrophy, presenting features most often included motor developmental delay (69%), and tone abnormalities (46%). With less frequent nystagmus (28%), cognitive delay (24%), feeding difficulties (14%), and social delays (12%). Over time affected individuals develop a broad range of symptoms

tte_event	percent_noted	number_noted	number_not_noted	number_unknown	total
asp_pneumonia	0.22	18	64	81	163
autonomic_issues	0.29	7	17	139	163
cardiovascular_issues	0.19	9	39	115	163
developmental_delay	0.93	55	4	104	163
failure_to_thrive	0.53	17	15	131	163
feeding_tube	0.44	62	79	22	163
gastric_feeds	0.33	36	72	55	163
gerd	0.68	27	13	123	163
hematological_issues	0.27	8	22	133	163
hip_dislocation	0.35	28	52	83	163
hip_surgery	0.19	16	67	80	163
incontinence	0.23	7	24	132	163
joint_flexibility	0.47	14	16	133	163
loa	0.52	42	39	82	163
loa_ass	0.46	41	48	74	163
recurrent_vomiting	0.43	16	21	126	163
scoliosis	0.42	50	70	43	163
scoliosis_surgery	0.11	9	75	79	163
seizures	0.33	46	93	24	163
seizures_anticonvulsants	0.11	3	25	135	163
spasticity_lower	0.61	27	17	119	163
ventilation	0.07	7	93	63	163

Daily living skills, expressive communication and motor function are most greatly affected. Surgeries are common particularly related to hip dislocation, scoliosis, baclofen pump implantation, feeding tubes.

Three subtypes exist: Mild (I), Moderate (II) and Severe (III). p.Asp249Asn mutations nearly always associated with a moderate presentation with predictable and narrow onset and progression.





In summary,

• TUBB4A Associated Leukodystrophy is most likely the most common hypomyelinating leukodystrophy, and relatively common amongst these rare disorders

• It has relative genotype phenotype correlation, in particular for p.AspD249Asn, the most common recurring mutation

• The disease spectrum includes early infantile, late infantile and older childhood presentations • Individuals have profound motor and communication difficulties that affect their activities of daily living and adaptive behavior

• Many individuals have high health care utilization

Patient Database (Michele Sloan, Foundation to Fight H-ABC)

In partnership with RareX, the Foundation to Fight H-ABC and UK H-ABC Foundation recently rolled out an H-ABC Database to allow families to provide key demographic and medical data for global access by researchers who are interested in pursuing treatments, drugs, and or clinical trials for H-ABC. This is a supplement to the Natural History Study already underway, but necessary for patient community representation.

Elouise, age 16, late onset

Overview. Typical pregnancy and birth. Initially typical development, walking independently but with arm extension at age 3 and with some age-appropriate speech development delays. Various diagnosis offered including Ataxia, Cerebral Palsy, H-ABC/Tubb4a diagnosis at 8 years old. Elouise is a happy child with a great demeanor. Since a period of several surgeries in her early teen to address skeletal

implications tied to the condition, she is stable and thriving. Our biggest concern at this point is her swallowing and dystonia localized in her neck. However, with recent orthodontist work and laser treatment, along with Botox injections, we appear to have her challenges under control.

Symptoms

► Can Do: Drive a wheelchair, bear weight/use all limbs w/ full supervision, verbal but incomprehensible, use ES and letterboard; At grade in LFI (learn for independence) program, cognitively fully intact with great sense of humor and happy

► Cannot Do: Walk, stand (no balance), articulate verbally, no independence, dependent as a toddler; Used to be fully mobile with minor balance issues and age-appropriate independence until around age 8 when significant decline began requiring increased support and supervision; Now she requires full supervision for eating, toileting, self-care, school work, everything; she can stand and bear weight with assistance. Most issues are oriented around digestive functions, musculoskeletal weakness and decline with no brain or organ related issues.

Disease Management

► Therapies: Communicates w/ device/letterboard, OT, PT, Botox, aqua therapy, hippotherapy – all for symptom management

► Equipment: Tram, Wheelchair, Orthotics, Gait Trainer, Stander, Adapted Bike, rehab single story house for access.

► Surgeries: multiple for hip dislocation, scoliosis (full spinal fusion), feeding tube - they have been literally a lifesaver; MRI originally showed abnormal myelination with some atrophy of the basal ganglia; recent MRI showed no meaningful change

► Medications: Baclofen (oral) and Botox injections quarterly for localized dystonia

Impact on family life

► Few friends due to communication limitations and immobility

► Activities restricted based on accessibility, inclusion and understanding by others

► Fear of the future; Support Services; guardianship

Risks / Benefits. Depends on her condition at the time and degree of risk presented, now Elouise is very healthy and relatively highly functional. Gain of communications would be an optimal benefit but not willing to put life at risk for this. Given her spinal surgery she is likely now not qualified to be treated using ASO.

Frankie, age 7, late onset

Overview. Typical pregnancy and birth. Initially typical development but wasn't walking independently. Diagnosed with Hypermobility at 2, then Cerebral Palsy at 3, then after genetic testing and MRI diagnosed with H-ABC/Tubb4a at 4 years old.

Symptoms

► Can Do: Walk with a walker, crawl, talk (albeit w/ difficulty) attends mainstream school

► Cannot Do: Walk unaided

► Lost: Frankie has yet to lose any skills, although his muscles are beginning to tighten making walking with his walker more difficult

Disease Management

► Therapy: OT, PT, Botox

► Devices: Walker, Wheelchair, Splints Impact on family life

► Frankie has friends but not like a typical child

► Difficult to do everyday family activities such as going to the park or days out

► Knowledge of future progression

Risk / Benefit. We know what will happen if there is no treatment and are willing to take part in trials to stop the progression of the disease. Frankie is at a stage that if the progression could be stopped, he would live a good life. An ideal outcome would be to regain some mobility but we are relatively lucky that Frankie is yet to lose many skills.

Martin, age 4, mid onset

Overview

Typical pregnancy and birth. Meeting expected milestones up to 8 months old. Diagnosed after performing Whole Exome Sequencing at 16 months old (TUBB4A mutation explained MRI performed at 13 months old, showing hypomyelination). Slowly gaining skills but significant gap versus expected performance, specifically on the motor side.

Symptoms

- CAN DO: Gross motor (walk with an anterior walker, walk if hand held, stand if assisted, crawl, sit in the tripod position), Fine motor (hold objects/ bottle - palmar grasp), Cognitive (good receptive communication)
- CANNOT DO: Walk/ stand without assistance, talk

Disease Management

- Therapy – OT, PT, Speech therapy
- Devices – Walker, Stander, Sleep orthotics, Therapy space at home

Impact on family life

- Very difficult to obtain qualified medical assistance

- Not able to go to kindergarten/ no perspective on going to school/ no perspective on inclusion around adult life
- Often need to compromise on variety of activities to spend family time, sometimes in the detriment of Martin's older sister

Risk vs. Benefit

- Given Martin is almost fully dependent on people around, it's difficult to assess what risk we would be able to assume and how a negative consequence could make things worse
- For us, him gaining hand control and the ability to perform fine motor movements would open up the much-needed possibility of expressive communication

Connor, age 3, mid onset

Symptoms

► Can Do: Hold head up, eat by mouth w/ difficulty, get into crawl position, army crawl, walk in a gait trainer, full range of emotions, happy, and attend school with help.

► Cannot Do: Walk, talk, sit-up, crawl properly, communicate well, or care for himself in any way.

► Other: About one year behind developmentally. Small head, generally small for age, mixed tone.

► Lost: Used to babble but now only yells/makes noises and says a couple of vowels.

Disease Management

► Food: spoon-fed purees

► Therapy: OT/PT/Speech/Feeding/Music Therapy

► Surgery: Strabismus – corrected his crossed-eyes

► Devices: gait trainer, wheelchair, ankle braces, bodysuit/Benik vest

► Medications: Periactin for appetite, Botox treatment for legs

Impact on family life

► Need a special-ed school, caregivers, difficult to travel/move, everything is more expensive

► Difficult to do everyday family activities or maintain friendships, his care can be all consuming

Risk / Benefit

► Any improvement in his motor skills could radically improve his life: walking/talking/eating

► Any slowing of the regression would allow for a longer and less painful life in the end

► We are aware of the risks of any new treatment, but the downside is already written while the upside is our only hope for him

Clara, age 5, early onset

Overview

Clara is an example of early onset and is currently 5 years old. She was born healthy without any signs of anything extraordinary but when she was three months old, her pediatrician noticed that she could not hold her head and presented nystagmus and sent her to be studied in Neuropediatrics at our hospital. The doctors' first suspicion was cerebral palsy but it was ruled out on brain MRI. Then came a multitude of diagnostic hypotheses and tests of all kinds (lumbar puncture, electroencephalograms, directed genetic tests, etc.). All of them were negative until exome sequencing indicated an alteration of the TUBB4A gene. A second MRI of the brain revealed hypomyelination and atrophy of the cerebellum, leading to a diagnosis of leukodystrophy. Clara is a child who still does not support her head and, therefore, she cannot sit alone, crawl, walk, etc., which makes her a child completely dependent. She sits on a PCI wheel chair and alternates it with a standing frame. We use sometimes a bodysuit and then she can do short steps. She goes to physical therapy three times a week. She is very giggly and very connected to us and the people she knows. She communicates with us non-verbally. She goes to speech therapy three times a week and now we're trying to make her use an ACC device with Eye Gaze. Her head management, Nistagmus and Strabismus makes it very hard but we're willing to help her communicate because she seems to be cognitively intact. She has had a great difficulty gaining weight and also has gastroesophageal reflux (GERD). She takes hyper caloric complete formula to compensate calorie consumption and facilitate gastric emptying. She also has had many urine and kidneys infections thoughout the years. She has had vesicoureteral reflux surgery which has helped her. She takes oxybutynin for overactive bladder and we do intermittent urine catheterization three times a day. Now this problem seems under control. Her condition makes her need full-time care-giving. She goes to a special needs class in a regular school and we're very happy with it. She has to attend many medical appointments, therapy sessions, etc. which makes it difficult to reconcile with work, personal activities and all kind of social interactions. It's hard to find professional or family caregivers due to her needs. Of course, it impacts financially because of the expenses of care-giving, therapies and devices although the Spanish government and some associations help us the time available for work is limited and it adds up to the financial struggles. All of it causes stress and also makes an emotional impact: in the background it's always the fear of losing her. On the other hand, she looks perfectly happy and we think she generally enjoys her life.

Symptoms

► CAN DO: eat by mouth, babble, yell, smile and laugh, does short steps with a bodysuit, point things.

► CANNOT DO: Hold her head, cannot walk, talk, sit up

► Other: Growth failure, Stiff muscles, Nystagmus, Epilepsy

Disease Management

► Food: Difficulty gaining weight and has gastroesophageal reflux (GERD); takes hyper caloric complete formula to compensate calorie consumption and facilitate gastric emptying

► Therapy: PT/Speech ► Surgery: Strabismus, vesicoureteral reflux

► Devices: Splints, wheelchair, standing frame, body suit, AAC device + Eye Gaze

► Medications: Oxybutynin for overactive bladder, Esomeprazole for GERD, Levetiracetam for epilepsy

► Other: Intermittent urine catheterization three times a day

Impact on family life

► Needs full-time caregiving and has lots of medical appointments, therapy sessions, etc.

► Difficulties to reconcile with work, personal activities and social interactions

► It's hard to find professional or family caregivers due to her needs

► Financial impact due to expenses of care-giving, devices, etc. and the limited time available for work

► Emotional impact as the time spent on caregiving plus all other daily activities is stressful and the lack of therapies or cure causes the fear of losing her

Risk / Benefit

► Risks: we're generally interested in taking part in a clinical trial but we cannot decide until the time comes. We know that there are risks and her participation will depend on her health status at that moment and the Trial prospects.

► Benefits: my hope is to avoid any degeneration and to be able to hold her head up, sit by herself and communicate using a device or by her own means.

Christian, age 2.5, early onset

Symptoms

► CAN DO: Able to hold head up and move side to side when in tummy time position. Struggles with head control when sitting upright. Able to respond to voices and singing. Responds well to lights for play. Interacts well with others. Uses sounds to vocalize needs / wants (Cooing, babble, crying) Able to grasp toys for short times.

► CANNOT DO: General development delay, mixed tone, cannot walk, talk, sit up, fed via g-tube as low muscle tone impacts volume he can eat by mouth. Unable to engage in typical play

► Other: Has small head and is generally small for his age. Mixed tone. Unable to move purposeful movement

► Lost: no known regression, but progress has been slow.

Disease Management

► Food: G-tube fed

► Therapy: OT/PT/Speech (AAC)/Feeding Therapy/vision therapy

► Devices: Benik vest, AFO's, squiggles chair, stander, bath chair

► Medications: Periactin for appetite

Impact on family life

► Difficult to find caregivers/nannies, they are more expensive and need to be trained on feeding

► Child does not really have friends

► Difficult to do no everyday family activities such as going to the park or visiting friends. More equipment needed. Accessibility is a necessity

► Will need an aid to attend school

Risk / Benefit

Would like cognitive functional and motor improvements without high-risk side effects

FDA Q&A (FDA questions, Patient Caregiver answers)

Question: Elaborate on difficulties with speech, how your child communicates?

Answer 1: Connor uses sounds, not words, he can't control his tongue, can't teach him sign language. Considered an eye gaze but due to his eye trembling, it's not possible

Answer 2. Christian can't use an eye gazer either because he has CVI (critical visual impairment)

Answer 3. Elouise had normal speech at early childhood with full vocabulary through her years in school. Later she had difficulty pronouncing words, and now use garbled words, communicates using finger signs / letterboard/joy stick, uses phone to text but given fine motor challenges, takes lot of time and concentration. Dental work done to open up mouth and laser on loose skin at back of throat, mostly to help with swallowing. Used prompt speech therapy which was good.

Answer 4. Carla is cognitively intact; she wants to do things but can't due to motor control, can't point, can't control tongue, intellect capacity and movement control don't match up

Answer 5. Martin also understands but can't use his body. Examples included waiving his hand over an image that answers the question from multiple choices, so long as the image is far enough apart from the others for him to do it. Another example is stacking toys using same size or color. When shown the toy after giving him direction, he will smile if it's the right toy, or turn away if wrong toy. To show an image of a dog on a page he will place his palm on the page, pull it down until his thumb gets to the dog.

Question. How do you find information to learn about risks tied to treatments and/ or surgeries?

Answer 1. Use parent social media page, parents have a lot of knowledge and perspective

Answer 2. Lucky to have great network of doctors and therapist who have experience and can treat the symptoms which are similar to CP and have universal treatment protocols. Foundation has gained ton

knowledge from the rare disease network, Dr. Vanderver is a great clinical resource, parents have best experience; often it's a process of elimination to get to resources that help

Answer 3. In Romania, Martin is the only child with H-ABC. Parents use H-ABC parents as resource as well as other families using media networks for similar disease. Parents bring this detail to the doctors who know little, who help them decide. Silver lining is living in 2022 with worldwide social media.

Question. Would you participate in a trial if you had to stop all treatments?

Answers (5): Overwhelmingly yes, with one caveat to be sure no negative side effects when stopping use of a specific medicine.

FDA Participants:

Office of the Commissioner (OC) – 4 *offices*

- OC/OCPP/OPA – Office of Clinical Policy and Programs/Office of Patient Affairs *(organizer)*

- OC/OCPP/OOPD – Office of Clinical Policy and Programs/Office of Orphan Products Development
- OC/OCE – Oncology Center of Excellence
- OC/OCPP/OCPR - Office of Combination Products

Center for Biologics Evaluation and Research (CBER) – 2 *offices/divisions*

- CBER/OCD – Office of the Center Director

- CBER/OTAT/DCEPT/GMBII – Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharmacology/Toxicology/General Medicine Branch II

Center for Drug Evaluation and Research (CDER) – *5 offices/divisions*

- CDER/OCOMM/PASES- Office of Communications/Professional Affairs and Stakeholder Engagement
- CDER/OND/ON - Office of New Drugs/Office of Neuroscience

- CDER/OND/ON/DNI – Office of New Drugs/Office of Neuroscience/Division of Neurology I
- CDER/OND/ORDPURM/DRDMG - Office of New Drugs/Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBI – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics I

Center for Devices and Radiological Health (CDRH) – 7 offices/divisions

- CDRH/OPEQ/OHTIII – Office of Product Evaluation and Quality/Office of Health Technology III: Office of Gastrorenal, ObGyn, General Hospital, and Urology Devices
- CDRH/OPEQ/OHTIII/DHTIIIA – Division of Health Technology IIIA: Division of Renal, Gastrointestinal, Obesity, and Transplant Devices
- CDRH/OPEQ/OHTIII/DHTIIIB - Division of Health Technology IIIB: Division of Reproductive, Gynecology, and Urology Devices
- CDRH/OPEQ/OHTIII/DHTIIIC - Division of Health Technology IIIC: Division of Drug Delivery and General Hospital Devices, and Human Factors

- CDRH/OPEQ/OHTV/DHTVB - Division of Health Technology V B: Division of Neuromodulation and Physical Medicine Devices

- CDRH/OSPTI/Office of Strategic Partnership and Technology Innovation
- CDRH/OSPTI/DAHRSSP- Office of Strategic Partnership and Technology Innovation/Division of All Hazards Response, Science and Strategic Partnerships

Disclosures

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the Foundation to Fight H-ABC's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of H-ABC, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire H-ABC patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

Resources

https://www.h-abc.org/

https://www.h-abcfoundation.org/

https://vimeo.com/692054249/4257d1b87d

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7255805/

https://medicine.yale.edu/pediatrics/news-article/h-abc-itsnot-easy-as-1-2-3/

https://www.prnewswire.com/news-releases/foundation-to-fight-h-abc-university-of-massachusetts-medical-school-and-yale-university-initiate-gene-therapy-study-targeting-cure-for-rare-disease-301150610.html?tc=eml_cleartime

https://www.bbc.co.uk/news/av/health-53890362

https://www.itv.com/news/meridian/2022-04-10/former-soldier-completes-fundraising-marathon-challenge-with-multiple-fractures

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