WASHINGTON STATE BOARD OF HEALTH

Notice of Public Meeting

Wednesday, April 12, 2023
10:00 a.m. – 3:10 p.m.
Hybrid Meeting
Language interpretation available (see below for more information)
Physical meeting at Labor & Industries Auditorium, 7273 Linderson Way SW, Tumwater, WA 98501
Virtual meeting via ZOOM Webinar
(hyperlink provided below)

Proposed Final Agenda

Time	Agenda Item	Speaker
10:00 a.m.	Call to Order & Introductions	Keith Grellner, Board Chair
10:10 a.m.	1. Approval of Agenda—Possible Action	Keith Grellner, Board Chair
10:15 a.m.	2. Approval of March 8, 2023, Minutes – Possible Action	Keith Grellner, Board Chair
10:20 a.m.	3. Public Comment	Please note: Verbal public comment may be limited so that the Board can consider all agenda items. The Chair may limit each speaker's time based on the number people signed up to comment.
10:50 a.m.	4. Announcements and Board Business	Michelle Davis, Board Executive Director
11:10 a.m.	5. Department of Health Update	Michael Ellsworth, Department of Health, Secretary's Designee Kelly Cooper, Department of Health
11:40 p.m.	6. Health Disparities Council Redesign	Victor Rodriguez, Council Vice Chair Jessica Zinda, Council Member Council Staff
12:10 p.m.	Lunch	
1:10 p.m.	7. Briefing/Update – Newborn Screening, Ornithine Transcarbamylase Deficiency (OTCD), Chapter 246-650 WAC	Dimyana Abdelmalek, Board Member Molly Dinardo, Board Staff
1:35 p.m.	8. Emergency Rulemaking – On-Site Sewage Systems, WAC 246-272A-0110, Proprietary Treatment Products and Supply Chain Shortages – Possible Action	Michael Ellsworth, Secretary's Designee Stuart Glasoe, Board Staff Jeremy Simmons, Department of Health

Time	Agenda Item	Speaker
1:50 p.m.	Break	
2:05 p.m.	9. Rulemaking Petition – Newborn Screening, Request to add Arginase 1 Deficiency (ARG1D) to Chapter 246-650 WAC – Possible Action	Socia Love-Thurman, Board Member Molly Dinardo, Board Staff John Thompson, Department of Health
2:35 p.m.	10. Legislative Update	Michelle Davis, Board Executive Director
2:50 p.m.	11. Board Member Comments and Updates	
3:10 p.m.	Adjournment	

- **To access the meeting online and to register:**
  https://us02web.zoom.us/webinar/register/WN_mu2A7ZgeSb-xy6NhUG6rog
- **You can also dial-in using your phone for listen-only mode:**
  Call in: +1 (253) 215-8782 (not toll-free)
  Webinar ID: 889 1392 5308
  Passcode: 660897

Important Meeting Information to Know:

- Times are estimates only. We reserve the right to alter the order of the agenda.
- Spanish interpretation and Communication Access Real-time Transcription (CART) services will be available.
- If you would like meeting materials in an alternate format or a different language, or if you are a person living with a disability and need reasonable modification, please contact the State Board of Health at (360) 236-4110 or by email wsboh@sboh.wa.gov. Please make your request as soon as possible to help us meet your needs. Some requests may take longer than two weeks to fulfill. TTY users can dial 711.

Information About Giving Verbal Public Comment at Hybrid Meetings:

- For the public attending in-person: If you would like to provide public comment, please write your name on the sign-in sheet before the public comment period begins. We strongly encourage people to sign up with the Board by sending an email by 12:00 Noon the day before the meeting to: wsboh@sboh.wa.gov. As this is a business meeting of the Board, time available for public comment is limited (typically 2 to 4 minutes per person). The Chair will call on those who have signed up to speak to the Board, first. The amount of time allotted to each person will depend on the number of speakers present. If time remains, those who have not signed up ahead of time to speak to the Board will be called on to speak until the scheduled time for Public Comment comes to an end.

- For the public attending virtually: If you would like to provide public comment, please sign up through the Zoom webinar link by 12:00 Noon the day before the meeting. Your name will be called when it's your turn to comment.

Information About Giving Written Public Comment:

- Please visit the Board's Meeting Information webpage for details on how to provide written public comment.

WASHINGTON STATE BOARD OF HEALTH

Draft Minutes of the State Board of Health
March 8, 2023
Hybrid Meeting
Physical meeting at Labor & Industries Auditorium,
7273 Linderson Way SW, Tumwater, WA 98501
Virtual meeting via ZOOM Webinar

State Board of Health members present:

Keith Grellner, RS, Chair
Kelly Oshiro, JD, Vice Chair
Patty Hayes, RN MN
Tao Sheng Kwan-Gett, MD, MPH, Secretary's Designee
Dimyana Abdelmalek, MD, MPH
Stephen Kutz, BSN, MPH
Melinda Flores
Kate Dean, MPA

State Board of Health members absent:

Umair A. Shah, MD, MPH
Socia Love-Thurman, MD

State Board of Health staff present:

Michelle Davis, Executive Director
Melanie Hisaw, Executive Assistant
Anna Burns, Communications Consultant
Stuart Glasoe, Health Policy Advisor
Molly Dinardo, Health Policy Advisor
LinhPhung Huỳnh, Council Manager
Jo-Ann Huynh, Administrative Assistant
Hannah Haag, Community Outreach Coordinator
Grace Cohen, Department of Health
Lilia Lopez, Assistant Attorney General

Guests and other participants:

Jamilia Sherls-Jones, Department of Health
Katherine Graff, Department of Health
John Thompson, Department of Health
Juan Gamez Briceño, Department of Health
Donna Walker, ASL Interpreter
Tami Berk, ASL Interpreter
Guillermo Ramirez, Spanish Interpreter
Patricia Cardona, Spanish Interpreter

Keith Grellner, Board Chair, called the public meeting to order at 10:32 a.m. and read from a prepared statement (on file). He then detailed operating procedure and ground rules for conducting a hybrid meeting and asked Board members to introduce themselves.

1. **APPROVAL OF AGENDA**
   Motion: Approve March 8, 2023 agenda
   Motion/Second: Vice Chair Oshiro/Member Kutz. Approved unanimously

2. **ADOPTION OF JANUARY 9, 2023 MEETING MINUTES**
   Motion: Approve the January 9, 2023 minutes.
   Motion/Second: Vice Chair Oshiro/Member Flores. Approved unanimously

3. **PUBLIC COMMENT**
   (Note: Public Testimony on Item 7, Rules Hearing for Handling of Human Remains, Natural Organic Reduction, Chapter 246-500-055 WAC, will begin at 1:30 p.m.)

   (Virtual public comment)

   Mary Cavanagh, from Sammamish, said she submitted a petition earlier to request to add mucopolysaccharidosis (MPS II), to Chapter 246-650 WAC. Ms. Cavanagh shared her personal story about her son and why she submitted the petition. Her son and family suffered a terrifying journey of misdiagnosis for over 10 years before a urine test led to a correct diagnosis and her son was able to begin enzyme replacement therapy.

   Kim Tuminello, co-founder & director of advocacy for creatine deficiencies, and mom of two children with GAMT. She submitted the petition requesting to amend Chapter 246-650 WAC to add Guanidinoacetate methyltransferase (GAMT) deficiency as a condition for newborn screening. GAMT is a recessive genetic disorder that can be easily detected with blood spot. Her children were both born with GAMT but her son was not diagnosed until age 10. He suffers 100 seizures a day and is in special education. Her daughter was diagnosed at birth has had no therapy, is a straight A student and leads a typical life. She hopes WA will consider adding Newborn Screening for GAMT now to save babies lives. She said it's effective, affordable, and considered the no brainier of NBS.

   Heidi Wallace, talked about GAMT deficiency disorder, which was recently added to the Recommended Universal Screening Panel (RUSP) that the Secretary of the Department of Health and Human Services (HHS) recommends for states to screen as part of their state universal newborn screening programs. She has 2 children, her daughter was originally mis-diagnosed and her youngest son was diagnosed early and is perfectly healthy. She said there are over the counter supplements with three ingredients that can counter the neurotoxin that builds up in the body, resulting in seizures and a myriad of issues that follow. Costs are around $15,000 from birth to adult, but astronomical costs to family and society for those not treated. New York, Australia and other places have been successful with screening.

Bill Osmunson, DDS, MPH, spoke about the National Toxicology Program (NTP) that included 159 studies showing that fluoride causes cognitive neuro damage to humans. He cited information regarding toxic issues and conditions caused by fluoride, including brain damage to children and lost wages.

Dennis Fynn, spoke in opposition to a COVID-19 immunization requirement for K-12 school entry, saying it should be an opt-in policy without coercion. He said children may be in the hospital for other reasons, that may have COVID and vaccination should not be required.

Sue Coffman, Informed Choice Washington (ICW), spoke in opposition to the COVID-19 vaccine requirement. She talked about the lack of trust with some government leaders and policy makers, and talked about the dangers of the vaccine, saying the safety and efficacy is being overlooked.

Natalie Chavez, spoke in opposition to the COVID-19 vaccine requirement. She talked about websites for support and a movie about vaccine injuries, saying we need to focus on answers not politics.

Melissa Leady, Clark County Resident, spoke in opposition to the COVID-19 vaccine requirement, and said there is missing, inaccurate and conflicting hospital and vaccine data by the Department of Health.
A.L. Rickard, King County resident, spoke in support for the mask mandate in healthcare facilities and prisons and overall support for universal masking in high-risk settings. Mr. Rickard said he had loved ones that are high risk. He said there are marginalized communities that are disproportionally affected, and we've already lost over 15,000 residents to COVID-19.

Sasha Anderson, Fremont resident, spoke in support for the mask mandate in healthcare facilities and prisons, for at least a year to come up with a plan. She said the majority of those dying are vaccinated and we need to prevent the spread by masking. She has long-covid and said vulnerable people must be able to access health care.

Sol Villarreal, spoke in support for the mask mandate in health care facilities and prisons. They shared statistics, saying masks are the best preventative measure, and talked about politicians trying to get re-elected.

Anna Wolak, King County resident, a research engineer, spoke in support for the mask mandate in health care facilities and prisons. They are immunocompromised and since the mask mandate, haven't had any problems. They said people can be maimed by long-term COVID and until there is a cure, we are all canaries in a coal mine.

Becca Peter, San Juan County resident, spoke in support for the mask mandate in health care facilities and prisons. They shared about their son's recent malignant brain tumor, that fortunately responded to radiation and chemo, saying he did well as he was able to avoid risk elsewhere. Their son sometimes removes his mask due to vomiting and nose bleeds, and masks give a valuable layer of protection. They said it's sad that lobbyists and hospital administrators are choosing this over protecting the most vulnerable.

Susanna Garrett, King County resident, spoke in support for the mask mandate in health care settings and prisons. They suffered a miscarriage due to COVID-19 and said there's a lot of data showing that health care settings and prisons should keep the mask mandate.

Sara Cohen, spoke in support for the mask mandate in health care settings and prisons, first for healthcare workers and second for patients. They said healthcare workers deserve a safe workplace, and sickness further disrupts our already strained system. Removing this mandate jeopardizes patients' health, and once the mandate is lifted, it's harder for providers to implement policies. They talked about death that still occurs from COVID and Severe Acute Respiratory Syndrome (SARS).

Tejal Mankad, King County resident, spoke in support for the mask mandate in health care settings and prisons, saying they suffer chronic sickness from asthma. She said 15,000 have already died from COVID-19 and she has personally lost loved ones. She said the pandemic is not over and that universal masking offers protection.

Elise Denham Probasco, Whatcom County resident, spoke in support for the mask mandate in health care settings and prisons. She has a chronic illness that makes her high risk for COVID. She said the public wants the burden on the sick and she's ok with staying away from restaurants and concerts. For the immunocompromised, this is not a cold or the flu, it's life and death. She can work and do some healthcare remotely, but those in prisons and long-term care cannot. Those with other options have a financial privilege. Please keep the mask requirement, just like universal gloves after the AIDS crisis.

There was a brief pause due to the loss of Internet connectivity in the building.

Lisa Templeton, spoke in opposition to the COVID vaccine for school requirement and the mask requirement. She asked the Board to pay attention to vaccine injury data. She said the notion of mask wearing is not founded in science, and she expressed her empathy to the earlier callers. She said countless studies show masks don't protect and that Dr. Fauci said in March 2020 that wearing masks may make people feel better, but they don't provide the protection assumed.

(In-person public comment)

Gerald Braude, Port Townsend resident, started by welcoming Commissioner Kate Dean from Jefferson County. He asked people to read the Cochrane Study that claims research studies show masks don't work. Mr. Braude talked about the dangers of the vaccine, saying the Board hasn't discussed once the Vaccine Adverse Event Reporting System (VAERS) data from the Centers for Disease Control (CDC) that shows 34,000 deaths from the COVID vaccine. He said there's only positive talk about the vaccine, but this doesn't change the fact of documented deaths from blood clotting, acute aortic dissection, and stillborn cases soon after the vaccine was administered.

Chair Grellner closed the public comment at 11:48 a.m.

4. BOARD ANNOUNCEMENTS AND OTHER BUSINESS

Michelle Davis, Board Executive Director greeted the Board and directed Board members to materials in their packets (see Tab 4).

Ms. Davis mentioned that all materials are on the Board's website and that TVW is livestreaming the meeting.

Ms. Davis noted that this is the first in person meeting since March 2020 and the first hybrid meeting of the State Board of Health (Board). She acknowledged the efforts of the staff team in supporting the Board and testing the technology. Ms. Davis highlighted that changes have been made to the meeting format to improve access—ASL and Spanish language interpretation is being provided. The meeting agenda and rules hearing materials are available in Spanish. Zoom closed caption options are also available. The Board is pleased to expand access in this way.

Ms. Davis stated that 5pm today is the cutoff for bills to get out of the house of origin.

Ms. Davis highlighted that the Health Impact Review team has received and completed 7 requests for Health Impact Reviews for this fiscal year. She mentioned the packet materials and asked if Board members had questions.

5. DEPARTMENT OF HEALTH UPDATE

Tao Sheng Kwan-Gett, Chief Science Officer and Secretary's Designee, provided an update on the COVID-19 response (see presentation on file), including current data, end of federal public health emergency, and end of state mask order in health care, long-term care, and correctional facilities. Member Kwan-Gett shared other population health data that the state health department is focusing on to reduce health inequities. Member Kwan-Gett highlighted transformational action the state health department was taking, including expanding leadership capabilities, refreshing external communications, and strengthening community links through various community engagement activities.

Member Kwan-Gett explored the challenge that the Department faces in addressing health disparities across the state and focused on several approaches the Department has adopted to begin this work, including the concept of 7 generation, a new Department structure which reflects equity, innovation and engagement, new branding and storytelling efforts, including a new quarterly speaker series called Public Health Connects, and a focus on OneHealth—health of humans, animals and the environment.

Steve Kutz, Board Member asked for information on how patients served by Medicaid impact the numbers and statistics presented on health disparities in Washington. He commented on the lack of ability to address health in the 5-10 minutes that doctors have with Medicaid-served patients, and the need for Medicaid to pay for preventative healthcare.

Member Kutz asked what the Department's plan is for continuing COVID-19 testing sites and vaccination sites once the federally allotted supplies are no longer available.

He would like to know what the plans are to transition to a long-term response to COVID-19 testing and vaccination.

Member Kwan-Gett responded that the question around Medicaid services highlights the need for the Department to have the ability to have flexible and de-aggregated data so we can have a better understanding of those impacts. He also commented that the Social Determinants of Health are really the biggest determinants of public health and highlighted the need to develop stronger collaboration with healthcare, housing employment, transportation, and called for a very collaborative approach.

Member Kwan-Gett responded to the second question that the challenges for COVID-19 testing and vaccination are great. He said the Department is committed to doing all it can to make sure that access to testing and vaccination is not dependent on your ability to pay. The Department will also work with their sister agencies on this as the Department does not control all pieces of this work.

The Board recessed for lunch at 12:25 p.m. and reconvened at 1:30 p.m.

6. **BRIEFING – SCHOOL ENVIRONMENTAL HEALTH & SAFETY, FINDINGS FROM THE UNIVERSITY OF WASHINGTON REPORT—moved to after Agenda item 10**

Stuart Glasoe, Board Staff, introduced the item, describing the genesis of the report as a legislative proviso in the 2021-23 state operating budget, the scope of the University of Washington's (UW) research on K-12 school environmental health and safety, and the intersection with Board rules for primary and secondary schools. Juan Gamez Briceño, Department of Health, gave an overview of the Department's project statement of work with the University of Washington, background on health and safety concerns with emphasis on polychlorinated biphenyls (PCBs), survey results of school regulations in other states and local school inspection programs in Washington, and key findings and recommendations (presentation on file).

Member Hayes asked if the report was forwarded to the legislature and if there was an invitation to present to any committee. Mr. Gamez Briceño said the report was sent to the legislature but no presentation. Member Hayes asked whether there is a plan for the interim to request committee discussion of the report and the issues around the school proviso and student health and safety. Mr. Gamez Briceño said there are currently no plans. Mr. Glasoe added that staff can look into it as next steps and will continue to work on the issues when staff update the Board in June on the school rules.

Member Kwan-Gett asked about indoor air quality and HVAC systems. Would upgrades have a meaningful impact on respiratory conditions and PCBs, or are they different issues requiring different strategies? Mr. Gamez Briceño said that for schools without modern systems there are ways to improve ventilation and the Department can provide guidelines, but many schools lack funding to improve indoor air quality. He offered to follow up in coming discussions and involve the Department's new indoor air quality specialist. Member Kwan-Gett said there are so many benefits to improving indoor air quality in schools.

Member Kutz said it would be good to educate Board members on the budget proviso and how the Board has not been able to do anything with the rules. He added that he hoped UW would have surveyed a couple schools for PCB rates. The issue needs conversation with industrial hygienists because ventilation repairs in old buildings can stir up PCBs.

Chair Grellner reflected that Friday is a cutoff day for bills and it might be an opportune time to work with Director Davis to craft a letter to budget writers asking for removal of the school proviso. He added that the next update of rules will take years, and the longer the proviso stays in place the further it pushes out the rule update. Chair Grellner added that, having done some of this work locally, schools need help from an independent entity working through these issues and there are things that can be done with schools under the old rules while working on updating the rules. The proviso is the biggest impediment. Mr. Gamez Briceño said the Department has used foundational public health funding to post videos on school practices and to offer additional training. Member Hayes offered support for writing a letter and suggested referencing the importance of foundational public health services funding and other funding in this work.

Motion: The Board directs Chair Grellner, other interested members, and Director Davis to draft a letter to the legislature regarding removal of the school proviso in the state operating budget and related issues.

Motion/Second: Member Kutz/Member Hayes. Approved unanimously

7. **RULES HEARING – HANDLING OF HUMAN REMAINS, NATURAL ORGANIC REDUCTION, CHAPTER 246-500-055 WAC**

Patty Hayes, Board Member, introduced this agenda item with a brief reminder of the Board's authority in this work. Member Hayes also reminded Board members about the presentation Board staff gave at the Board's January 9th meeting, that included a request to initiate exception rulemaking to fix a typo and clarify rule language in WAC 246-500-055. The Board approved this proposal and directed staff to submit the proposed edits to the rule, which were filed on January 31st.

Molly Dinardo, Board Staff introduced the hearing and directed Board members to the English and Spanish translated hearing materials in their Board packets. She noted that Board staff are in the process of testing the translation of Board hearing materials into Spanish based on a recent directive from the Department of Health's Office of Public Affairs and Equity (OPAE) to agency staff to ensure vital rules hearing documents are translated. The goal is to make rules hearings more accessible. She also gave a brief overview of this rulemaking, including background on the rule, the scope of this rulemaking project, the timeline for this work, the proposed edits to the rule, and comments received during the open public comment period (see presentation on file).

There were no questions from Board members before the rules hearing began.

Chair Grellner began the rules hearing at 1:43 pm. He announced that no one had signed up to give public testimony and closed the public hearing at 1:44 pm.

Motion: The Board adopts the proposed revisions to WAC 246-500-055, as published in WSR 23-04-100, with any revisions described and agreed upon by the Board at today's meeting. The Board directs staff to file a CR-103, Order of Adoption, and establish an effective date.

Motion/Second: Member Kutz/Member Hayes. Approved unanimously.

8. **BRIEFING – NEWBORN SCREENING, MUCOPOLYSACCHARIDOSIS (MPS II) QUALIFYING ASSUMPTION ANALYSIS FINDINGS, – POSSIBLE ACTION**

Kelly Oshiro, Board Vice Chair gave a brief reminder of the Board's authority to adopt rules for screening Washington-born infants for hereditary conditions. Vice Chair Oshiro also reminded Members that the Board received a petition in October requesting to add Mucopolysaccharidosis Type II (MPS II) as a candidate condition for newborn screening (NBS) in Washington. At the Board's November meeting, Board members declined the petition and directed staff to return to the Board to present a qualifying assumption analysis on the condition for further consideration.

Molly Dinardo, Board Staff provided an overview of the Board's policy when evaluating candidate conditions for the newborn screening panel. She reminded Board members of the Board's process for evaluating conditions, and that before a technical advisory committee (TAC) can be convened to review a condition against the Board's five newborn screening criteria, a preliminary review should be done to determine whether there is enough scientific evidence available to apply the Board's criteria for inclusion. Ms. Dinardo and John Thompson, Director of Newborn Screening Program, Department of Health, then presented findings on MPS II based on their review of the federal committee's report recommending MPS II for the recommended uniform screening panel (RUSP), in relation to the Board's newborn screening criteria (presentation on file).

Member Hayes asked what questions are being explored by the New York pilot program. Dr. Thompson said that New York in the past twenty years has been at the forefront of newborn screening and expanding panels. For MPS II screening, New York is an early adopter state. He said he is unsure what their research questions are.

Member Hayes asked that since MPS II screening cannot be integrated in the newborn screening lab's current workflow, would a potential proposal to add MPS II to Washington's screening panel require the proposal to go to the state legislature for approval? Dr. Thompson shared that the Department would need to either develop a screening method specifically for MPS II to piggyback on existing methods, or the Department would need to purchase new instruments and install them. Either way, there would be a fair amount of work required.

Member Oshiro asked if a TAC would address how Washington would screen babies for MPS II. Dr. Thompson responded that TACs typically make recommendations to the Board, and the Board would decide whether to add a condition to the NBS panel. If the Board adds a condition, the Department usually leads in implementation. The NBS

Program would identify necessary resources and how to leverage those resources, which may require requesting additional funding to support additional testing.

Member Kwan-Gett asked if other states, particularly those screening or doing a pilot program for MPS II, have performed a cost analysis or provided public health rationale for screening. Dr. Thompson said that he did not think so from an economic analysis standpoint, and he could contact other states to gather more information. He said MPS II screening in other states may have been mandated through the legislative process. He added that studies have modeled how many babies would be born with MPS II, but have not modeled medical outcomes thereafter.

Member Flores asked about the volume of tests performed at Seattle Children's Hospital and whether it is the only facility performing tests in the area. Dr. Thompson said the Department's NBS Program runs the screening program that screens all babies in the state. Seattle Children's Hospital is a diagnostic lab that runs tests with a different panel. They are different types of labs, and Seattle Children's Hospital has the capability of doing diagnostic testing to either confirm or rule out MPS II.

Member Flores asked if Seattle Children's Hospital is seeing demand or an uptick for diagnostic testing. Dr. Thompson said Seattle Children's Hospital has been taking care of babies with clinically identified MPS II for decades and that clinical identification has existed for 20 to 30 years. MPS II is coming to the attention of the Board because there have been advances in technology for screening and treatment. He continued that the predictive value means that for every 10 babies with a positive screen for MPS II through the NBS Program, approximately 1 baby would be confirmed to have MPS II. If Washington screens for MPS II, Seattle Children's Hospital would receive more specimens to do diagnostic testing, and there would be false positives within those specimens.

Member Dean asked for clarification on the meaning of the prevalence for MPS II. Dr. Thompson responded that the prevalence rate means we expect 1 baby to be born with MPS II every 9 or 10 months in Washington. If the state screens for MPS II, the NBS Program would be making a referral to a diagnostic lab for a positive NBS result every month or so. Member Dean asked if there are cases of MPS II not being caught or identified because the state is not screening. Dr. Thompson responded yes. He said the prevalence estimate is based on data from Illinois and Missouri, with no known missed cases.

Member Kutz asked about the turnaround rate for diagnostic testing. Dr. Thompson said the NBS Program includes a follow-up team that sends specimen for every positive screening result to the diagnostic lab. Seattle Children's Hospitals' turnaround time may be around 2 to 5 days and its results are reliable. Member Abdelmalek said she also had questions about confirmatory testing and capacity.

Chair Grellner asked how likely it is for a family with a history of MPS II to be referred to Seattle Children's Hospital by their healthcare provider. Dr. Thompson said if the medical system runs the way it should, there is a high likelihood for referral. However, not all pregnant individuals receive prenatal care and not all families with a history of MPS II understand their current risk or what they can do about it.

Member Kwan-Gett said it would be worth convening a Technical Advisory Committee (TAC) to dig into the data and explore the NBS criteria in depth. Member Hayes said there may not be enough data for a TAC to consider. Member Hayes made the following motion: *The Board determines that there is insufficient information available at this time to know whether MPS II meets the qualifying assumption for the Board's criteria for evaluating conditions for inclusion in the rule. The Board directs staff to update the information in two years and return to the Board for consideration at that time.*

Member Kutz affirmed Member Hayes' motion. He said information from other states' studies may become available within two years, which could give reason for the Board to address the topic sooner. When asked if the NBS Program monitors study results, Dr. Thompson confirmed that the NBS Program monitors the field and often learns from early adopter states. Vice Chair Oshiro said she would be interested in a staff analysis of other states' studies as well as hearing from Seattle Children's Hospital.

Member Hayes said the question before the Board is whether to move forward with a TAC. She provided rationale for her motion, saying there would be a lot of holes in the information the TAC considers, including not being able to look at a cost-benefit analysis. Member Kutz said there seems to be barriers with diagnostic testing. Member Kwan-Gett agreed with Member Hayes about the challenge for the TAC and said he would be interested in hearing from a clinician as well as other states. He asked if it would be possible to access additional information without convening a TAC.

Member Hayes and Member Kutz withdrew their initial motion. Chair Grellner said these are some of the hardest decisions for the Board. He also confirmed with Dr. Thompson that without convening a TAC, the NBS Program could continue to monitor information on MPS II testing and alert the Board sooner than two years if there is additional information to consider.

Member Oshiro made a motion (below). Member Dean agreed with the motion and said information from larger states that have adopted newborn screening for MPS II would be valuable.

Motion: The Board determines that there is insufficient information available at this time to know whether Mucopolysaccharidoses Type II (MPS II) meets the qualifying assumption for the Board's criteria for evaluating conditions for inclusion in the rule. The Board directs staff to update the information *within* two years and return to the Board for consideration at that time. *Additionally, the Board will potentially receive another briefing within a year to hear from early adopter states, clinicians, or families.*

Motion/Second: Vice Chair Oshiro/Member Hayes. Approved unanimously

9. PETITION – NEWBORN SCREENING, REQUEST TO ADD GUANIDINOACETATE METHYLTRANSFERASE (GAMT) DEFICIENCY TO CHAPTER 246-650 WAC

Kelly Oshiro, Board Vice Chair gave a brief introduction to the petition process and

stated that on February 24th, the Board received a petition to add GAMT deficiency as a condition for newborn screening in chapter 246-650 WAC

Molly Dinardo, Board Staff, and John Thompson, Director of Newborn Screening Program, Department of Health, provided a presentation on GAMT deficiency guided by the Board's five criteria for newborn screening for the Board's consideration (see presentation on file).

Chair Grellner opened the topic to discussion and invited Board members to ask questions.

Board Member Kwan-Gett asked for differences between the GAMT Deficiency Screening and the MPS II Screening that were just discussed. Dr. Thompson stated that the main differences are: 1) GAMT deficiency screening can be done in conjunction with already existing testing of amino acids, and 2) the treatment is much less involved, with a home-level dietary modification as opposed to weekly medical visits. Board Member Kwan-Gett followed up to ask if there is more experience in general with the GAMT deficiency screening given the number of states, as well as other countries conducting the screening. Dr. Thompson stated no, not really, and shared that because the condition is so rare, there have been few cases identified to date.

Board Member Dean asked after the provided economic analysis provided, if they thought it was applicable to Washington state and if they had any other insights. Dr. Thompson stated that he had not reviewed that portion in detail.

Board Member Abdelmalek reflected from her perspective as a clinician and shared several things that stood out to her for GAMT deficiency. Member Abdelmalek noted the rarity of GAMT deficiency, the importance of early screening, and the effectiveness of treatment. Member Abdelmalek also shared that she recognized that while data is limited, the case studies and stories describing the outcome disparities in sibling pairs and their time of treatment stood out as showing a potential to mitigate the majority of impacts.

Board Member Hayes agreed with Member Abdelmalek and put forward the motion for the Board to decline the petition for rulemaking at this time but directed staff to work with the Department to move forward with convening a technical advisory committee for the condition.

Board Member Dean asked a clarifying question regarding the prevalence of cases in Washington. She clarified that based on the data presented, in Washington, we might expect to find 1 case every 7 years. Dr. Thompson confirmed that this was correct.

Board Member Kutz asked if this would be relatively simple to add to existing processes, to which Dr. Thompson replied that yes, that is their expectation.

Motion: The Board declines the petition for rulemaking to add GAMT deficiency as a condition for newborn screening in Chapter 246-650 WAC but directs staff to work with the Department of Health to convene a technical advisory committee to evaluate GAMT

deficiency using the Board's process and criteria to evaluate conditions for inclusion in WAC 246-650-020 and then make a recommendation to the Board.

Motion/Second: Member Hayes/Member Abdelmalek. Approved unanimously

10. UPDATE – CHILD IMMUNIZATION RATES IN WASHINGTON STATE

Tao Sheng Kwan-Gett, Secretary's Designee, gave a brief introduction to the update. He said that the last briefing on this topic was in 2021 and that this would be an informational briefing, with no action required. He then introduced the Office of Immunization Director and Staff.

Jamilia Sherls-Jones, Office of Immunization Director, Department of Health, and Katherine Graff, School and Childcare Immunization Nurse Consultant, Department of Health, introduced themselves and gave a presentation about immunization laws and rules, current childcare and school-age immunization data, and strategies to improve vaccination rates for children and adolescents in Washington state (presentation on file).

Stephen Kutz, Board Member, asked the presenters whether they had data on which schools had staff tracking vaccination compliance. Ms. Jones said they are working on a plan within the Department to provide technical support for schools with limited staff capacity, but they do not have data on hand to identify how many schools might need this support. Ms. Graff talked about the Department's strategy to onboard schools to the Immunization Information System (IIS) modules, which makes it easier for schools to do immunization compliance work as it integrates students' medical records. She said about two-thirds of students in K-12 public schools attend a school that uses IIS modules, and the Department is looking to increase that number over time.

Member Kutz asked whether Medicaid childcare providers are required to provide vaccines as a condition for being reimbursed. Ms. Jones replied that she was not sure about the reimbursement condition, but she knows that if a Medicaid provider is enrolled in the Childhood Vaccine Program, they are required to offer all of the vaccines on the Centers for Disease Control and Prevention (CDC) schedule. Member Kutz replied that a step forward could be to talk to managed care companies about adding that requirement into contracts and the Office of Insurance Commissioner about reducing reimbursement rates for providers that do not provide vaccinations.

11. BOARD MEMBER COMMENTS

Keith Grellner, Board Chair called for any comments.

Member Kutz, said this is a different meeting than what we've been having.

Vice Chair Oshiro, thanked Board staff, and enjoyed visiting at lunch. She spoke about convening a TAC for GAMT. She said the Board will have a chance to solicit feedback, and it brought to her attention that there is a coalition of various community health Boards. She said it would be a wonderful opportunity to have a coalition come speak to the Board as they hear recommendations from TAC.

Executive Director Davis expressed her gratitude to the Board for the rich discussion. She mentioned feedback from her team on how Board members can raise items and how to navigate requests. She encouraged Board members to connect with policy advisors to identify topics the Board might find informative. She mentioned opportunities to practice leadership skills with committees and TACS, and she extended the offer to all Board members. She encouraged Board members to share the Board's work with other colleagues in other spaces. She commented on Member Hayes participation on the Public Health Advisory Board, and Member Abdelmalek participation on a local health officers' group, she said that Member Kutz serves as Chair of the American Indian Health Commission (AIHC). Consumer members can also bring issues within their communities to bring the work forward. Member Dean could connect the Board to the Washington State Association of Counties (WSAC) to share what's happening more on the county level for public health. She said the team is here to support Board members, and could explore these topics and partnerships on their behalf.

Member Kutz told the new Board members this is a great opportunity to serve on the TACs, and experts are available, and it is a great learning experience.

Member Hayes asked about the April and June meeting locations. Ms. Davis said it is likely we'll meet at the Labor & Industries auditorium again and possibly the Capitol Campus where the public can join physically and virtually. Member Hayes mentioned a tour of NBS lab, and asked if there was a way to have a future meeting at the Public Health Lab, and that it may help to align with the TAC report. Member Kutz said he recalls there is not much room for parking and Director Davis commented on potential challenges in maintaining an Open Public meeting during tours.

ADJOURNMENT

Keith Grellner, Board Chair, adjourned the meeting at 4:27 p.m.

WASHINGTON STATE BOARD OF HEALTH

_____

Keith Grellner, Chair

From: Melissa Leady
Sent: 4/5/2023 12:43:42 PM
To: DOH WSBOH
Cc:
Subject: My Public Comments

External Email

☐SHARE DATA TO (RE)GAIN TRUST

I have concerns about lack of data sharing and transparency by the Washington State Department of Health (DOH). By only sharing data supportive of COVID-19 policies/vaccines and withholding data that may be critical or cast a more nuanced light on the policies/vaccines, DOH erodes rather than builds trust in Public Health. I include two examples: COVID-19 vaccine mandate data, and All-cause mortality data.

COVID-19 VACCINE MANDATE DATA

1. How many fully-vaccinated (2 doses) working-age adults were hospitalized or died from COVID-19 last month? Last year?

2. What is the RATE for cases, hospitalizations, and deaths for working-age adults who are fully-vaccinated? (Rate, not rate comparison)

3. How many unvaccinated, working-age adults with natural immunity from previous infection were hospitalized or died from COVID-19 last month? Last year?

4. What is the RATE for cases, hospitalizations, and deaths form working-age, unvaccinated adults?

The answers to questions 1 and 2 should be found in the DOH monthly report, COVID-19 Hospitalization and Deaths by Vaccination Status in Washington State. The answers to questions 3 and 4 should be found in the discontinued DOH report, Reported COVID-19 Reinfections in Washington State. Without these data, the vaccine mandate is unsupported.

Given recent studies on effectiveness of natural immunity (source 1) and waning effectiveness of the primary vaccine series (source 2), it is incumbent on DOH to justify the ongoing Washington mandate for state employees. Most Federal vaccine mandates have been rescinded. The Washington mandate appears to be out-of-date.

To (re)gain trust in Public Health and dispel misunderstandings, DOH should openly and transparently share the data outlined above, by reporting data for all vaccination statuses: unvaccinated, partially vaccinated (one dose), completed the primary series (two doses), monovalent booster dose, and bivalent booster dose.

ALL-CAUSE MORTALITY DATA, 2021 and 2022

DOH has not reported all-cause mortality for 2021 or 2022. COVID-19 deaths are reported monthly; all-cause mortality deaths ought to be reported in a similar timely fashion. According to CDC estimates, Washington's all-cause mortality was 68,697 in 2021 and 68,632 in 2022. This is an 8% jump from 2020, which was already up 7.7%

from 2019. This spike in deaths is alarming. Equally alarming: why would DOH not share all-cause mortality data during such a large spike?

The rise in all-cause mortality cannot be explained solely by COVID-19 deaths; the average age of death from COVID-19, at 80 years, is above the age of life expectancy. Concerns have been raised about the role of lockdown restrictions and the COVID-19 vaccination program on the spike in all-cause mortality during the pandemic. Currently, residents are left to speculate.

By DOH sharing 2021 and 2022 all-cause mortality, using the same format as for COVID-19 deaths – broken down by month, age, race, gender, and all vaccination statuses – Washington residents could clearly see when the spikes in mortality occurred and in which age groups. DOH would build trust, clear up any speculation, and dispel misunderstandings (which is always more likely when there is a lack of communication, data, etc.)

I encourage the Board to ask about these two areas where data are lacking. Open and transparent sharing of vaccine mandate effectiveness data and all-cause mortality data will help inform Washington residents and policy makers, and help DOH regain trust in Public Health.

SOURCES

1) NATURAL IMMUNITY: "Protection from past infection against re-infection from pre-omicron variants was high and remained high even after 40 weeks. Protection was substantially lower for the omicron BA.1 variant and declined more rapidly over time than protection against previous variants. Protection from severe disease was high for all variants."

Stein, C, et.al. Past SARS-CoV-2 infection protection against re-infection; a systematic review and meta-analysis. Lancet. 2023; 401: 833-842.

2) VACCINE IMMUNITY: "Our analyses indicate that vaccine effectiveness generally decreases over time against SARS-CoV-2 infections, hospitalizations, and mortality. The baseline vaccine effectiveness levels for the omicron variant were notably lower than for other variants." INTERPRETATION.

"We found that the vaccine effectiveness of the primary vaccine series against SARS-CoV-2 infections begins at an adequate level...however, vaccine effectiveness decreased significantly by 112 days after vaccination, reaching 47% by 280 days after vaccination, well below an adequate level." DISCUSSION.

Wu, N., et. al. Long-term effectiveness of COVID-19 vaccines against infections, hospitalisations, and mortality in adults: findings from a rapid living systematic evidence of synthesis and meta-analysis up to December, 2022. Lancet. 2023. DOI: https://doi.org/10.1016/S221302600(23)00015-2.

From: Garry Blankenship
Sent: 4/1/2023 12:14:08 PM
To:
mozias@co.clallam.wa.us,rjohnson@co.clallam.wa.us,shahidafatin@gmail.com,gbsjrmd@sisna.com,ncarr@

Subject: mRNA Harms

External Email

Good Day,

I am concerned that the North Olympic Peninsula Health District makes little effort to independently educate themselves on historical and current "pandemic" events. Positions taken by Federal and State COVID health management have thus far without exception proven complete failures. Below is a recent article authored by two experts more credentialed than any of us; particularly BOH members. It is the boards continued support and promotion of these harmful mRNA drugs when they clearly have a negative risk / reward ratio that must be explained. "Vaccinated" people are now seven times more likely to acquire COVID than non-vaccinated. The possibility of mitigating symptoms simply does rise to justification for risking the drug adverse reactions. I ask that the board publically explain their support of these drugs in order that the fear of "vaccine hesitancy" not be further fomented.

Sincerely,

Garry Blankenship
Concerned Constituent

Serious Harms of the Covid-19 Vaccine: A Systematic Review

BY MARYANNE DEMASI
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fbrownstone.org%2Fauthor%2Fma
demasi%2F&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cfcf39c43bde3485de78408db32e541d9%7C11
MARCH 30, 2023 VACCINES
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fbrownstone.org%2Ftag%2Fvaccin
3 MINUTE READ

SHARE | PRINT | EMAIL

Recently, my colleague and I completed a systematic review of the serious harms associated with covid-19 vaccines.

My co-author Peter Gøtzsche
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fbrownstone.org%2Fauthor%2Fpet
c-
gotzsche%2F&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cfcf39c43bde3485de78408db32e541d9%7C1
, is a Danish physician with four decades of research experience, publishing 97 papers in the “big five” (BMJ, Lancet, JAMA,Annals of Internal Medicine, and New England Journal of Medicine) and 19 Cochrane reviews.

My previous report

<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fmaryannedemasi.substack.com%2
adverse-events-in-covid-19-vaccine-trials-under-
reported&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cfcf39c43bde3485de78408db32e541d9%7C11d0
on how serious harms were downplayed or excluded from the covid-19 trials, became the impetus for this review.

Also, concerns have been raised about the reliability of clinical trial data because of the pharmaceutical industry's long history
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medicines-organised-crime-peter-
gotzsche&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cfcf39c43bde3485de78408db32e541d9%7C11d0
of falsifying data and deliberately hiding harms.

In the case of covid-19 vaccines, neither the vaccine manufacturers, nor the drug regulators allowed independent researchers to examine
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.bmj.com%2Fcontent%2F376
the raw trial data, forcing transparency advocates to sue the FDA
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fmaryannedemasi.substack.com%2
to-release-pfizer-data-but-the-devil-could-be-in-the-
detail&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cfcf39c43bde3485de78408db32e541d9%7C11d0e21
for access to the documents.

In our review, we focused on serious adverse events (SAEs) associated with covid-19 vaccines, documented in the published literature (search cut-off date was 4 April 2022).

We defined SAEs according to the European Medicines Agency definition
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adverse-
reaction&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cfcf39c43bde3485de78408db32e541d9%7C11d0e
:

An adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect.

Here are the salient points:

1. Many of the studies we reviewed were of very poor quality and published in journals that failed to identify fundamental errors.
2. To date, the most methodologically rigorous systematic review of SAEs was conducted by Fraiman
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et al
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.ncbi.nlm.nih.gov%2Fpmc%2
, which reanalysed trial data from two pivotal randomised trials of the mRNA vaccines (Pfizer & Moderna), including SAEs from the websites of the FDA and Health Canada. The risk of an SAE following vaccination exceeded the risk of hospitalisation from covid-19.
3. The adenovirus vector vaccines increased the risk of venous thrombosis and thrombocytopenia. (Authorities have responded by suspending
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.aljazeera.com%2Fnews%2F
countries-have-halted-use-of-astrazenecas-covid-
vaccine&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cfcf39c43bde3485de78408db32e541d9%7C11d0e
the use of AstraZeneca's vaccine across many European countries, and in the US, regulators have advised restricted use
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.fda.gov%2Fnews-
events%2Fpress-announcements%2Fcoronavirus-covid-19-update-fda-limits-use-
janssen-covid-19-vaccine-certain-

individuals&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cfcf39c43bde3485de78408db32e541d9%7C11d
of Janssen's vaccine).
4. The mRNA-based vaccines increased the risk of myocarditis, with a mortality of about 1-2 per 200 cases. It was more common in younger males.
5. We found evidence of serious neurological harms, including Bell's palsy, Guillain-Barré syndrome, myasthenic disorder, and stroke, which are likely due to an autoimmune reaction from mRNA and adenoviral vector vaccines.
6. Severe harms, i.e. those that prevent daily activities, were underreported in the randomised trials.
7. Severe harms were very common in studies of fully vaccinated people receiving boosters (3rd dose), and in a study of vaccination of previously infected people (i.e. those with naturally acquired immunity).
8. Drug regulators and other authorities have been very slow in following up signals of serious harms.
9. Given the difficulties of accessing regulatory data, obfuscations, and documented underreporting, we find it likely that there are other serious harms of the covid-19 vaccines, than those uncovered so far.
10. Population-wide recommendations for covid vaccination and boosters ignore the negative benefit to harm balance in low-risk groups such as children and people who have already recovered from covid-19 (natural immunity).

The full manuscript has been uploaded as a PRE-PRINT
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harms-of-the-covid-19-
vaccines&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cfcf39c43bde3485de78408db32e541d9%7C11d0

Author

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Maryanne Demasi
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fbrownstone.org%2Fauthor%2Fma
demasi%2F&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cfcf39c43bde3485de78408db32e541d9%7C11

Maryanne Demasi is an investigative medical reporter with a PhD in rheumatology, who writes for online media and top tiered medical journals. For over a decade, she produced TV documentaries for the Australian Broadcasting Corporation (ABC) and has worked as a speechwriter and political advisor for the South Australian Science Minister. Her work can be accessed on her website at maryannedemasi.com.

From: Laura Breymann
Sent: 3/7/2023 7:38:13 PM
To: DOH WSBOH
Cc:
Subject: Public comment re: healthcare mask mandate

External Email

To whom it may concern at WA State Board of Health,

I am a Kirkland, WA resident and practicing Family Medicine physician, and I am very concerned that the mask mandate in healthcare, long-term care, and correctional facilities is set to end on April 3.

Removing the mask mandate will further endanger our families and community members. Patients should never have to worry that they may contract Covid-19 when accessing healthcare, and that is the situation we're in now. Covid-19 is still very prevalent in the community, and our transmission levels are greatly undercounted as testing is often not being performed when indicated.

My 80 year old father is a cancer patient, and he is extremely Covid-cautious in his personal life because he knows he could be very high risk if he contracts Covid. The highest risk setting that he enters currently is the hospital, which is very scary and sad. I also have many patients that are scared to go to doctors appointments and enter hospitals because of the risk of Covid. Ending the mask mandate removes another very important layer of protection, and I fear that our vulnerable patients either won't get the care they need, OR they'll get sick while trying to access necessary care.

As a physician, I also want the mask mandate to remain for my own safety. I am very concerned about the long-term risks of Covid-19, and I do not want to contract this illness at work and get sick myself nor bring it home to my young kids. I may end up stopping working if I do not feel safe in the workplace.

High quality masks, when worn consistently, DO work. There is strong evidence that masks (especially N95s) significantly reduce the risk of Covid-19 in healthcare settings and in the community, but unfortunately the recent studies often cited have problems with their methodology and are therefore not conclusive. If anything, we should be encouraging high quality masks (N95s or similar) in healthcare settings instead of taking masks away.

Abandoning public safety and health measures is counterproductive to stopping the spread of this disabling and deadly virus as it continues to mutate and evolve. The WA Department of Health's mission to "to protect and improve the health of all people in Washington state" cannot be accomplished without masks in healthcare, long-term care, and prisons.

I am extremely passionate about Covid-safe practices, and I am very concerned about the above. Please feel free to contact me if you have any questions regarding the above.

Sincerely,
Laura Breymann, MD

From: Allison Taylor
Sent: 3/8/2023 12:07:15 AM
To: DOH WSBOH
Cc:
Subject: masks in healthcare, LTC, and prisons

External Email

Hello,

My name is Allison. I am a King County resident and I call on Secretary of Health Umair Shah to keep masks in healthcare, long-term care, and prisons.

I am disappointed to be unable to attend this meeting in person but wanted to add my voice to the many others who are desperate to keep masks in these settings where removal will be devastating to our most vulnerable community members.

I am a Registered Nurse, but I am not currently working because I have a high-risk child at home that I am caring for. A Covid infection could be devastating for my child, and our whole family. She has a history of infection-triggered autoimmune encephalitis. It's essential for us to do everything we can to keep her from getting infected. As public health measures have fallen away, we have had to make many sacrifices. We can't safely attend school in-person, travel on an airplane, or attend live theater - all things we used to love before the pandemic.

But healthcare is not optional. By making masks optional, you make seeking healthcare dangerous for every member of our family. My daughter needs braces and is overdue for her routine dental care. How can I possibly feel safe sending her into these settings where she must remove her mask if masks become optional? If my husband or I were to get infected while seeking healthcare and passed it on to our daughter, how could we ever live with ourselves?

We often hear that masks should be optional and that if we prefer to wear one, we are welcome to do so. What about the children under 2 years old who cannot mask and need their well-child checks or may need to visit a hospital? What about the fact that there are no N-95 level masks approved for children to protect themselves? What about the hospitalized patient who must remove their mask at least to eat or drink? None of these people can properly protect themselves in a mask-optional setting.

It has become clear that when masks are not required, very few will wear them. Consider the fact that an estimated 40% of people with active Covid infections are asymptomatic. If unmasked, they can easily transmit Covid to other vulnerable people.

Without a requirement, even individual clinics or providers who wish to continue to require masks become vulnerable to vicious attacks. It becomes nearly impossible for individual providers to enforce a mask requirement without a state mandate to back them up.

One-way masking is still worthwhile, but we know that universal masking offers far superior protection. Our high-risk community members must spend an inordinate amount of time and energy seeking out safe providers for their healthcare needs already, but without mask requirements, it will become even more difficult to receive safe care. Many of us have postponed essential care because we felt it was too dangerous. I don't think any of us ever imagined that it would become infinitely more dangerous with every passing day. Dropping mask requirements in healthcare settings will lead to deferred and delayed care for high-risk patients like my family. It's not fair for us to have to balance the need for care with the very real danger of possible infection.

There is a lot of talk about how things have changed now that we have vaccines. And while the danger of the acute phase of infection may be lesser for many people, that's not true for everyone. We are still losing HUNDREDS of Americans every day. And while we might not die from our initial infection, we are ALL at risk for Long Covid. My daughter would likely survive the acute phase of Covid. But the subsequent brain inflammation that would likely follow could lead to a lifetime of disability and pain. It's a risk we absolutely cannot afford to take.

"Living with Covid" means that we must adapt. Keeping healthcare safe and accessible to all is absolutely essential. It is cruel to even consider removing mask requirements in these settings. I resigned from my job as a pediatric nurse to care for my own sick child. Over the past several years I have often thought of how distressing it would be to have to work in a hospital during a pandemic because I would never feel safe and confident coming home to my vulnerable child. But without mask requirements, we are putting not only our vulnerable patients at risk, but also all of the providers and staff who help care for them. Many of them are vulnerable or have vulnerable family members. It is not fair for them to work in an environment without this protection.

The news of Washington abandoning mask requirements in healthcare, LTC, and prison settings was an absolute gut punch for our family. I am devastated and frightened. I honestly thought that our state was better than this and that it would show more care and concern for its citizens.

I am begging for this matter to be reconsidered.

Thank you for your time and consideration.

Allison Taylor

*

From: Laurie Swanson
Sent: 3/8/2023 2:22:32 PM
To: DOH WSBOH
Cc:
Subject: Please keep masks in healthcare settings

External Email

I want to be as safe as possible when visiting healthcare providers and I will be more afraid/less likely to make appointments if masks aren't required. It doesn't seem like a lot to ask in healthcare settings where people are actively sick, to protect everyone.

I am also a LMT and it has been important to have an official requirement backing me up in my masking policy. I have high risk family members and clients, and I am not comfortable at this point having masks be optional. So I will probably lose some clients who have been willing to wear masks since it was a requirement, but won't be willing now that it has been dropped.

Please do anything you can to continue to protect public health.

Thank you,

Laurie Swanson, LMT
Seattle

From: D Poland
Sent: 4/5/2023 8:59:07 AM
To: DOH WSBOH
Cc:
Subject: My Public Comments

External Email

Board members,
I have recently viewed the letter of appreciation to Dr. Fauci from Keith Grellner dated January 13, 2023. I am a concerned citizen that this board of health is towing the line of the Covid propaganda that has clearly harmed more citizens of Washington state than has helped them. Have you not looked at the facts surrounding Dr. Fauci's participation in the production of the Covid-19 virus? He has lied under oath to Congress about gain of function research and the origin of the virus. Dr. Fauci is a disgrace. He has lied over and over on the the effectiveness of masks and the Covid-19 vaccines. The Covid-19 vaccines do not prevent people from getting Covid. Everyone knows this! There is a nearly 30% increase in death from heart attacks in adults 25 to 44 years old during the first two years of the pandemic cause by the Covid-19 vaccine! The majority of the citizens of Washington state have lost trust in the federal and state governmental agencies because you do not speak the truth on the Covid-19 vaccines and the facts about the Covid-19 pandemic. The truth is out and you seem to be on the wrong side. Shame on you! Admit you have been wrong, start speaking the truth, and you will gain the trust of the people again.

In truth,
Darcy Poland

From: Sasha Anderson
Sent: 3/8/2023 8:34:40 PM
To: DOH WSBOH
Cc:
Subject: March 8 public comment

External Email

Hi,

Submitting my comment for the record:

My name is Sasha Anderson, I grew up in King County and currently live in Seattle. I am representing all medically fragile people when I ask you today to keep masks in place in healthcare settings because it does not align with what science is telling us. Community covid transmission remains high according to the CDC's map. We need to practice good source control as recommended by aerosol scientists which means preventing infectious droplets from leaving the mouths of those with covid to infect other patients around them. Vulnerable people must be able to access medical care safely without catching covid. I have long covid and am working with my care team to figure out ongoing cardiac and neurological issues. I am in and out of the eER and doctors visits right now. My medical team has been very clear that my highest priority is avoiding covid reinfection. How am I supposed to do that if we aren't practicing source control in medical settings? If you don't value my life, what about the lives of immunocompromised children receiving care at Seattle Children's? What about my 85 year old grandmother in a full time care facility? Why isn't the Department of Health following best practices to reduce transmission in the most high risk care settings? As suggested by my conversations with experts at UW Medicine, I am asking you to keep the current mask mandate in place for 1 year while we develop science-driven mask guidance applicable to not just covid but all airborne diseases in WA state healthcare settings.

Sasha Anderson, Guest Faculty
University of Washington Information School

_____

From: Dennis Flynn
Sent: 3/31/2023 7:22:28 PM
To: DOH WSBOH
Cc:
Subject: Public Comments for WSBOH Members from March EH Committee Special Meeting

External Email

To the WA BoH:

In the March 8, 2023 meeting, Dr. Kwan-Gett presented on behalf of the Department of Health, providing a briefing in which the Doctor falsely represented COVID as the cause of death for hundreds of people in the USA and dozens of people every week in our state.

The Doctor rightly calls out that most of the mortality are of elderly and/or chronically ill and/or immune deficient persons, but then he questions our desire to get back to normal when the risk to these populations is still "very real" and "very high".

The question you need to ask is: is it true?

For the majority of these deaths, COVID is not the primary reason for the death (though it may be a contributing factor), so the Doctor stating that these are COVID deaths is NOT true.

Stating COVID is the sole "very real" and "very high" risk to these persons as a reason to hesitate returning to normal is also NOT true, because the right question to ask is: are these people at "very real" and "very high" risk from the flu or a common cold or some other viral or bacterial infection? Obviously these persons are always at risk.

I saw this same disregard for the "is it true?" question when I reviewed some of the information presented to the TAG committee last year. Yes, we should listen to subject matter experts, but when making public policy you should also do our own research and use our own critical thinking skills, incorporating multiple factors instead of the silo of one subject matter expert.

Additionally, this is the same Dr. Kwan-Gett who presented the Washignton State DOH position as being 110% in support of vaccines for infants when he led a webinar with Dr. Dunn, Dr. Getz, Lacy Fehrenbach (WA DOH), and nurse Lindsay Kirsch back in April 2022. We were well over 1-year into the pandemic, and the evidence was readily available that the younger you are the less risk there was from contracting COVID, that

natural immunity was effective, and the evidence of vaccine adverse events in children were readily available in VAERS and VSAFE. Yet Dr. Kwan-Gett advocated for vaccinating children and infants even if they had already recovered from previous infection. The Doctor even went so far as to insinuate that anyone who doesn't get their children vaccinated is risking the health of the community. And then he dumbfounded me by later saying it is "rare for young kids" to be impacted by COVID (so why the authoritarian diktat to vax the kids, then?)!

I don't write this to disparage Dr. Kwan-Gett, but instead I write this to encourage you to actually do the work of bringing some of your own research and reading to your discussions and deliberations so that your critical thinking skills may be brought to bear in asking clarifying questions and having crucial conversations, because your decisions impact millions of people in Washington state and you cannot constrict yourselves to outsourcing everything to the Tragedy of the Tyranny of THE Expert.

For example, the follow-up questions for Dr. Kwan-Gett included asking about testing and, oh my, what is going to be done when all the free tests run out? Really, that's the question? The answer is obvious: COVID is now a part of our lives, and we learn to live with it, including all the normal precautions we take when we don't feel well. Dr. Kwan-Gett's response to this and the other questions included factoring in every aspect of society in coming up with producing positive outcomes for everyone is pure fantasyland. His response is exactly to my point about one expert with expertise in one subject matter: utopia doesn't exist; the board members need to see reality when it is right in front of you and help guide public policy that makes the most benefit for the most people, with the understanding that will be restricted by realities of society and funding.

Instead your position calls for questioning the expert, getting contradictory expertise, identifying other public impacts, considering all of it, and then, and only then, setting public policy.

_____
From: Ellen Kuwana
Sent: 3/10/2023 2:20:19 PM
To: DOH WSBOH
Cc:
Subject: pls keep masks in sites with vulnerable populations

External Email

Please keep the mask mandate in places such as healthcare settings, prisons, and long-term care facilities.
Thank you,
Ellen

Founder, We Got This Seattle.org who fed 75,000 frontline workers during the height of the pandemic

Ellen Kuwana, MS (she/her)

mobile 206.963.0997
Freelance scientific writer and editor

ellenkuwana.com
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.ellenkuwana.com%2F&data=

https://www.linkedin.com/in/ellenkuwana

-Recipient, Diane McGurgan Service Award
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.nasw.org%2Farticle%2Fscie
writers-nasw-2022-mcgurgan-volunteer-service-award-carmen-drahl-ellen-
kuwana&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cc1904ffe8b2644b5139308db21b59f53%7C11d0e

-Founder, WeGotThisSeattle.co
<https://gcc02.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwegotthisseattle.co%2F&data=05%

-President, Northwest Science Writers Association
<https://gcc02.safelinks.protection.outlook.com/?url=http%3A%2F%2Fnwscience.org%2F&data=05%7C0

-Host, National Association of Science Writers Freelancers Chat

-Pro bono editor, Academic Editing Circle
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Facademic-
editing-
circle.us%2F&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cc1904ffe8b2644b5139308db21b59f53%7C1

_____
From: melleady
Sent: 3/8/2023 12:47:28 PM
To: DOH WSBOH
Cc:
Subject: public comment 03-08-2023

 *attachments\B0CEF56E375548D4_SBOH-Leady-2023-03-08.docx*

External Email

Dear Board Members,

I am providing an attached file with the 3-minute written version of my public comments at today's board meeting.

I would like to make a suggesting also, for future meetings when there is a large number of participants interested in speaking. Perhaps if you know the speaking time will be shortened, you could email those on the list, and they could have a bit of time to adjust their comments to fit the new time constraints. I know that certainly would have helped me, and not taxed the sign language interpreter so much.

Thank you for taking public comment today and for considering my concerns about the lack of data supporting the current vaccine mandate.

Sincerely,

Melissa Leady
Clark County

From: Arne Christensen
Sent: 3/28/2023 4:51:53 PM
To: DOH WSBOH
Cc:
Subject: overseas damage from lockdowns

External Email

Hello:
I recommend that someone at the Board of Health watch this 29-minute film about what covid lockdowns did to one village in central India:
https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fcollateralglobal.org%2Farticle%2Fth children-of-nowhere%2F&data=05%7C01%7Cwsboh%40sboh.wa.gov%7C1773212ba40c4e3b1da208db2fe766ae%7C

Our actions in Washington and the U.S., by setting a bad example, helped cause the lockdown harms, to children in particular, shown and described in the film. And, Washingtonians are experiencing some of the same harms as the people in the village. There is one particularly good quote about the mental state of students in the village post-lockdowns: "Their grasping power had reduced significantly."

From: Anna Neher
Sent: 3/8/2023 6:42:44 PM
To: DOH WSBOH
Cc:
Subject: Mask Mandates in Washington State

External Email

Hello,

I am writing to urge the Washington State Board of Health to keep mask mandates in place in prisons, health care facilities, and long term care facilities. We know that masks are an effective way to limit the spread of COVID-19 and other respiratory illnesses, and masking is critical to preventing the spread of disease. This is particularly relevant in prisons (where people do not have the choice to leave), health care and long term care facilities where again, people have to access essential services and care.

We should do this not only because of the risk of immediate term illness but because of the long-term risks. We are still learning about Long Covid, but an estimated 10% - 30% of Covid infections generate long term symptoms.

Best regards,

Anna Neher

From: Doug G
Sent: 4/4/2023 1:35:53 PM
To: DOH WSBOH
Cc:
Subject: Re: Ahora disponible: Propuesta de orden del día para la reunión pública de la Mesa Directiva de Salud del 12 de abril


attachments\3AB83449247B4C60_image001.png


attachments\E5C38DD184A14076_image001.png

External Email

What does It say?

On Wed, Mar 29, 2023, 1:29 PM DOH WSBOH <WSBOH@sboh.wa.gov <mailto:WSBOH@sboh.wa.gov> > wrote:

La propuesta de orden del día <https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fsboh.wa.gov%2Fsites%2Fdefault%03%2FWSBOH-Agenda-2023-04-12-Draft_Spanish.pdf&data=05%7C01%7CWSBOH%40sboh.wa.gov%7C3a2c2b45b0be4ce2242c08db354bf8c ya está disponible para la reunión pública de la Mesa Directiva de Salud del 12 de abril de 2023. Nos reuniremos de 10:00 a.m. a 3:10 p.m.

Lea la propuesta de orden del día para obtener más información sobre la reunión, incluso sobre cómo hacer comentarios públicos. Podrá acceder a la reunión de las siguientes formas:

1. Acceda en línea y regístrese:

https://us02web.zoom.us/webinar/register/WN_mu2A7ZgeSb-xy6NhUG6rog

2. Llame y participe usando su teléfono:

    0. Llamada telefónica al seminario web: +1 (253) 215-8782
    1. Id. del seminario web: 889 1392 5308
    2. Contraseña del seminario web: 660897

Comentarios públicos escritos:

* Lo invitamos a enviar comentarios públicos por escrito a la Mesa antes de la reunión. Para poder garantizar que los integrantes de la Mesa tengan lo oportunidad

de leer y tener en cuenta sus comentarios antes de la reunión, envíenos sus comentarios por correo electrónico <mailto:wsboh@sboh.wa.gov?subject=My%20Public%20Comments> antes del viernes 7 de abril al 12:00 del mediodía. Los comentarios escritos que se reciban después de las 12:00 del mediodía del viernes se comunicarán a los integrantes de la Mesa, sin embargo, es posible que no los tengan en cuenta o no puedan leerlos durante el fin de semana antes de la reunión o durante la reunión. Los comentarios públicos que se reciban por escrito se publicarán en la página web del material de la reunión el 7 de abril de 2023.

Hacer comentarios públicos verbales en las reuniones híbridas:

* Para el público que asiste en persona: Consulte el orden del día adjunto para saber cómo hacer un comentario público si asiste en persona.
* Para el público que asiste virtualmente: Si desea hacer un comentario público, inscríbase a través del enlace del seminario web de Zoom antes de las 12:00 del mediodía del día anterior a la reunión. Se mencionará su nombre cuando sea su turno para hacer comentarios.
* Para hacer una declaración pública en las audiencias sobre normas, por favor use el mismo proceso.

Más información sobre la reunión:

* Esta reunión tendrá un formato híbrido. La reunión virtual se llevará a cabo a través de la aplicación Zoom para seminarios web. La reunión presencial se llevará a cabo en el Auditorio de Trabajo e Industrias, 7273 Linderson Way SW, Tumwater, WA 98501.

Phone: (360) 236-4110

Mailing Address: P.O. Box 47990, Olympia, WA 98504-7990

Location <https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.google.com%2Fmaps%2Fpla
122.9083621%2C17z%2Fdata%3D!3m1!4b1!4m5!3m4!1s0x549173f074205aa3%3A0x552ddc5f79ee44b6!
122.9061681%3Fhl%3Den&data=05%7C01%7CWSBOH%40sboh.wa.gov%7C3a2c2b45b0be4ce2242c08db
· Website <https://gcc02.safelinks.protection.outlook.com/?url=http%3A%2F%2Fsboh.wa.gov%2F&data=05%7C01%
· Email <mailto:wsboh@sboh.wa.gov> · Facebook <https://gcc02.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.facebook.com%2FWashington
· Twitter <https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Ftwitter.com%2FWASBOH&data=0
· Subscribe <mailto:wsboh@sboh.wa.gov?subject=Please%20Add%20My%20Name%20to%20the%20WSBOH%20Ema

Please send us an email with the subject “unsubscribe” if you no longer wish to receive communications from us

---

From: Micah
Sent: 3/8/2023 8:15:49 PM
To: DOH WSBOH
Cc:
Subject: your writing's cool...

External Email

Hello,

I read your writing and had to reach out. This section specifically:

"...Shortly after having attended the Orthodox liturgy, I happened to attend mass at the proto-Cathedral of St. James in downtown Vancouver. The priest there was a traditional curmudgeon who used the building's status as an historical landmark to remove the free-standing altar and restore the sanctuary to what it had been before Vatican II. It was the first time I'd experienced the mass said ad orientum (toward God) instead of vox populi (toward the congregation). The Orthodox always celebrate the liturgy ad orientum and go one step further by placing the priest behind a screen, with only a door through which to view him. If he's on the other side of the screen, he's praying to God. To address the congregation, even to give a peace blessing, he comes through the door to our side of the screen. It was the mass at St. James that made me realize what an insidious heresy it was to say the mass vox populi. By orienting the priest towards the congregation, he quits being the leader of the congregation leading the prayer directed at God, but becomes the focus of attention, removing our attention from God. When the priest says mass ad orientum, we're naturally inclined to direct our attention at that which the priest is attending, and the focus is on God. Using vox populi, the priest's attention is either on us or behind us, and our attention is on him, interrupting our attention which should be towards God...."

Your writing is able to explain a complex concept in a succinct and engaging way - a true demonstration of skillful storytelling. Your discussion of moralistic therapeutic deism immediately reminded me of this writing I read from James on Plexus recently:

"...moralist therapeutic deeism and cultural religion is interesting to me but also strange. It's interesting that there is a subset of people who believe in some form of theism and an afterlife but totally rebuke the law that exists in their book. I think especially in modern times premarital sex and various other sins are considered commonplace/antiquated. I have even heard of some more progressive protestant priests explaining this idea. Interested in how much the book actually matters at that point vs a cultural community. Crazy that you can choose to not be an originalist in the view of godly law."

I came across James's writing in Plexus (mentioned above) - an online community I'm building that's designed for authentic conversation among thoughtful writers. (I think you'd thrive there, link if interested: https://plexus.earth/micah-invite <https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fplexus.earth%2Fmicah-invite&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cb1c799ccdebb4a7b0ba908db2054f3c6%7C11d0e21
) Anyway, just writing to say really enjoyed what you put out.

—Micah

purpose of plexus <https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fplexus.substack.com%2Fp%2Fsca
intimacy&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Cb1c799ccdebb4a7b0ba908db2054f3c6%7C11d0

<https://www.google-analytics.com/collect?v=1&t=pageview&tid=G-V6Q7QER3X6&cid=cid_6292c03531683ff2a496a85b&aip=1&npa=1&ds=email&dl=https%3A%2F%2Fstatis

From: Angie Sowell
Sent: 3/7/2023 6:47:35 PM
To: DOH WSBOH
Cc:
Subject: Masks in health care settings

External Email

Hello,

I’m writing to request that you choose to keep masks in healthcare, long-term care, and prisons.

Mask requirements keep vulnerable populations safe, including people who don’t have a choice to not be in these places.

Thank you,
Angie Sowell
Immunocompromised resident of Seattle

_____

From: Trish Nilsen
Sent: 3/16/2023 4:19:18 AM
To: DOH WSBOH
Cc:
Subject: Late response to March 8th meeting

External Email

I'm sorry to have been delayed in responding to your first in-person BOH meeting March 8th but wanted you to know I will be closely following the Board's actions related to Covid abatement measures/policies and the Covid shots, in that I believe they have caused harm to many. I staunchly support bodily autonomy and a free person's right to choose whether or not their own risk-benefit analysis merits in deciding to/not to take the shot, as opposed to mandates forcing the decision. I also believe children do not need the Covid shots and that parents have the sole right to choose whether or not the shots should be given to their children, rather than having that mandated or pushed on them through public health-endorsed coercion, especially given there is no non-biased research showing clear benefit and no harm in these populations.

Please remember you are public servants and that public health measures should not be weaponized, as they have been during the covid endemic, as this alienates those you are intending to serve. The research on Covid is yet to fully be transparent nor conclusive and does not approximate full endorsement of many of the measures you have put in place the past 3 years, so please be cautious on implementing any broad, sweeping or permanent policies. Respectfully, Trish (Patricia) L. Nilsen,RNC

From: Theresa Everest
Sent: 4/5/2023 3:16:18 PM
To: DOH WSBOH
Cc:
Subject: Re: Ahora disponible: Orden del día definitivo de la reunión pública de la Mesa Directiva de Salud del 12 de abril

attachments\0B23C3FBCA084EE9_image001.png

External Email

No hablo espanol.

Theresa Everest
Everest Ranch, LLC
509-680-5393

On Apr 5, 2023, at 12:19 PM, DOH WSBOH <WSBOH@sboh.wa.gov> wrote:

☐

Ya está disponible el orden del día definitivo propuesto <https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fsboh.wa.gov%2Fsites%2Fdefault%
04%2FTab01a-WSBOH-Agenda-2023-04-12-Final_Spanish_3.pdf&data=05%7C01%7CWSBOH%40sboh.wa.gov%7C1fe23ecbd98646a7c3f308db362322 para la reunión pública de la Mesa Directiva de Salud del miércoles 12 de abril de 2023. Nos reuniremos de 10:00 a. m. a 3:10 p. m.

Lea la propuesta de orden del día para obtener más información sobre la reunión, incluso sobre cómo hacer comentarios públicos. Podrá acceder a la reunión de las siguientes formas:

1. Acceda en línea y regístrese:

https://us02web.zoom.us/webinar/register/WN_mu2A7ZgeSb-xy6NhUG6rog

2. Llame y participe usando su teléfono:

    0. Llamada telefónica al seminario web: +1 (253) 215-8782
    1. Id. del seminario web: 889 1392 5308
    2. Contraseña del seminario web: 660897

Comentarios públicos escritos:

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(360) 236-4110

P.O. Box 47990, Olympia, WA 98504-7990

Ubicación <https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.google.com%2Fmaps%2Fpla
122.9083621%2C17z%2Fdata%3D!3m1!4b1!4m5!3m4!1s0x549173f074205aa3%3A0x552ddc5f79ee44b6!
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· Sitio web <https://gcc02.safelinks.protection.outlook.com/?url=http%3A%2F%2Fsboh.wa.gov%2F&data=05%7C01%
· Correo electrónico <mailto:wsboh@sboh.wa.gov> · Facebook <https://gcc02.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.facebook.com%2FWashington

· Twitter
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Ftwitter.com%2FWASBOH&data=0
· Subscríbase
<mailto:wsboh@sboh.wa.gov?subject=Please%20Add%20My%20Name%20to%20the%20WSBOH%20Ema

From: Megan Davis
Sent: 3/9/2023 1:04:01 AM
To: DOH WSBOH
Cc:
Subject: Please keep masking in health care!

External Email

Please reverse your recent announcement that masks will no longer be required in all WA state healthcare facilities, long term care facilities and jails as of April 3rd. This decision will put many of the most vulnerable in our community in grave danger. I work in a hospital and hear how some of the staff are excited about being able to take their masks off at work. This will put me, and two other family members who are high risk in more danger as I have no choice but to attend work in person, encountering dozens (100s?) of people during my day. My parents are in their 80s and already dealing with chronic health issues. They isolate as much as they can to protect themselves but need to attend many medical appointments. My mother in law (also nearly 80) lives in a long term care facility where she already caught COVID last summer during an outbreak of nearly 100 residents, and that was WITH masking being required. I am quite worried for her and others who live in similar settings where outbreaks will undoubtedly increase. Today she continues to experience long COVID. A neighbor has ME/CFS long COVID that she is unable to care for her children, get her own groceries, prepare food, etc. The most important thing for her is to avoid any more COVID infections. Ending the mask mandate will make more infections likely.

I work with newborn babies every day who are unable to mask and don't deserve to have their nurse, doctor and lab technician breathe on them with potentially infectious aerosols. What about the babies in the NICU who are already at very high risk?

Lastly the decision to remove mask requirements in these settings sends a strong message to the community that our state believes the pandemic is over and that COVID is no longer a concern. While less people are now dying of acute infection we know that many people are developing long COVID after their first or subsequent infections. Many are unable to work. Many are dying of heart attacks, pulmonary embolisms, etc. as a direct result of their infections. Others have new diagnoses of POTS or diabetes due to COVID infection. Is it really the message you want to send that COVID is not longer a risk? Because more an more of the population is already believing that despite the facts.

I had hoped that medical facilities would forever require masking. I had hoped that we would have learned something from this pandemic that would continue protecting us from this and other infections, both routine and emergent. I'm so sad about the state's decision and what it will mean for our community. Healthcare is already not accessible to so many people because of cost. Now it will also not be accessible because many people will feel unsafe. People will skip their colonoscopy, mammogram, or dental check up.

From: Arne Christensen
Sent: 3/24/2023 12:29:49 PM
To: DOH WSBOH
Cc:
Subject: face covering policies

External Email

The Board needs to apologize for forcing people to put masks on their faces in order to receive health care for nearly 3 years, and apologize for misleading people about the effectiveness of face coverings against respiratory viruses. Has anyone on the Board looked at the evidence from Sweden and other Nordic countries? Hardly anyone there wears face masks, and their covid burden is much less than America's. For that matter, why not ask for advice from Idaho and Utah?

_____

From: martha hykel
Sent: 3/20/2023 7:40:25 PM
To: DOH WSBOH
Cc:
Subject: Subject: KC Health Dept. employee- Ms. Thea Oliphant-Wells

External Email

I was HORRIFIED to read the recent article about Seattle / KC METRO bus drivers describing how difficult and dangerous it is to drive their buses while having occupants smoking Crack and Fentanyl in public and noticing they were not being supported or helped.
I was even MORE HORRIFIED , and I repeat, MORTIFIED AND HORRIFIED, that some employee working at our Seattle KC Health Dept. (Ms. Thea Oliphant-Wells,) stated in the SAME article that it was not harmful and she even offered advice that it is BETTER to have addicts and the public smoke drugs and Fentanyl, in our public places, like on public transportation !!!!!!!!!!!
(Her reason supposedly was to have better access in case they OD)

OMG - OMG - OMG !!!!!!

Am I living in an alternate universe or are all of you CRAZY to think that think is something normal and helpful to say to the public?

I am a senior who has lived in this area since 1957, who has always leaned a little on the liberal side,
BUT....
THIS IS TOOOOOOOO MUCH !!!!!!

I pay TAXES and I have a RIGHT to have a safe place to live and enjoy.
The Metro bus drivers have a right to a safe working environment.
We do not need a person like Ms.Oliphant-Wells making harmful, and dangerous remarks about this subject.

I HAVE NOT been able to ride a city bus, ride the light rail, visit the public market or go to a Mariners game in years. Crime around the city is RAMPANT and worse on city transportation.
So when she states that public drug use is safe and encourages it, it DOES NOT MAKE OUR AREA SAFER!!!!!!!!!!

I CONTINUE TO REMAIN SHOCKED AND ANGRY. that YOUR agency , KC HEALTH, HAS ALLOWED an employee OF YOURS, to be able to tell the public and our Metro bus drivers , that it's SAFE and it's OK to have PUBLIC DRUG USE on our city transportstion???????????

How does Ms. Thea Oliphant-Wells and the rest of county agencies, city council and public officials, who allow THESE CRAZY IDEAS and STATEMENTS to be said out loud, sleep at night?

YOU SHOULD ALL BE SHOCKED AND HORRIFIED!!!!!!!!
You should all be ashamed and should be working to make our city SAFER and NOT doing what you are currently saying and doing.

Ms. Oliphant-Wells should NOT BE working in any capacity at the Health Dept!!!!!!!!!!
(Or any agency)

I will be sending this opinion email of mine to other state, county and city officials. You have my name and email and number below if you want to respond.

Martha Hykel
253-880-9960

_____
From: Brian Harris
Sent: 4/6/2023 7:08:50 PM
To: mimswede@gmail.com,Mike Glaze,max@gmail.com,mailer@email.theblaze.com,Eric Metaxas,MyLegion,Kenneth Price,jenersen@king5.com,Amy's Kitchen,dave scott,Children's Health Defense,dariusvincenthughes@gmail.com,drrobertjeffress@ptv.org,governorron.desantis@eog.myflorida.co Anderson,Rep.Vos@legis.wisconsin.gov,Kevin Veenhuizen,bob loyd,WA Civil Rights Council,DOH WSBOH,zarah_aingeal@yahoo.com,Bruce Harris,rickdrives1@hotmail.com,pmcgrath1@comcast.net,XM RADIO,The_Gray_Iron_Fitness_Newsletter@senior-exercise-central.com,John.H.Teske,Turning Point,Herschel
Cc:
Subject: Fwd: Daily e-Truth—The F-E-A-T of Resurrection: Appearances of Christ

External Email

---------- Forwarded message ---------
From: Christian Research Institute <Webmaster@equip.org <mailto:Webmaster@equip.org> >
Date: Thu, Apr 6, 2023, 3:00 AM
Subject: Daily e-Truth—The F-E-A-T of Resurrection: Appearances of Christ
To: <brianhrrs17@gmail.com <mailto:brianhrrs17@gmail.com> >

Daily e-Truth—The F-E-A-T of Resurrection: Appearances of Christ
<https://gallery.mailchimp.com/1b87777256955d4a4f1bd513b/images/c3a7a81f-3ffa-4988-8438-a30cf6613a0f.jpg>

Fatal torment
Empty tomb
Appearances
Transformation

In the Acts of the Apostles, Dr. Luke writes that Jesus gave the disciples "many convincing proofs that he was alive. He appeared to them over a period of forty days and spoke about the kingdom of God" (Acts 1:3). Likewise, Peter in his powerful Pentecost proclamation declared that many credible eyewitnesses could confirm the fact of Christ's physical post-resurrection appearances:

Brothers, I can tell you confidently that the patriarch David died and was buried, and his tomb is here to this day. But he was a prophet and knew that God had promised him on oath that he would place one of his descendants on his throne. Seeing what was ahead, he spoke of the resurrection of the Christ, that he was not abandoned to the grave, nor did his body see decay. God has raised this Jesus to life, and we are all witnesses of the fact (Acts 2:29–32 NIV1984).

Like the apostle Peter, the apostle Paul exudes confidence in the appearances of Christ. In his first letter to the Corinthian Christians he provides details and descriptions:

For what I received I passed on to you as of first importance: that Christ died for our sins according to the Scriptures, that he was buried, that he was raised on the third day according to the Scriptures, and that he appeared to Peter, and then to the Twelve. After that, he appeared to more than five hundred of the brothers at the same time, most of

whom are still living, though some have fallen asleep. Then he appeared to James, then to all the apostles, and last of all he appeared to me also, as to one abnormally born (1 Cor. 15:3–8 NIV1984).

One thing is sure. The apostles did not merely propagate Christ's teachings; they were absolutely certain that he had appeared to them in the flesh. Although two thousand years removed from the actual event, we too can be absolutely confident in Christ's post-resurrection appearances.

First, in the passage cited above, Paul is reiterating a Christian creed that can be traced all the way back to the formative stages of the early Christian church. Incredibly, scholars of all stripes agree that this creed can be dated to within three to eight years of the Crucifixion itself—James D. G. Dunn says within months. The eminent scholar Joachim Jeremias calls this creed "the earliest tradition of all," and Ulrich Wilckens says it "indubitably goes back to the oldest phase of all in the history of primitive Christianity." Dr. Gary Habermas concludes that the creed is not only early but "that it's free from legendary contamination, that it's unambiguous and specific, and that it's ultimately rooted in eyewitness accounts."

Furthermore, Peter, Paul, and the rest of the apostles claimed that Christ appeared to hundreds of people who were still alive and available for cross-examination (1 Cor. 15:6). It would have been one thing to attribute these supernatural experiences to people who had already died. It was quite another to attribute them to multitudes who were still alive. Suppose I announced publicly that I had played a private round of golf with Arnold Palmer at Bay Hill County Club in Orlando. During the round I hit the longest drive Palmer had ever seen, made a hole-in-one, and set a new course record. As long as Palmer was living, my credibility could easily be called into question. Likewise, Paul's assertions regarding the eyewitnesses who had seen the resurrected Christ could have easily been refuted if in fact they were not true.

Finally, no one has ever come up with a credible means to explain away the post-resurrection appearances of Christ. As previously noted, the references to Christ's appearances are early and free from legendary corruption. Thus, skeptics are often reduced to pawning them off as mere hallucinations.

In reality, hallucinations are subjective and scarce. Yet Christ appeared to many people over a long period of time. In addition, hallucinations are typically relegated to people with certain personality disorders, are stimulated by expectations, and do not stop abruptly. In the case of Christ, he appeared to all kinds of personality types with no expectations, and then the appearances stopped abruptly.

Perhaps Professor Perrin, the late New Testament scholar at the University of Chicago, said it best. In summing up the consensus of both liberal and conservative scholarship, he wrote, "The more we study the tradition with regard to the appearances, the firmer the rock begins to appear upon which they are based."

At this point, there should be no doubt that Christ suffered fatal torment; that the empty tomb is a factual reality; and that Christ's post-resurrection appearances cannot be explained away as legends or hallucinations. Tomorrow, Good Friday (Western calendar), we will explore the final letter in the acronym F-E-A-T, which represents the word Transformation.

For further study see our special Resurrection Resources <https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fequip.us11.list-manage.com%2Ftrack%2Fclick%3Fu%3D1b87777256955d4a4f1bd513b%26id%3D31532a51c6%26e%3D
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For my article, "The F-E-A-T that Demonstrates the Fact of Resurrection," which provides

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, from which this Daily e-Truth is adapted.

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From: Bill Osmunson
Sent: 3/15/2023 12:42:46 PM
To: DOH WSBOH
Cc:
Subject: Washington State Board of Health and Fluoride Neurotoxicity

External Email

Dear Washington State Board of Health Members Keith Grellner, Chair; Kelly Oshiro, JD, Vice Chair; Socia Love-Thurman, MD; Stephen Kutz, BSN, MPH; Dimyana Abdelmalek, MD, MPH; Patty Hayes, RN, MN; Melinda Flores, Elisabeth Crawford, and Umair Shah Umair Shah, MD, MPH, wsboh@sboh.wa.gov <mailto:wsboh@sboh.wa.gov> .

RE: The US Office of Health Assessment and Translation, US National Toxicology Program, and US Health and Human Services report, multiple peer reviews and comments, and meta-analysis on fluoride's effect on the developing brain.

The Court finally forced HHS to release the latest NTP Draft on fluoride's effect on the developing brain. I was one of those nominating fluoride to OHAT/NTP for review in 2015 and was told it would take two or three years to finish. Due to vested interest of industry and public health politics, the latest draft review is now available, more than 1,500 pages. HHS has tried to delay or quash the science, but the Court over-ruled.

DRAFT NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review NTP Monograph 08 September 2022
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fntp.niehs.nih.gov%2Fntp%2Fabou

The conclusion? Depends on which part of the report is read. The similarity between the divergent polarized opinions of the January 6 controversy exist with fluoridation. Was January 6 an insurrection or simply sightseeing? Fluoridation is not a "sightseeing" safe and effective drug as proponents of fluoridation would like you to believe.

OHAT (Office of Health Assessment and Translation) concluded fluoride is "presumed" to be a developmental neurotoxin.

NTP (National Toxicology Program) uses the words "moderate confidence" of neurotoxicity, essentially the same level of confidence.

NTP is clear in responses, full meta-analysis and supplements they found no evidence of a lower threshold of fluoride ingestion to be safe. Keep in mind the NTP report is 8 years in the making and cut off for research does not include some of the most recent studies reporting harm. To expect the vast majority of studies reporting harm will be refuted in the future with further studies is highly unlikely. As scientists learn where to look and how to do the studies, more precision and confidence will be demonstrated. Fluoride ingestion is not safe for many or most, especially the fetus and infant.

NTP stresses in comments the need to evaluate total fluoride exposure, not just fluoride in water.

Proponents attempt to protect fluoridation by ignoring total exposure.

Fluoridation proponents, industry, American Dental Association (one of my friends a

reviewer), political and public health reviewers pushed back against NTP to protect fluoridation at 0.7 mg/L and claimed evidence is weaker below 1.5 mg/L fluoride in water than above 1.5 mg/L . . . which makes no scientific sense and the controversy becomes clear. Why?

1. OHAT/NTP reviewed total fluoride ingestion. Fluoridation proponents attempt to isolate out fluoride concentration in water. Concentration of fluoride is not a dosage because some people drink little or no water and others a great deal. The statistical mean drink about 1 liter of water a day. The 90th percentile about 2 liters a day which is similar to drinking 1 liter at 1.4 mg/L of fluoride. And some drink over 10 liters/day. The fetus and infants are most vulnerable.

2. Individuals have many sources of fluoride and some people get a great deal of fluoride from other sources. Attempting to isolate out just fluoride dosage from water and claim the water is safe, is not real world. Some swallow fluoride toothpaste, some drink more water than mean, infants are smaller, synergistic effects, foods, medications and air are all additional sources of fluoride which must be included. No one only gets fluoride only from water. Total fluoride must be evaluated.

3. An uncertainty factor of at least 10 must be included. Anyone prescribing medications knows, individuals do not all react the same to any drug, food, or substance.
Some NTP quotes:

"Our meta-analysis confirms and extends prior meta-analyses that reported associations between higher fluoride exposures and lower IQ levels of children. The results were robust to stratifications by risk of bias, gender, age group, outcome assessment, study location, exposure timing, and exposure type (including both drinking water and urinary fluoride). Therefore, the data support a consistent inverse association between fluoride exposure and children's IQ."

"Our meta-analysis confirms results of previous meta-analyses and extends them by including newer, more precise studies with individual-level exposure measures. The data support a consistent inverse association between fluoride exposure and children's IQ."

"There is also evidence of a dose response relationship between lower children's IQ and higher fluoride exposures. Although the estimated decreases in IQ may seem small, research on other neurotoxicants has shown that subtle shifts in IQ at the population level can have a profound impact on the number of people who fall within the high and low ranges of the population's IQ distribution. For example, a 5-point decrease in a population's IQ would nearly double the number of people classified as intellectually disabled."

And doubling the number of intellectually disabled has a serious impact on special education numbers, employers, incarceration, and family grief.

The Washington State Board of Health has full authority to caution/warn pregnant mothers and care givers to reduce fluoride exposure:

"Do Not Drink Fluoridated Water or Swallow Fluoridated Toothpaste"

The Board has full authority to stop fluoridation's harm.

The harm is on the shoulders of the WSBOH.

Sincerely,

Bill Osmunson DDS MPH
Smiles of Bellevue
bill@teachingsmiles.com <mailto:bill@teachingsmiles.com>
1418 112th Ave NE
Bellevue, Washington 98004
425.466.0100

American Environmental Health Studies Project
Board Chair

_____

From: Glen Felkins
Sent: 3/22/2023 5:42:14 PM
To: DOH WSBOH
Cc:
Subject: Commit to no COVID vaccine mandates on children

External Email

Dear Washington State Board of Health,

I urge you to accept the TAGs recommendation and choose to NOT mandate covid vaccines on our children. Our state government should NOT be mandating Covid vaccines on our children. They are at extremely low risk for Covid and these medical decisions should be left in the hands of parents and their family doctors.

Sincerely,

The Citizens of Washington State

From: Yan Leigh
Sent: 3/7/2023 3:05:09 PM
To: DOH WSBOH
Cc:
Subject: Comment for WA Board of Health meeting, March 7

External Email

I was disappointed to hear that WA state is dropping mandatory masking in healthcare, correctional facilities, and long-term care facilities.

I am writing to request that WA state continues the mask mandate for these facilities indefinitely.

Healthcare facilities are an irreplaceable necessity to those who are most at risk from COVID or other airborne diseases, such as senior citizens, those undergoing chemotherapy, those who are immunocompromised, pregnant women, and newborns and other babies who are not yet able to be vaccinated. Our population should not have to risk their health, or the health of those they live with, in order to access healthcare.

A mask mandate represents a significant reduction in risk, alongside stringent ventilation and filtration requirements, especially for congregate settings such as long-term care and correctional facilities. These are settings serving some of our community's most vulnerable populations, and they deserve to be protected.

By keeping the mask mandate, this helps ensure that these facilities continue to be accessible to everyone, promoting health equity and ensuring a healthier community.

Thank you for your consideration.

_____

From: Sol Villarreal
Sent: 3/8/2023 11:23:17 AM
To: DOH WSBOH
Cc:
Subject: Public comments on repealing the state's mask mandate in healthcare settings

External Email

Hi Members--

In your January meeting Secretary Shah said two things that made sense at the time: 1) based on the current case rates as well as the rate at which new variants were still continuing to develop, COVID-19 couldn't yet be considered to have made the transition from a pandemic to an endemic disease. And 2) because of that, it was unlikely in his opinion that the mask mandate would be removed for healthcare facilities. Case rates haven't changed meaningfully since that January 9th meeting, but between then and now Governor Inslee moved forward anyway with announcing the end of the state's last remaining mask mandate.

Research has shown both that nosocomial COVID-19 infections are widespread in the absence of effective preventative measures and that they have a dramatically higher mortality rate than community-acquired COVID infections, with the largest difference in mortality showing up for immunocompromised individuals.

We know that people who are already sick enough to need to go to the doctor's office or hospital are at increased risk of hospitalization or death if they catch COVID-19. We know that the current variants are more transmissible than any that we've seen to date. We know that by some estimates only 5% of actual cases are being reported and showing up in official data, but that even with such severe underreporting our case rate for all of 2023 has been higher than it was for almost all of 2020 and for a good chunk of 2021. And while vaccines are effective at preventing hospitalization and death in most of the population, an average of 2,784 Americans and 48 Washingtonians per week are still dying from this disease. We know that wearing masks is the best tool we have to prevent the spread of COVID-19. I encourage you to keep that mandate in place to protect the highest-risk Washingtonians and help prevent anyone's parent, sibling, or child from dying so that a politician has a better chance of getting get re-elected.

-Sol Villarreal

--

via desktop | 206-765-6108 | solvillarreal.com
<https://gcc02.safelinks.protection.outlook.com/?url=http%3A%2F%2Fsolvillarreal.com%2F&data=05%7C

From: Brad Loosveldt
Sent: 3/12/2023 11:45:13 AM
To: DOH WSBOH
Cc:
Subject: MRNA shots

External Email

Incredibly important information for you to be aware of with the link down below. Please DO NOT hurt our children by following the harmful recommendation of the unsafe, ineffective mRNA so-called vaccines. Please protect our kids from these experimental shots. Thank you!

Doctors Around the World Say It's Time to Stop the Shots

https://www.theepochtimes.com/health/doctors-around-the-world-say-its-time-to-stop-the-shots_5103024.html
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.theepochtimes.com%2Fheal
around-the-world-say-its-time-to-stop-the-
shots_5103024.html&data=05%7C01%7Cwsboh%40sboh.wa.gov%7C8b5082587bc543053c3608db2329d4

Sent from Yahoo Mail for iPhone
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Foverview.mail.yahoo.com%2F%3F

_____

From: Becca Gillespy Peter
Sent: 3/8/2023 12:29:42 PM
To: DOH WSBOH
Cc:
Subject: Public Comments for WSBOH Members from March EH Committee Special Meeting

External Email

My name is Becca Peter and I am a resident of San Juan County.

Last spring, we received the devastating news that my son Eddie had a malignant brain tumor. It was aggressive, inoperable, and had already metastasized to other parts of his brain and spine.

Fortunately for us, his cancer responded well to radiation and chemo and he is currently enjoying a good quality of life at home on Lopez Island while we try experimental therapies.

One of the reasons he did so well during treatment is that we managed to avoid any infectious diseases that would have caused setbacks. As a family we can, and do, choose to avoid risk elsewhere, but if I do not take my son to the hospital for cancer treatment he will die.

I am fortunate that Eddie is old enough to be able to wear a mask, but he still struggles with vomiting and nosebleeds. We have had multiple times in hospital waiting rooms where he has had to remove his mask. Many families at Seattle Children's Hospital have immune compromised children who are unable to mask at all.

Universal masking in healthcare facilities is an effective form of source control and a valuable layer of protection for the most vulnerable members of society.

It is incredibly disappointing that the Department of Health has chosen the desires of lobbyists and hospital administrators over the needs of children like Eddie. Being able to access healthcare safely should be a basic human right and that is being taken away from us.

From: Arne Christensen
Sent: 4/6/2023 1:51:20 PM
To: DOH WSBOH
Cc:
Subject: drug overdoses carnage

External Email

Hello:
Why isn't the health department talking more about the alarming increase in drug overdose deaths so far this decade? I believe daily opioid deaths surpassed daily covid deaths sometime last year, and of course drug overdoses kill younger people than covid does. The numbers on King County's overdose dashboard (https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fkingcounty.gov%2Fdepts%2Fhealt prevention%2Fdata.aspx&data=05%7C01%7Cwsboh%40sboh.wa.gov%7C63f55bfb83294592d31708db36e are
alarming.

Arne Christensen

_____

From: Olemara Peters
Sent: 3/8/2023 9:58:01 AM
To: DOH WSBOH
Cc:
Subject: Health Code must prioritize safety and transparency

External Email

Dear BOH Members,

Please look at HB 1610, "Restoring Trust in Public Health Through Consumer Protection," https://app.leg.wa.gov/billsummary?BillNumber=1610&Initiative=false&Year=2023 <https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fapp.leg.wa.gov%2Fbillsummary%
. Please ensure that any changes to the WA Health Code are congruent with its standards, and notice (in preparation to correct) parts of the existing Code that currently fail its standards.

I hope that bipartisan bill will pass; but whether or not it passes, it's an appropriate standard for Washington's Health Code.

As a Democrat (for reasons of conservation and biodiversity, gun safety, labor rights, racial equity, voting rights, reproductive rights, refugees' rights, etc.), I'd always expected Democrats/ "progressives"/ "liberals" et al to be alert to polluting industries' spin — to stand for the Nuremberg Code, Never Again, the Principle of Informed Consent.

Instead, all product-safety questions/ questioners, about some industries, are being labeled, vilified, and dismissed as "extreme right-wing" etc., regardless of our actual politics. Even the mention of the Nuremberg Code or Informed Consent is eliciting these character-assassinating assumptions.

This ridiculing, mislabeling and censoring of researchers, whistleblowers, and people/ families injured by the products/ wastes/ emissions of certain polluting industries is extremely convenient for these sacred-cow industries (including Big Wireless, and Big Chem/ Ag/ Food/ Pharma/ Biotech).

This has gone on for a number of years. It has now escalated hugely further, apropos of vaccines in particular (vaccines experimental yet mandated, while yet devoid of industry liability, transparent labeling, accurate injuries-counting); and the other industries (and their tools — witting and unwitting — among the media, "regulatory" agencies, and lawmakers) jump on its bandwagon. It's highly convenient for all these industries to be able to elicit so much of society's obedience, unawareness, complicity.

I am personally paying the price of society's complicity. I experience onerous bodily harm from several of these industries' products/ emissions/ wastes. I have direct bodily reasons to avoid such exposures where possible, and not to consent to more; and I'm aware that they're affecting, also, both
— other humans (who may or may not yet have recognized the connections), and
— other species, ecosystems, the biosphere.

It offends me deeply that raising any concern of safety/ transparency about these industries will get me automatically categorized as a climate-denier etc.
I’m not too surprised at Trump-voters going along with these industries — I'm just pleased and thankful about those who don’t — and, well, I would have expected these issues to be bipartisan.

However, I’m utterly mystified (as well as outraged) that Democrats et al, in particular, seem to’ve uniformly fallen for these industries' spin, and to be actively helping harden it into more and more layers of law — discarding and trashing Never Again and everyone who speaks up for it. This crossup makes no sense. I would’ve thought standing up for the Nuremberg Code would be — certainly bipartisan — but especially the pride and privilege of Democrats et al. In short, I would’ve expected Democrats et al, in particular (who purport commitment to public health and safety), to be more congruently alert.

Please, help turn this around. Please read HB 1610, and make sure any BOH decisions meet its standards for safety and transparency.

Thank you.
Sincerely,
Olemara Peters
Bainbridge Island WA 98110 (but please make any replies by email, let’s save a tree — thanks)

_____

From: Bill Osmunson
Sent: 3/21/2023 10:03:28 AM
To: DOH WSBOH
Cc:
Subject: Lack of fluoride's prenatal benefit

attachments\0A26F9202A944A48_F Lack of benefit WSBH March 21 2023 .pdf

External Email

Dear Washington State Board of Health Members Keith Grellner, Chair; Kelly Oshiro, JD, Vice Chair; Socia Love-Thurman, MD; Stephen Kutz, BSN, MPH; Dimyana Abdelmalek, MD, MPH; Patty Hayes, RN, MN; Melinda Flores, Elisabeth Crawford, and Umair Shah Umair Shah, MD, MPH, wsboh@sboh.wa.gov <mailto:wsboh@sboh.wa.gov> .

RE: Scientific evidence does not find prenatal fluoride ingestion has benefit.

Our request is for the WSBH to post on their website that mothers should not drink fluoridated water and caregivers should not use fluoridated water to make infant formula.

The best science to date does not support the theory that mothers ingesting fluoride during pregnancy reduces the dental caries in their children. The FDA says the evidence is incomplete. The following studies are reasonably representative of the literature on prenatal ingestion of fluoride and possible BENEFIT to the child.

The benefits of fluoride ingestion can and should be tested with the highest quality of research, randomized controlled trials (RCT). Only one RCT study has been published and it was with pregnant mothers ingesting fluoride to see if there was a reduction in dental caries in their children's primary teeth. Leverett (1997)
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F916
[1]
<file:///C:/Users/Bill%20Osmuson/Desktop/WSBOH%202023/F%20Lack%20of%20benefit%20WSBH%20M
did the only published RCT on fluoride ingestion and gave 1 mg/day fluoride supplements during the last six months of pregnancy and concluded, "These findings do not support the hypothesis that prenatal fluoride has a strong caries-preventive effect."
Driscoll (1981)[2]
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Feuropepmc.org%2Farticle%2Fmed
". . . administration of dietary fluoride supplements to pregnant women cannot be recommended at this time, because conclusive clinical evidence that the procedure reduces dental caries in the teeth of offspring is lacking."
Castiblanco-Rubio (2022)[3]
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.mdpi.com%2F2218-1989%2F12%2F4%2F324&data=05%7C01%7Cwsboh%40sboh.wa.gov%7Caf8d20e4d31d42e542d008db2
is one of the few human studies published on the mechanism of prenatal fluoride exposure. "The available evidence indicates that fluoride is found in the maternal plasma and urine, placenta, amniotic fluid and fetus. Although plasma and urinary fluoride vary across gestation, there is insufficient quality evidence to determine the direction or extent of such variation. Furthermore, there is no doubt that fluoride from maternal blood crosses the placenta and is absorbed and excreted by the fetus; however, the biological mechanisms behind this placental passage are unknown."

The fetus does not benefit from mothers ingesting fluoridated water and the developing brain is harmed.[4]
<file:///C:/Users/Bill%20Osmuson/Desktop/WSBOH%202023/F%20Lack%20of%20benefit%20WSBH%20N
The developing fetus has no benefit and only harm from fluoridation of public water.

The WSBH would provide only benefit without harm by advising mothers to not drink fluoridated water or swallow fluoridated toothpaste while they are pregnant.

Our request is for the WSBH to post on their website that mothers should not drink fluoridated water and caregivers should not use fluoridated water to make infant formula.

Sincerely,
Bill Osmunson DDS MPH
bill@teachingsmiles.com <mailto:bill@teachingsmiles.com>
Smiles of Bellevue
1418 112th Ave NE, Bellevue, WA. 98004. 425.466.0100
American Environmental Health Studies Project, Board Chair
Green, R., Lanphear, B., Hornung, R., Flora, D., Martinez-Mier, E.A., Neufeld, R., Ayotte, P. and Muckle, G., 2019. Till C Fluoride Exposure during Fetal Development and Intellectual Abilities in a Canadian Birth Cohort. JAMA Pediatr, 173(10), pp.940-8. [Google Scholar] [PubMed]
Connett E. American Environmental Health Studies Project. Unpublished. Link and Fluoride and IQ Accessed Dec. 27, 2022.

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[1]
<file:///C:/Users/Bill%20Osmuson/Desktop/WSBOH%202023/F%20Lack%20of%20benefit%20WSBH%20N
Leverett DH, Adair SM, Vaughan BW, Proskin HM, Moss ME. Randomized clinical trial of the effect of prenatal fluoride supplements in preventing dental caries. Caries Res. 1997;31(3):174-9. doi: 10.1159/000262394. PMID: 9165186.
[2]
<file:///C:/Users/Bill%20Osmuson/Desktop/WSBOH%202023/F%20Lack%20of%20benefit%20WSBH%20N
Driscoll WS. A review of clinical research on the use of prenatal fluoride administration for prevention of dental caries. ASDC Journal of Dentistry for Children. 1981 Mar-Apr;48(2):109-117. PMID: 7012207.
[3]
<file:///C:/Users/Bill%20Osmuson/Desktop/WSBOH%202023/F%20Lack%20of%20benefit%20WSBH%20N
Castiblanco-Rubio GA, Martinez-Mier EA. Fluoride Metabolism in Pregnant Women: A Narrative Review of the Literature. Metabolites. 2022; 12(4):324. https://doi.org/10.3390/metabo12040324
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.3390%2Fmetabo12

[4]
<file:///C:/Users/Bill%20Osmuson/Desktop/WSBOH%202023/F%20Lack%20of%20benefit%20WSBH%20N
Till C, Green R, Flora D, Hornung R, Martinez-Mier EA, Blazer M, Farmus L, Ayotte P, Muckle G, Lanphear B. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. Environ Int. 2020 Jan;134:105315. doi: 10.1016/j.envint.2019.105315. Epub 2019 Nov 16. PMID: 31743803; PMCID: PMC6913880. [PubMed]

US Department of Health and Human Services, Office of Health Assessment and Translation, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health. Systemic Review of Fluoride

Exposure and Neurodevelopmental and Cognitive Health Effects, Draft NTP Monograph. September 6, 2019. (Note: an NTP final determination or Policy has been blocked from release politically and should be available in May) ASDWA Accessed December 1., 2022.
2 . Bashash M, Thomas D, Hu H, et al. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6 – 12 Years of age in Mexico. Enviromental Heal Perspect. 2017;125(9):097017. doi: 10.1289/EHP655. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

Dear Washington State Board of Health Members Keith Grellner, Chair; Kelly Oshiro, JD, Vice Chair; Socia Love-Thurman, MD; Stephen Kutz, BSN, MPH; Dimyana Abdelmalek, MD, MPH; Patty Hayes, RN, MN; Melinda Flores, Elisabeth Crawford, and Umair Shah Umair Shah, MD, MPH, wsboh@sboh.wa.gov.

RE: Scientific evidence does not find prenatal fluoride ingestion has benefit.

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The best science to date does not support the theory that mothers ingesting fluoride during pregnancy reduces the dental caries in their children. The FDA says the evidence is incomplete. The following studies are reasonably representative of the literature on prenatal ingestion of fluoride and possible BENEFIT to the child.

The benefits of fluoride ingestion can and should be tested with the highest quality of research, randomized controlled trials (RCT). Only one RCT study has been published and it was with pregnant mothers ingesting fluoride to see if there was a reduction in dental caries in their children's primary teeth. Leverett (1997)[1] did the only published RCT on fluoride ingestion and gave 1 mg/day fluoride supplements during the last six months of pregnancy and concluded, *"These findings do not support the hypothesis that prenatal fluoride has a strong caries-preventive effect."*

Driscoll (1981)[2] **". . .** *administration of dietary fluoride supplements to pregnant women cannot be recommended at this time, because conclusive clinical evidence that the procedure reduces dental caries in the teeth of offspring is lacking."*

Castiblanco-Rubio (2022)[3] is one of the few human studies published on the mechanism of prenatal fluoride exposure. *"The available evidence indicates that fluoride is found in the maternal plasma and urine, placenta, amniotic fluid and fetus. Although plasma and urinary fluoride vary across gestation, there is insufficient quality evidence to determine the direction or extent of such variation. Furthermore, there is no doubt that fluoride from maternal blood crosses the placenta and is absorbed and excreted by the fetus; however, the biological mechanisms behind this placental passage are unknown."*

The fetus does not benefit from mothers ingesting fluoridated water and the developing brain is harmed.[4] The developing fetus has no benefit and only harm from fluoridation of public water.

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[1] Leverett DH, Adair SM, Vaughan BW, Proskin HM, Moss ME. Randomized clinical trial of the effect of prenatal fluoride supplements in preventing dental caries. Caries Res. 1997;31(3):174-9. doi: 10.1159/000262394. PMID: 9165186.

[2] Driscoll WS. A review of clinical research on the use of prenatal fluoride administration for prevention of dental caries. ASDC Journal of Dentistry for Children. 1981 Mar-Apr;48(2):109-117. PMID: 7012207.

[3] Castiblanco-Rubio GA, Martinez-Mier EA. Fluoride Metabolism in Pregnant Women: A Narrative Review of the Literature. *Metabolites*. 2022; 12(4):324. https://doi.org/10.3390/metabo12040324

[4] Till C, Green R, Flora D, Hornung R, Martinez-Mier EA, Blazer M, Farmus L, Ayotte P, Muckle G, Lanphear B. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. Environ Int. 2020 Jan;134:105315. doi: 10.1016/j.envint.2019.105315. Epub 2019 Nov 16. PMID: 31743803; PMCID: PMC6913880. [PubMed]

US Department of Health and Human Services, Office of Health Assessment and Translation, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health. Systemic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects, Draft NTP Monograph. September 6, 2019. (Note: an NTP final determination or Policy has been blocked from release politically and should be available in May) ASDWA Accessed December 1., 2022. 2 . Bashash M, Thomas D, Hu H, et

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Sincerely,

Bill Osmunson DDS MPH

bill@teachingsmiles.com

Smiles of Bellevue

1418 112th Ave NE, Bellevue, WA. 98004. 425.466.0100

American Environmental Health Studies Project, Board Chair

Green, R., Lanphear, B., Hornung, R., Flora, D., Martinez-Mier, E.A., Neufeld, R., Ayotte, P. and Muckle, G., 2019. Till C Fluoride Exposure during Fetal Development and Intellectual Abilities in a Canadian Birth Cohort. JAMA Pediatr, 173(10), pp.940-8. [Google Scholar] [PubMed]

Connett E. American Environmental Health Studies Project. Unpublished. Link and Fluoride and IQ Accessed Dec. 27, 2022.

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al. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6 – 12 Years of age in Mexico. Enviromental Heal Perspect. 2017;125(9):097017. doi: 10.1289/EHP655. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

_____
From: Ruth L
Sent: 4/7/2023 11:32:53 AM
To: DOH WSBOH
Cc:
Subject: Re: Ahora disponible: Orden del día definitivo de la reunión pública de la Mesa Directiva de Salud del 12 de abril


attachments\40588D36AAEF4F97_image001.png

External Email

UNSUBSCRIBE

_____

From: DOH WSBOH <WSBOH@SBOH.WA.GOV>
Sent: Wednesday, April 5, 2023 12:19 PM
To: DOH WSBOH <WSBOH@SBOH.WA.GOV>
Subject: Ahora disponible: Orden del día definitivo de la reunión pública de la Mesa Directiva de Salud del 12 de abril

Ya está disponible el orden del día definitivo propuesto <https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fsboh.wa.gov%2Fsites%2Fdefault%
04%2FTab01a-WSBOH-Agenda-2023-04-12-Final_Spanish_3.pdf&data=05%7C01%7CWSBOH%40SBOH.WA.GOV%7C722c4d7d8e5840c7b2c808db379
para la reunión pública de la Mesa Directiva de Salud del miércoles 12 de abril de 2023.
Nos reuniremos de 10:00 a. m. a 3:10 p. m.

Lea la propuesta de orden del día para obtener más información sobre la reunión, incluso sobre cómo hacer comentarios públicos. Podrá acceder a la reunión de las siguientes formas:

1. Acceda en línea y regístrese:

https://us02web.zoom.us/webinar/register/WN_mu2A7ZgeSb-xy6NhUG6rog

2. Llame y participe usando su teléfono:

    0. Llamada telefónica al seminario web: +1 (253) 215-8782
    1. Id. del seminario web: 889 1392 5308
    2. Contraseña del seminario web: 660897

Comentarios públicos escritos:

* Lo invitamos a enviar comentarios públicos por escrito a la Mesa antes de la reunión. Para poder garantizar que los integrantes de la Mesa tengan lo oportunidad de leer y tener en cuenta sus comentarios antes de la reunión, envíenos sus comentarios

por correo electrónico
<mailto:wsboh@sboh.wa.gov?subject=My%20Public%20Comments> antes del viernes 7 de abril al 12:00 del mediodía. Los comentarios escritos que se reciban después de las 12:00 del mediodía del viernes se comunicarán a los integrantes de la Mesa, sin embargo, es posible que no los tengan en cuenta o no puedan leerlos durante el fin de semana antes de la reunión o durante la reunión. Los comentarios públicos que se reciban por escrito se publicarán en la página web del material de la reunión el 7 de abril de 2023.

Hacer comentarios públicos verbales en las reuniones híbridas:

* Para el público que asiste en persona: Consulte el orden del día adjunto para saber cómo hacer un comentario público si asiste en persona.
* Para el público que asiste virtualmente: Si desea hacer un comentario público, inscríbase a través del enlace del seminario web de Zoom antes de las 12:00 del mediodía del día anterior a la reunión. Se mencionará su nombre cuando sea su turno para hacer comentarios.

Más información sobre la reunión:

* Esta reunión tendrá un formato híbrido. La reunión virtual se llevará a cabo a través de la aplicación Zoom para seminarios web. La reunión presencial se llevará a cabo en el Auditorio de Trabajo e Industrias, 7273 Linderson Way SW, Tumwater, WA 98501.

(360) 236-4110

P.O. Box 47990, Olympia, WA 98504-7990

Ubicación
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.google.com%2Fmaps%2Fpla
122.9083621%2C17z%2Fdata%3D!3m1!4b1!4m5!3m4!1s0x549173f074205aa3%3A0x552ddc5f79ee44b6
122.9061681%3Fhl%3Den&data=05%7C01%7CWSBOH%40SBOH.WA.GOV%7C722c4d7d8e5840c7b2c808
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· Correo electrónico <mailto:wsboh@sboh.wa.gov> · Facebook
<https://gcc02.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.facebook.com%2FWashingtor
· Twitter
<https://gcc02.safelinks.protection.outlook.com/?url=https%3A%2F%2Ftwitter.com%2FWASBOH&data=0
· Subscríbase
<mailto:wsboh@sboh.wa.gov?subject=Please%20Add%20My%20Name%20to%20the%20WSBOH%20Ema

From: Deb Kiesig
Sent: 3/8/2023 1:26:24 AM
To: DOH WSBOH
Cc:
Subject: Please keep the mask mandate as is!

External Email

To the WA State Board of Health,

I want my voice heard. I feel forgotten along with so many others. Our immunocompromised health will be even more at risk when we can no longer go to our doctor's appointments safely. Of course we will be masked, do we have a choice? But what about the babies, our children with health issues who cannot mask? How do we keep them safe?

What about healthcare workers, already short staffed, now even more exposed and getting sick? I will be wearing a mask as a healthcare professional and an immunocompromised person, but others will not, even though it is recommended by you folks. Will my masking alone protect me in an environment with so many sick? I have managed to stay covid free all this time. But now I ask what about my freedom and my liberty?

Please keep this mandate as is, I am begging you to reconsider!

Sincerely,

Deb Kiesig
Tacoma, WA

_____

From: Jessica Gorger
Sent: 3/8/2023 4:56:04 PM
To: DOH WSBOH
Cc:
Subject: Masking in healthcare, LTC, and incarcerated people

External Email

Washington State Board of Health,

Please reconsider and do NOT drop the mask mandate April 3rd. This is an equity issue; ALL people deserve access to healthcare, and dropping the mandate means you're cutting off healthcare for high risk folks. I cannot believe this is even in question. It will also protect healthcare workers who are already overworked and overstressed after the past three years. Do not stress the system by making them sick!

Thank you,
Jessica Kelly (she/her)

Dear Washington State Board of Health Members Keith Grellner, Chair; Kelly Oshiro, JD, Vice Chair; Socia Love-Thurman, MD; Stephen Kutz, BSN, MPH; Dimyana Abdelmalek, MD, MPH; Patty Hayes, RN, MN; Melinda Flores, Elisabeth Crawford, and Umair Shah Umair Shah, MD, MPH, wsboh@sboh.wa.gov.

RE: Scientific evidence does not find prenatal fluoride ingestion has benefit.

Our request is for the WSBH to post on their website that mothers should not drink fluoridated water and caregivers should not use fluoridated water to make infant formula.

The best science to date does not support the theory that mothers ingesting fluoride during pregnancy reduces the dental caries in their children. The FDA says the evidence is incomplete. The following studies are reasonably representative of the literature on prenatal ingestion of fluoride and possible BENEFIT to the child.

The benefits of fluoride ingestion can and should be tested with the highest quality of research, randomized controlled trials (RCT). Only one RCT study has been published and it was with pregnant mothers ingesting fluoride to see if there was a reduction in dental caries in their children's primary teeth. Leverett (1997)[1] did the only published RCT on fluoride ingestion and gave 1 mg/day fluoride supplements during the last six months of pregnancy and concluded, *"These findings do not support the hypothesis that prenatal fluoride has a strong caries-preventive effect."*

Driscoll (1981)[2] **". . .** *administration of dietary fluoride supplements to pregnant women cannot be recommended at this time, because conclusive clinical evidence that the procedure reduces dental caries in the teeth of offspring is lacking."*

Castiblanco-Rubio (2022)[3] is one of the few human studies published on the mechanism of prenatal fluoride exposure. *"The available evidence indicates that fluoride is found in the maternal plasma and urine, placenta, amniotic fluid and fetus. Although plasma and urinary fluoride vary across gestation, there is insufficient quality evidence to determine the direction or extent of such variation. Furthermore, there is no doubt that fluoride from maternal blood crosses the placenta and is absorbed and excreted by the fetus; however, the biological mechanisms behind this placental passage are unknown."*

The fetus does not benefit from mothers ingesting fluoridated water and the developing brain is harmed.[4] The developing fetus has no benefit and only harm from fluoridation of public water.

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[1] Leverett DH, Adair SM, Vaughan BW, Proskin HM, Moss ME. Randomized clinical trial of the effect of prenatal fluoride supplements in preventing dental caries. Caries Res. 1997;31(3):174-9. doi: 10.1159/000262394. PMID: 9165186.

[2] Driscoll WS. A review of clinical research on the use of prenatal fluoride administration for prevention of dental caries. ASDC Journal of Dentistry for Children. 1981 Mar-Apr;48(2):109-117. PMID: 7012207.

[3] Castiblanco-Rubio GA, Martinez-Mier EA. Fluoride Metabolism in Pregnant Women: A Narrative Review of the Literature. *Metabolites*. 2022; 12(4):324. https://doi.org/10.3390/metabo12040324

[4] Till C, Green R, Flora D, Hornung R, Martinez-Mier EA, Blazer M, Farmus L, Ayotte P, Muckle G, Lanphear B. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. Environ Int. 2020 Jan;134:105315. doi: 10.1016/j.envint.2019.105315. Epub 2019 Nov 16. PMID: 31743803; PMCID: PMC6913880. [PubMed]

US Department of Health and Human Services, Office of Health Assessment and Translation, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health. Systemic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects, Draft NTP Monograph. September 6, 2019. (Note: an NTP final determination or Policy has been blocked from release politically and should be available in May) ASDWA Accessed December 1., 2022. 2 . Bashash M, Thomas D, Hu H, et

The WSBH would provide only benefit without harm by advising mothers to not drink fluoridated water or swallow fluoridated toothpaste while they are pregnant.

Our request is for the WSBH to post on their website that mothers should not drink fluoridated water and caregivers should not use fluoridated water to make infant formula.

Sincerely,

Bill Osmunson DDS MPH

bill@teachingsmiles.com

Smiles of Bellevue

1418 112th Ave NE, Bellevue, WA. 98004. 425.466.0100

American Environmental Health Studies Project, Board Chair

Green, R., Lanphear, B., Hornung, R., Flora, D., Martinez-Mier, E.A., Neufeld, R., Ayotte, P. and Muckle, G., 2019. Till C Fluoride Exposure during Fetal Development and Intellectual Abilities in a Canadian Birth Cohort. JAMA Pediatr, 173(10), pp.940-8. [Google Scholar] [PubMed]

Connett E. American Environmental Health Studies Project. Unpublished. Link and Fluoride and IQ Accessed Dec. 27, 2022.

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al. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6 – 12 Years of age in Mexico. Enviromental Heal Perspect. 2017;125(9):097017. doi: 10.1289/EHP655. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

State Board of Health, March 8, 2023
Melissa Leady, Clark County

Dear Board Members,

I am concerned that the Washington Department of Health (DOH) does not share data relevant to the covid vaccine mandate, so it appears as though the state has no data supporting the mandate. The mandate requires state employees to get the two-shot primary vaccine series, and denies exemptions for natural immunity from previous infection. DOH should be reporting data showing the primary vaccine series is currently effective, as well as the current ineffectiveness of natural immunity from previous infection to compare it with. They share neither.

The current DOH report, "Hospitalizations and Deaths by Vaccination Status" (Feb 13, 2023) only shows the effectiveness of the monovalent boosters. No data for the mandated primary series or the bivalent boosters. Recent New England Journal of Medicine studies (1,2) show primary series effectiveness against covid waning to zero after six months. And by DOH removing the primary series data from what was previously a combined effectiveness of all vaccine doses, the rate for monovalant boosters was improved, meaning the primary series was a drag on the data. Does the Washington data currently support the vaccine mandate? Why can't the public see that data?

The other missing data has to do with effectiveness of natural immunity from previous infection. Last October DOH discontinued the "Reported COVID-19 Reinfections in Washington State" report, claiming they were not able to accurately count reinfections because, they admitted, they are not able to accurately count the first infections. If DOH is not looking at the effectiveness of natural immunity, then it does not seem they have any basis for denying it. Just last month the Lancet published a meta-analysis (3) showing that over time, natural immunity was more durable and effective than the vaccines, especially against hospitalization and death.

One reason for denying exemptions for natural immunity is the claim that getting vaccinated as well slightly improves effectiveness, but the original DOH "Reported COVID-19 Reinfections in Washington State" report dated Jan 6, 2022, showed the opposite. Those with natural immunity who also got vaccinated were more likely to be hospitalized. After that initial report, DOH stopped sharing reinfection data by vaccination status in all subsequent reports.

This pattern of removing data that contradicts policy rather than updating policy to reflect what current science and data are showing serves to undermine trust in public health and questions the need for the vaccine mandate. If DOH has data showing the primary vaccine series is still effective then please share it with the public and the governor. It seems you should either share the data, or advise the governor to remove the mandates.

SOURCES

(1) Altarawneh HN, et. al., Effects of Previous Infection and Vaccination on Symptomatic Omicron Infections. New England Journal of Medicine. 2022 Jul 7;387(1):21-34.

(2) Lin DY, et al., Effects of Vaccination and Previous Infection on Omicron Infections in Children. New England Journal of Medicine. 2022 Sep 22; 387(12):1141-1143.

(3) Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. Lancet. 2023 Feb 16 (online). DOI: https://doi.org/10.1016/S0140-6736(22)02465-5: 1-11.

WASHINGTON STATE BOARD OF HEALTH

Kate Dean, MPA

Kate Dean was elected to join the Jefferson County Board of County Commissioners in 2017 and represents District 1, Port Townsend. Kate moved to Jefferson County in 1999 and spent 10 years farming and working to grow the local food economy through businesses she co-founded including FinnRiver Farm and Mt. Townsend Creamery. Her experience as an entrepreneur is critical to her understanding of the local economy and community.

Kate left the farm but didn't go far; she started a consulting business that had her working on natural resource and rural economic development issues locally and regionally. Kate coordinated the Jefferson Landworks Collaborative (a farmland preservation and enterprise development initiative), managed Washington State University (WSU) Extension's Small Farm Program, worked for Washington State Department of Labor and Industries, and was the Regional Director for the North Olympic Development Council.

Kate holds her master's in public administration from the Evans School of Public Policy and Governance at the University of Washington (UW). Her publications include USDA Farmland Changing Hands and Preparing for Climate Change on the North Olympic Peninsula.

Commissioner Dean serves on several statewide boards including the Puget Sound Partnership Leadership Council, the Washington Sea Grant Advisory Council and she co-chairs the Association of Counties Legislative Steering Committee.

STATE OF WASHINGTON
WASHINGTON STATE BOARD OF HEALTH
PO Box 47990 • Olympia, Washington 98504-7990

March 17, 2023

Dear House Budget Leaders:

As you begin your deliberations on the 2023-2025 Operating and Capital budgets, the Washington State Board of Health (Board) respectfully requests that you consider the following recommendations:

Please include the increased investment in Foundational Public Health Services (FPHS) as reflected in the Governor's budget. Prioritizing continued and expanded foundational public health investments in the 2023-2025 biennium and future biennia to builds and strengthens the capacity of Washington's governmental public health system. These investments ensure that Foundational Public Health Services are available in every community across Washington.

Remove or amend the budget proviso in the Department of Health's budget that prevents the update and implementation of school and environmental health rules, chapter 246-366A WAC. Removing the proviso will allow the Board to update the suspended rules, enabling public health to provide schools with clear, uniform guidance and standards for indoor air quality, laboratory and playground safety standards, and drinking water standards. The current rules are outdated and do not provide the critical information necessary for schools and local public health to assure students can learn and thrive in a safe environment. Over the course of the COVID-19 pandemic, local health jurisdictions have worked to strengthen their relationships with schools and is continuing to work them to improve school indoor air quality. This request is consistent with the findings and recommendations of the University of Washington Department of Environmental & Occupational Health Sciences legislatively mandated report regarding school environmental health policies, recommendations, and standards.

Continue funding in the Operating and Capital budgets to allow the Department of Health to continue conducting lead testing in schools and the Office of Superintendent of Public Instruction to provide funds to schools for drinking water fixture remediation. This funding is included in the Governor's budget and is important to assure that water fixtures containing lead can be identified and schools have access to funds that will enable them to fix or replace those fixtures.

Sincerely,

Keith Grellner
Chair

STATE OF WASHINGTON
WASHINGTON STATE BOARD OF HEALTH
PO Box 47990 • Olympia, Washington 98504-7990

March 17, 2023

Dear Senate Budget Leaders:

As you begin your deliberations on the 2023-2025 Operating and Capital budgets, the Washington State Board of Health (Board) respectfully requests that you consider the following recommendations:

Please include the increased investment in Foundational Public Health Services (FPHS) as reflected in the Governor's budget. Prioritizing continued and expanded foundational public health investments in the 2023-2025 biennium and future biennia to builds and strengthens the capacity of Washington's governmental public health system. These investments ensure that Foundational Public Health Services are available in every community across Washington.

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Sincerely,

Keith Grellner
Chair

WASHINGTON STATE BOARD OF HEALTH

2023 Meeting Schedule

Dates Approved by the Board November 9, 2022
(Hybrid & Meeting Location Updates February 15, 2023)

	Meeting Date	Location
Board	**Monday January 9, 2023**	**Virtual: Virtual Meeting via ZOOM Webinar, hyperlink provided on website and agenda. Public Attendees can pre-register and access the meeting online.**
Board	**Wednesday March 8, 2023**	**Hybrid:** • **Physical Location; Labor & Industries Auditorium, 7273 Linderson Way SW, Tumwater, WA 98501** • **Virtual via ZOOM Meeting, hyperlink provided on website and agenda. Public Attendees can access the meeting online.**
Board	**Wednesday April 12, 2023**	**Hybrid:** • **Physical Location; Labor & Industries Auditorium, 7273 Linderson Way SW, Tumwater, WA 98501** • **Virtual via ZOOM Meeting, hyperlink provided on website and agenda. Public Attendees can access the meeting online.**
Board	**Wednesday June 14, 2023**	**Hybrid:** • **Physical Location; WA State Capitol Campus John A. Cherberg Building, Rooms ABC 304 15th Avenue S.E. Olympia, WA 98501** • **Virtual via ZOOM Meeting, hyperlink provided on website and agenda. Public Attendees can access the meeting online.** *(Note: WA State Association of Local Public Health Officials (WSALPHO) Annual meeting is at the Icicle Inn, Leavenworth June 12-14, 2023.)*
Board	**Wednesday July 12, 2023**	**Hold date – meet only if necessary**

Board	**Wednesday** **August 9, 2023**	**Hybrid:** • **Physical Location; WA State Capitol Campus** **John A. Cherberg Building, Rooms ABC** **304 15th Avenue S.E.** **Olympia, WA 98501** • **Virtual via ZOOM Meeting, hyperlink provided on website and agenda. Public Attendees can access the meeting online.**
Board	**Monday** **October 9, 2023**	**Hybrid:** • **Physical Location; Likely Wenatchee, WA** **Coast Wenatchee Hotel (Room TBD)** **201 N Wenatchee Ave** **Wenatchee, WA 98801** • **Virtual Meeting via ZOOM Webinar, hyperlink provided on website and agenda. Public Attendees can pre-register and access the meeting online.** *(Note: WA State Public Health Association (WSPHA) Annual meeting is at the Coast Wenatchee Hotel October 10-13, 2023, tentative plan to co-locate with WSPHA)*
Board	**Wednesday** **November 8, 2023**	**Hybrid:** • **Physical Location; TBD** • **Virtual via ZOOM Meeting, hyperlink provided on website and agenda. Public Attendees can access the meeting online.** *(Note: WA State Association of Counties (WSAC) County Leaders Conference is November 14-16, 2023, Davenport Grand, Spokane)*

Start time is 9:30 a.m. unless otherwise specified. Time and locations subject to change as needed. See the Board of Health Web site and the Health Disparities Council Web site for the most current information.

Last updated 11/09/2022
(Locations updated 2/15/23)

STATE OF WASHINGTON
WASHINGTON STATE BOARD OF HEALTH
PO Box 47990 • Olympia, Washington 98504-7990

March 15, 2023

Kim Tuminello
Association for Creatine Deficiencies
6965 El Camino Real #105-598
Carlsbad, CA, 92009

Sent Via Email

Dear Ms. Tuminello,

Thank you for the rulemaking petition you submitted to the State Board of Health (Board) on February 24th, 2023, requesting to amend Chapter 246-650 WAC to add Guanidinoacetate methyltransferase (GAMT) deficiency as a condition for newborn screening.

The Board met on March 8th, 2023, and after reviewing and discussing your petition, voted to deny your request at this time. The Board concluded that there was not enough information to accept the petition to begin rulemaking and instead instructed staff to follow the Board's process for evaluating candidate conditions.

The Board directed staff to work with the Department of Health to convene a technical advisory committee (TAC) to evaluate GAMT deficiency using the Board's process and criteria to evaluate conditions for inclusion in WAC 246-650-020. After the TAC completes its review of GAMT deficiency using the Board's process for evaluating candidate conditions, staff will present its findings to the Board. The Board will then revisit whether to add GAMT deficiency to the state's newborn screening list at that time.

Under RCW 34.05.330, a petitioner may appeal an agency's decision to deny a petition to repeal or amend a rule. An appeal must be made to the Governor within 30 days of denial.

If you require further assistance, please don't hesitate to contact Molly Dinardo, Health Policy Advisor in our office, at 564-669-3455 or at Molly.Dinardo@sboh.wa.gov.

Sincerely,

Keith Grellner, Chair

STATE OF WASHINGTON
DEPARTMENT OF HEALTH
OFFICE OF ENVIRONMENTAL HEALTH AND SAFETY
243 Israel Road SE • PO Box 47824 • Olympia, Washington 98504-7824 Telephone: 360-236-3330 • Fax: 360-236-2257
TTY: 1-800-833-6388 (TDD/TTY 711)

March 3, 2023

TO: Michelle Davis, Executive Director, Washington State Board of Health

FROM: Todd Phillips, Office Director

SUBJECT: ANNUAL REPORT OF VARIANCES IN WATER RECREATION PROGRAM

As required in WAC 246-260-201(2), attached is our annual report on variances granted during 2022. The materials provided are a summary of the variances. If more details are requested by you or the board, we will do our best to provide the details.

2022 Variance Report

Summary of Variances to WAC 246-260

This is the annual report to the State Board of Health providing a summary of the variances processed in 2022 as stipulated in WAC 246-260-201(2). Under this authority, the Department of Health (DOH) and local health officers review and approve or deny variances to the design, construction, and operation requirements related to water recreation facilities. The approved variances reflect applicant's ability to provide adequate documentation that the variance to the rule is consistent with overall intent of the chapter and our goal of providing a safe environment for users.

Variance approvals were submitted to us from three local health jurisdictions: Tacoma-Pierce County Health Department (TPCHD), Seattle King County (PHSKC) and Spokane Regional Health District (SRHD) in addition to those processed by DOH. There were 28 variances that were either approved or conditionally approved in 2022. TPCHD granted 1 variance; PHSKC granted 3; SRHD granted 8; and DOH granted 16.

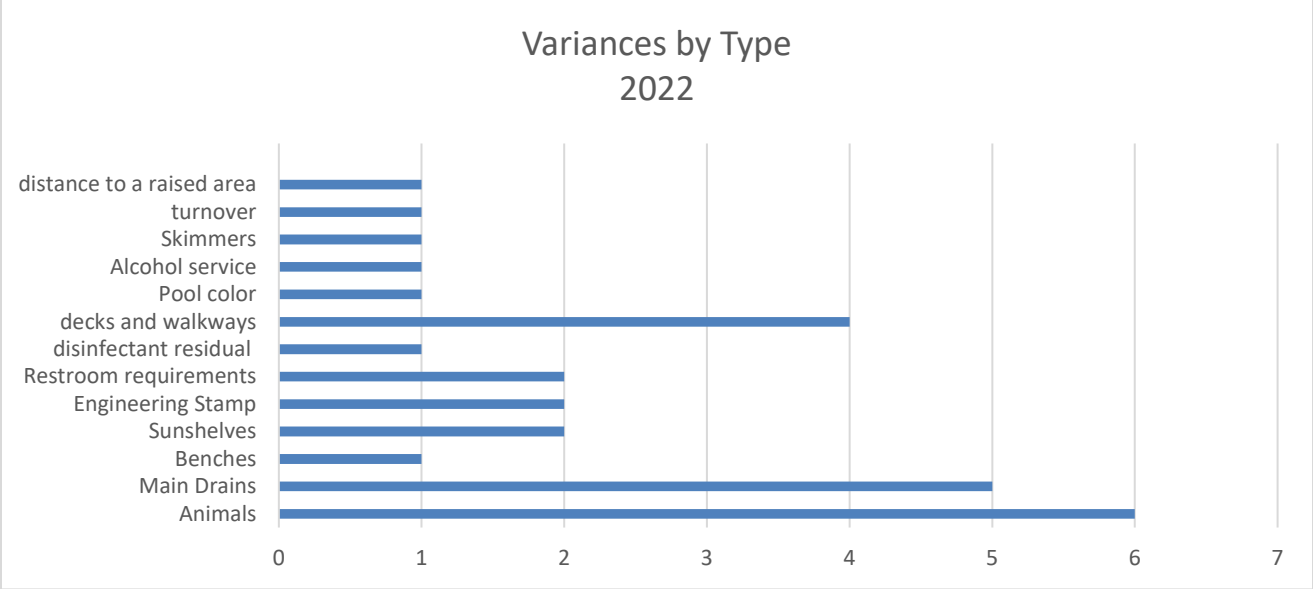
The most common variance is for dog swim events. In Spokane County, six dog swim events were held, for which variances were granted. These events are generally held at the end of the pool season, and no people are allowed in the pools to be with the dogs. The restriction on animals in WAC 246-260 is virtually the same as the requirement in the Model Aquatic Health Code.

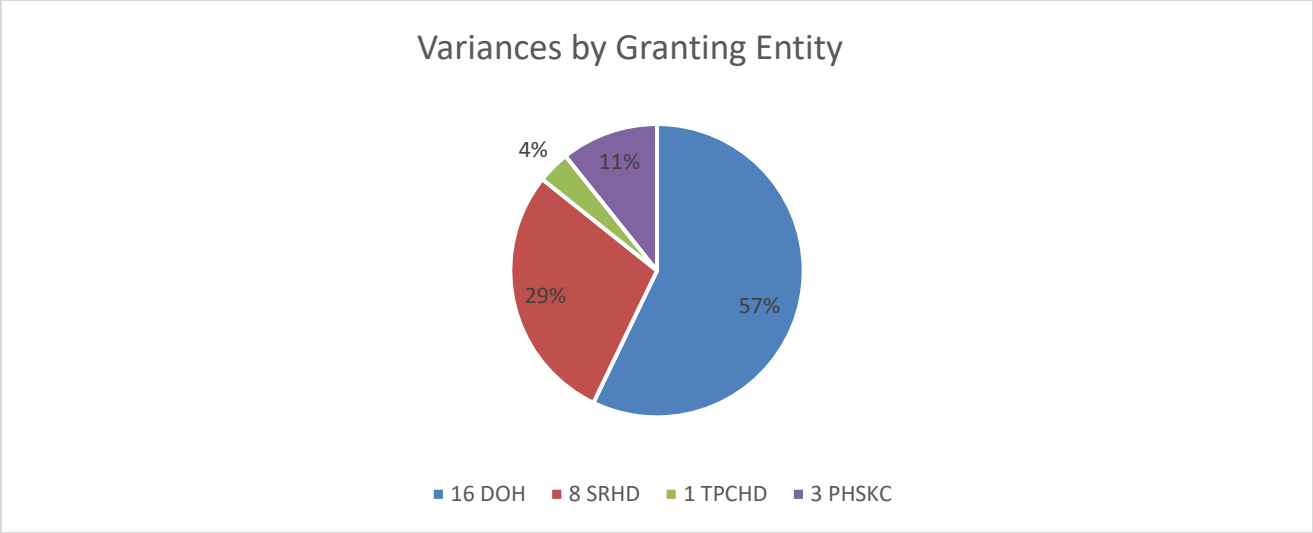
Main Drain variances in 2022 were the second most common (WAC 246-260-031(8)(e). These variances were not all for the same main drain requirement, however, some were due to the update to the federal main drain standard (APSP-16). This new standard was not recognized in Chapter 246-260 WAC and a variance was necessary until the rule language could be updated through expedited rule making.

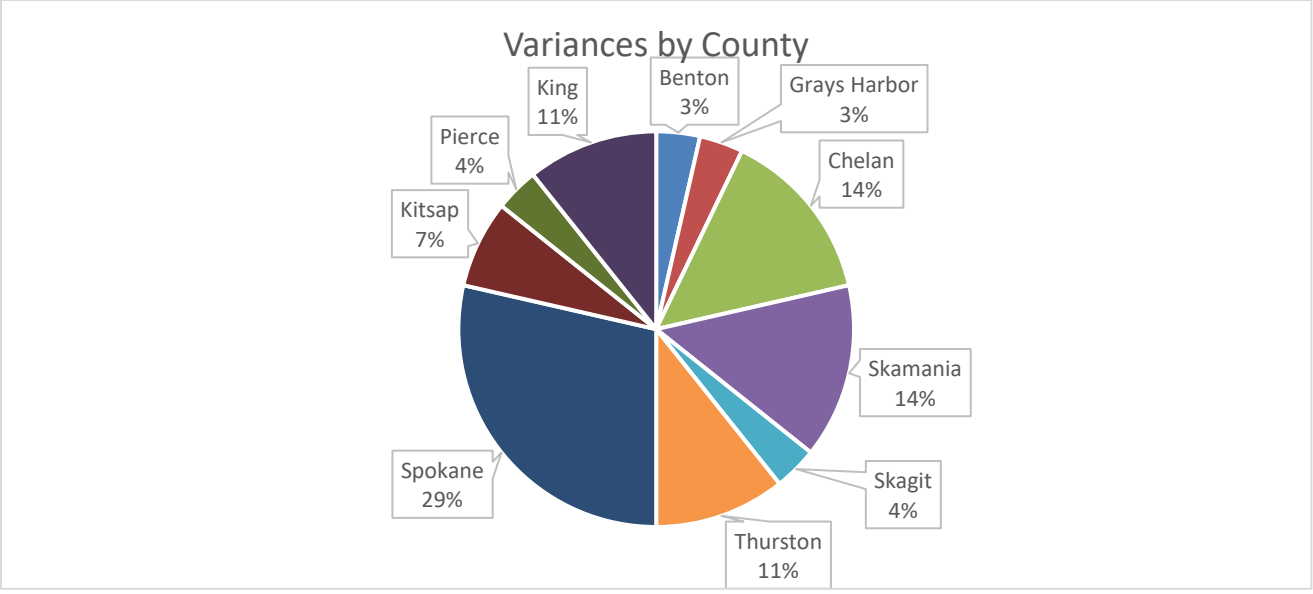
Two other kinds of variances granted this year worth mentioning are:

1. sunshelves and
2. alcohol service at general use pools.

Chapter 246-260 WAC does not recognize sunshelves nor does it allow alcohol service at general use pools. These variances foreshadow the need for the current rule making process to address these issues. The MAHC has language that allows sunshelves and alcohol service. The MAHC language for sunshelves may be too permissive to adopt without modification, because these rules allow for a sunshelf to be a "wading area" with a potential drop off from an area just inches deep to an area that may be as deep as 5 feet. Alcohol service requirements may also need careful consideration to ensure that swimming under the influence or supervising children under the influence are minimized.


Variances by Type
2022
distance to a raised area
turnover
Skimmers
Alcohol service
Pool color
decks and walkways
disinfectant residual
Restroom requirements
Engineering Stamp
Sunshelves
Benches
Main Drains
Animals
0
1
2
3
4
5
6
7


Variances by Granting Entity
4%
11%
29%
57%
16 DOH
8 SRHD
1 TPCHD
3 PHSKC


Variances by County
King 11%
Benton 3%
Grays Harbor 3%
Pierce 4%
Chelan 14%
Kitsap 7%
Skamania 14%
Spokane 29%
Skagit 4%
Thurston 11%

Variance Data Sheet 2022

County	Granting Entity	Name	WAC	Descriptor	Mitigation Proposed	Action
Thurston	DOH	Steamboat Tennis & Athletic Club	246-260-031(8)(e)(iv)(B)	Main Drains separated by 3 feet.	Drains in the spa are spaced 34 inches apart. Each spa pump equipped with an SVRS device.	Approved
Kitsap	DOH	Hazel Creek Montessori	246-260-031(21)(i)	Showers designed for showering in the nude.	Rinse Showers provided on Deck. Education to staff and parents.	Approved
Chelan	DOH	Enzian Inn	246-260-091(2)	Bench size and number limitation.		Approved
Chelan	DOH	Der Ritterhof Motor Inn	246-260-041(4)	dimensional design for safety - sun shelf requested	Shelf is designed as the top step of a staircase. Additional postings for enhanced supervision of children.	Conditionally Approved
Chelan	DOH	Lincoln Park Splash Pad	246-260-081(4)(c)(iii)	two or more drains manifolded with a junction fitting placed in the middle of branch line piping between outlets.	Drains are not fully submerged.	Approved
Skagit	DOH	Grandy Creek	WAC 246-260-031(8)(e)	Main Drains must be 3 feet apart.	Drains are 32 inches apart. Each drain cover is an un-blockable channel drain.	Approved
Kitsap	DOH	The Reserve at Bucklin Hill	246-260-021(1)(b) & 246-260-021(6)(b)	Requirements for engineer stamp/signature.	Project is a fence replacement. The fence design, construction, and installation are standard, well described in the code and does not require the expertise of an engineer for a barrier that meets safety requirements.	Approved
Chelan	DOH	Marina's Edge Resort	WAC 246-260-041(3)(a)	Owners shall ensure floor and wall designs provide for safety	Redesign shelf so that it does not have a drop-off into deep water.	Approved

Benton	DOH	Clipper Ridge	246-260-021(1)(b) & 246-2	Plans are required to be prepared and signed by an architect or engineer.	Simple project - replacement of a chlorinator.	Denied
Grays Harbor	DOH	Seabrook Sunrise Pool	246-260-031(8)(e)(iv)(C)	Main drain covers must meet APSP-16 2011 standard.	Covers meet APSP-16, 2017 standard.	Approved
Thurston	DOH	Lions Park Sprayground	246-260-031(21)(f)	Distance to restrooms	Complies with MAHC. Supplemental UV disinfection. redesign walking path to be as straight and short as possible.	Approved
Thurston	DOH	Nouvelle Apartments	246-260-031(8)(e)(iv)(C)	Main drain covers must comply with APSP-16 2011 standard.	covers comply with APSP-16 2017 standard.	Approved
Skamania	DOH	Tenzen	246-260-031(17)(a)(i)	Residual disinfectant requirements	Partial flow through, UV system, bacteriological testing, no children, shower requirements, frequent draining, and cleaning, occasional hyperchlorination	Approved
Skamania	DOH	Tenzen	246-260-031(3)(b)	Minimum deck slope of 1/4 inch per foot to drain	1% minimum slope with smooth finish. Compliance with MAHC. Proper maintenance.	Approved
Skamania	DOH	Tenzen	246-260-051(1)	Perimeter deck provided	shallow and narrow spas, local EMS ok, emergency action plan developed	Approved
Skamania	DOH	Tenzen	246-260-051(2)(a)	Spa surface color white or light if greater than 100 square feet	shallow spa, plenty of light, no hydrotherapy jets, frequent draining, and cleaning.	Approved
Spokane	SRHD	Historic Davenport Hotel	246-260-031(3)	Walking surfaces - carpet	Signage to towel off. Carpet care specified.	Approved

Spokane	SRHD	Cannon Pool-City of Spokane Parks	246-260-151	Restrictions on Animals - dog swim	1) provide lifeguards at the event, 2) humans are prohibited from entering the water, 3) disinfection residuals must conform to WAC 246-260, 4) the recirculation system must remain on throughout the event, 5) dogs must be evaluated by a veterinarian for aggression and health issues before entering the pool area, 6) dogs must be bathed before entering the water, 7) all dogs must be older than six months and currently vaccinated against rabies.	Approved
Spokane	SRHD	Comstock Pool-City of Spokane Parks	246-260-151	Restrictions on Animals - dog swim	see above	Approved
Spokane	SRHD	Hillyard Pool-City of Spokane Parks	246-260-151	Restrictions on Animals - dog swim	see above	Approved
Spokane	SRHD	Liberty Pool-City of Spokane Parks	246-260-151	Restrictions on Animals - dog swim	see above	Approved
Spokane	SRHD	Shadle Pool-City of Spokane Parks	246-260-151	Restrictions on Animals - dog swim	see above	Approved
Spokane	SRHD	Mission Pool City of Spokane Valley	246-260-152	Restrictions on Animals - dog swim	see above	Approved
Spokane	SRHD	Wellness Center at Central Park	246-260-031(20)	Locker Rooms - carpeting	Signage to towel off. Carpet care specified. Maintain non-slip mats on tile near the carpet.	Approved

Pierce	TPCHD	Tacoma Lawn Tennis Club	246-260-131(3)(a),(d)	Alcohol prohibited at general use pools	Written operations plan required including additional staff training on alcohol impairment; food/alcohol only allowed at certain areas of the pool deck, pool deck must be clearly marked with painted lines showing this area; required deck surface area must still be provided (no food/alcohol in this space); additional signage and member correspondence required; no glass allowed; 6 month assessment required after starting.	Conditional Approval
King	PHSKC	Fox Run	(WAC) 246-260-031(8)(d)(iii)	skimmers to be equipped with a device such as an equalizer line to prevent air lock in the recirculation suction line.	operator will monitor water levels to prevent pump cavitation	Approved
King	PHSKC	Boren Towers	WAC 246-260-051 (4)	Turnover rate and bather load	Turnover 30-60 minute turnover rate, bather load limited to 25 people, maximum temp ≤93°F	Approved; note: constructed before plan review approval
King	PHSKC	Ovation	WAC 246-260-041 (1)	Location. Owners shall ensure pump houses, planters, balconies, landscape features, trees, and structures are located fifteen feet or more horizontally away from any swimming pool or provide barriers or other means to prevent diving or ready access to a pool from the structures.	signage posted in pool area prohibiting jumping from cabana. Added to lease agreement pool rules notification that are signed annually.	Approved

Department of Health Updates

Washington State Department of HEALTH

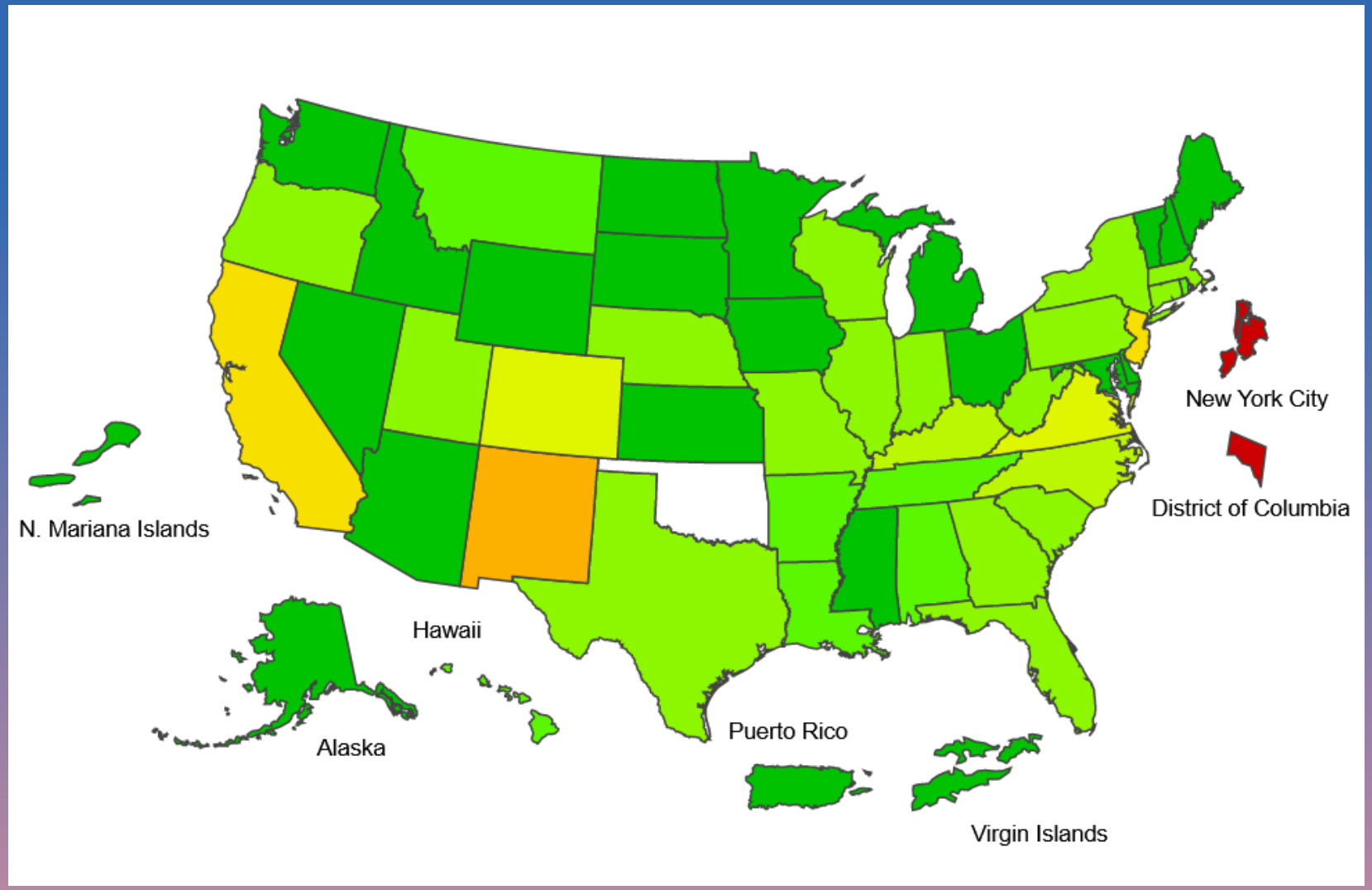
State Board of Health Meeting

April 12, 2023

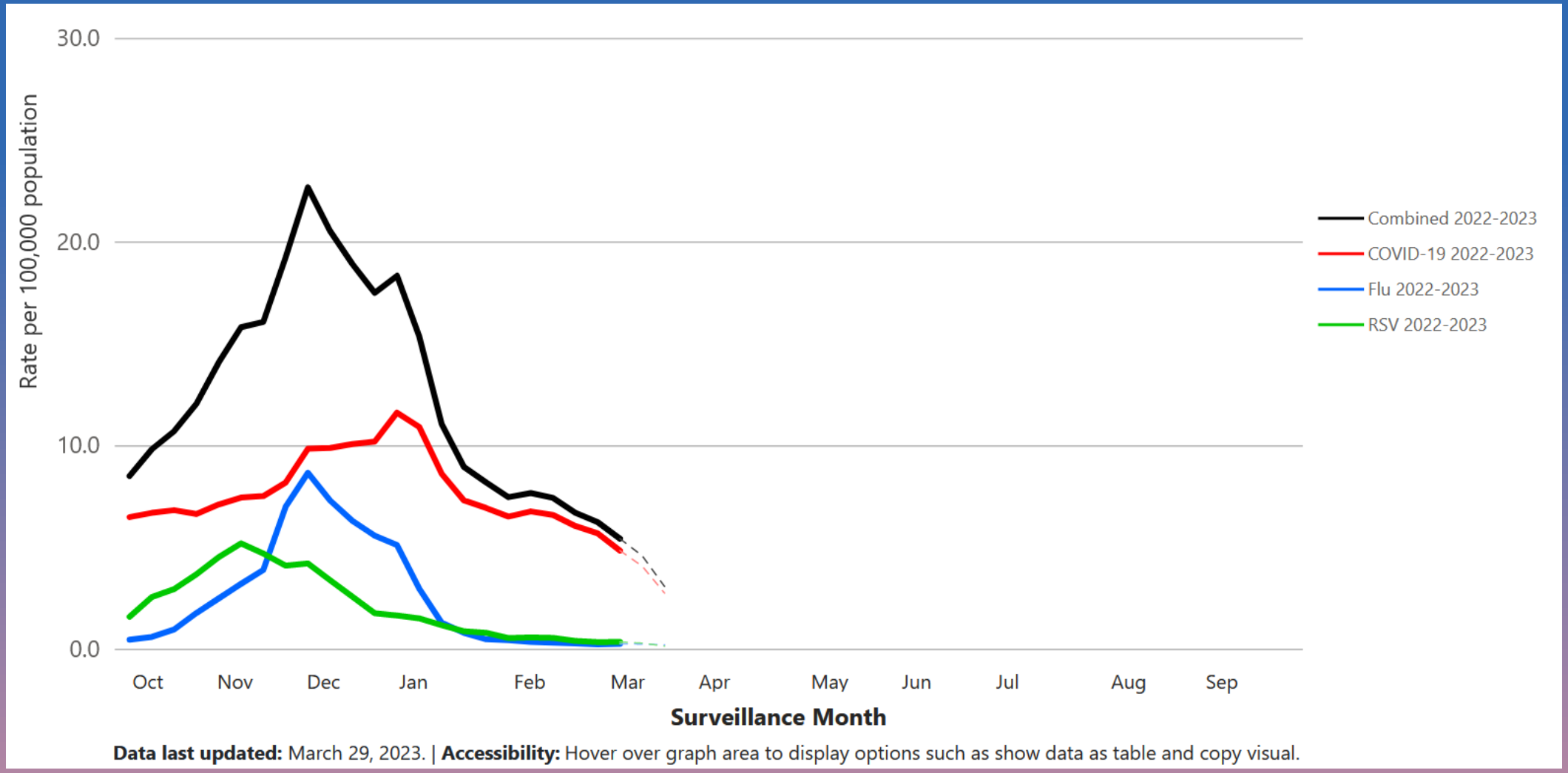
@WaDeptHealth
@WaHealthSec
@Ushahmd

Public Health Updates

U.S. Influenza Activity



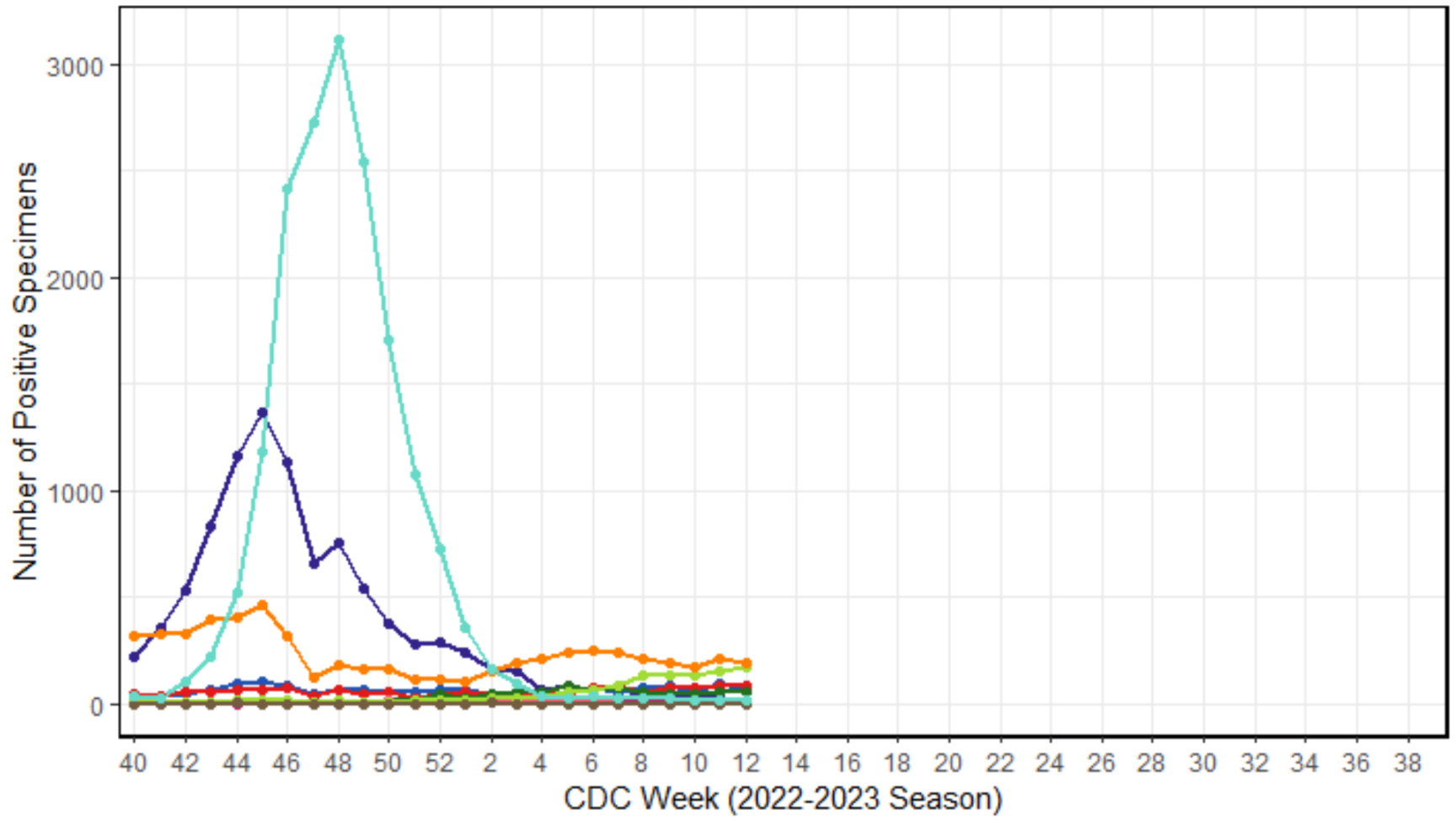
U.S. Rates of Respiratory Virus Hospitalizations



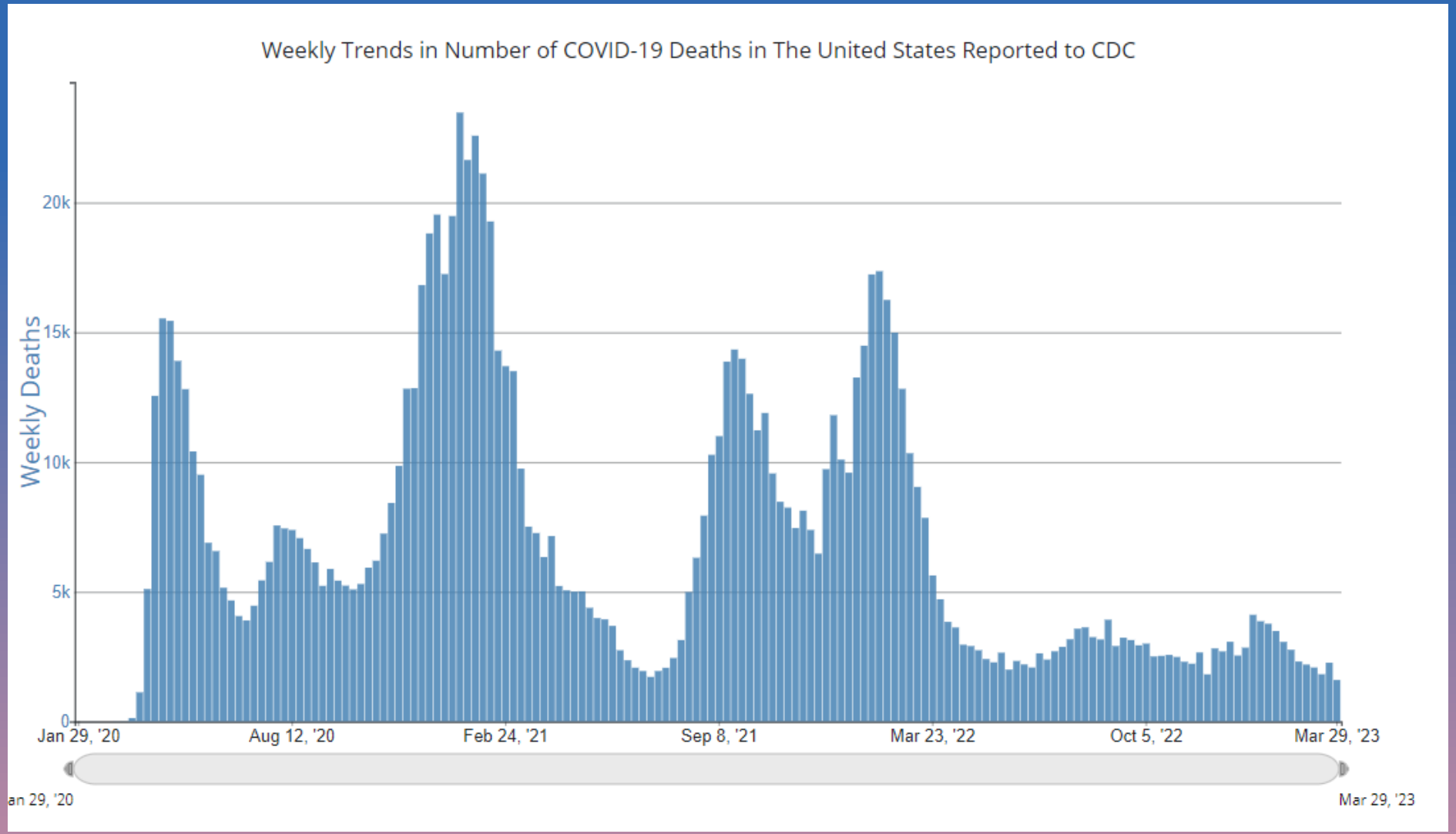
Data last updated: March 29, 2023. | **Accessibility:** Hover over graph area to display options such as show data as table and copy visual.

Respiratory and Enteric Viruses in WA 2022-2023

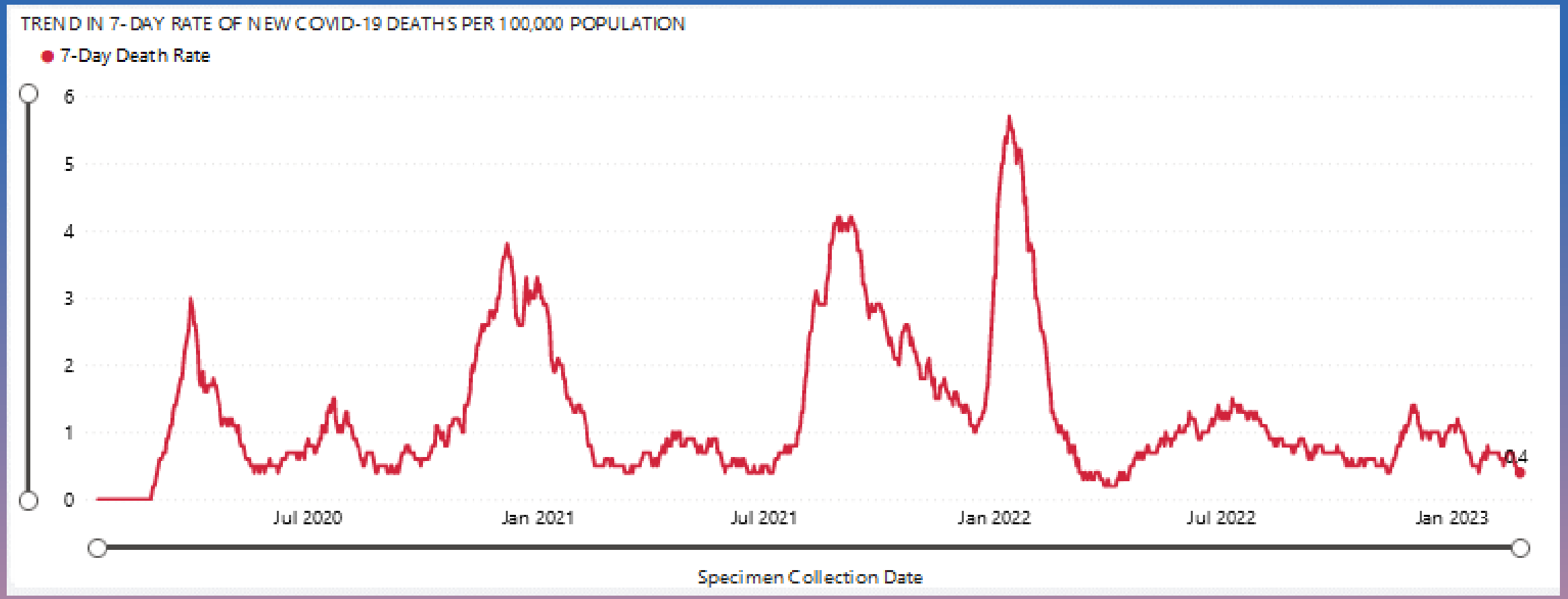
Figure 6: Respiratory and Enteric Viruses, Washington, 2022-2023 Season to Date



COVID-19 in the United States



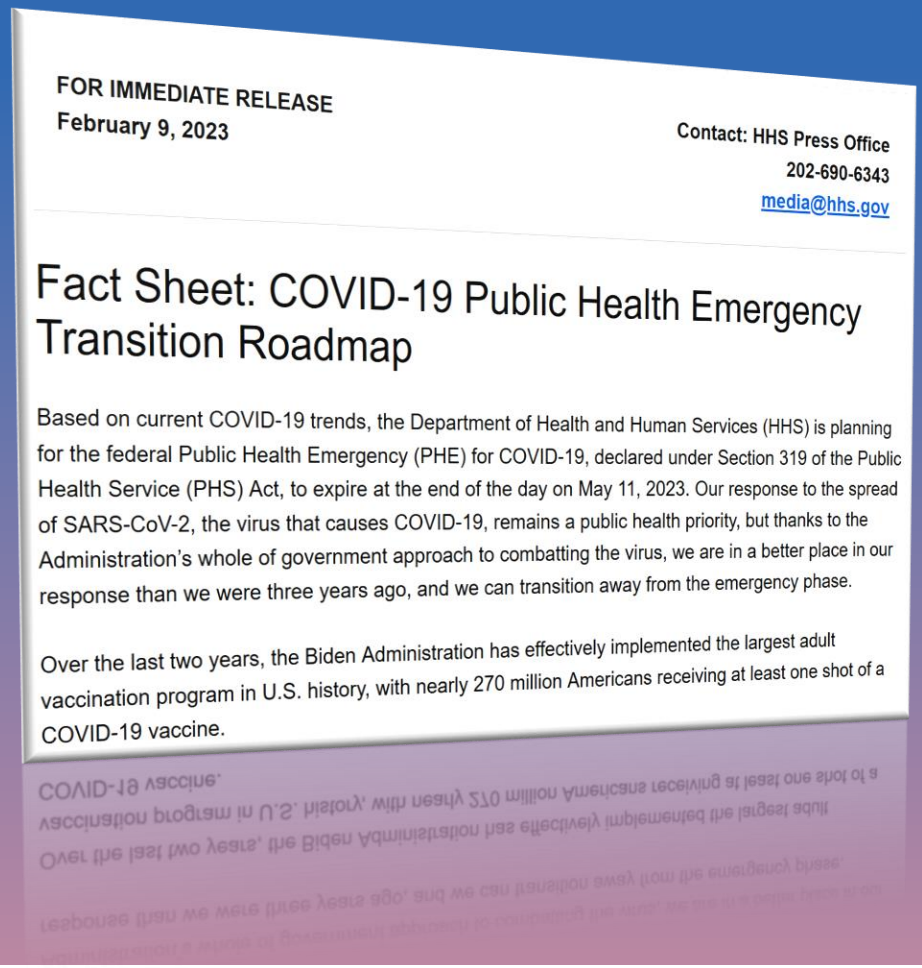
COVID-19 in Washington State



Washington State Department of HEALTH

@WaDeptHealth
@WaHealthSec
@Ushahmd

COVID-19 Federal Public Health Emergency Transition Roadmap



FOR IMMEDIATE RELEASE
February 9, 2023

Contact: HHS Press Office
202-690-6343
media@hhs.gov

Fact Sheet: COVID-19 Public Health Emergency Transition Roadmap

Based on current COVID-19 trends, the Department of Health and Human Services (HHS) is planning for the federal Public Health Emergency (PHE) for COVID-19, declared under Section 319 of the Public Health Service (PHS) Act, to expire at the end of the day on May 11, 2023. Our response to the spread of SARS-CoV-2, the virus that causes COVID-19, remains a public health priority, but thanks to the Administration's whole of government approach to combatting the virus, we are in a better place in our response than we were three years ago, and we can transition away from the emergency phase.

Over the last two years, the Biden Administration has effectively implemented the largest adult vaccination program in U.S. history, with nearly 270 million Americans receiving at least one shot of a COVID-19 vaccine.

- **H.J. Res. 7 - Relating to a national emergency declared by the President on March 13, 2020**
- **May 11, 2023, end of Section 319 Public Health Emergency (PHE)**
- **Congress extended Telehealth flexibility through 2024 and expanded Medicaid eligibility through FY23 Federal Omnibus**
- **US Health & Human Services must determine how to apply PREP Act as COVID-19 vaccines and therapeutics become commercialized**

Washington State Department of HEALTH

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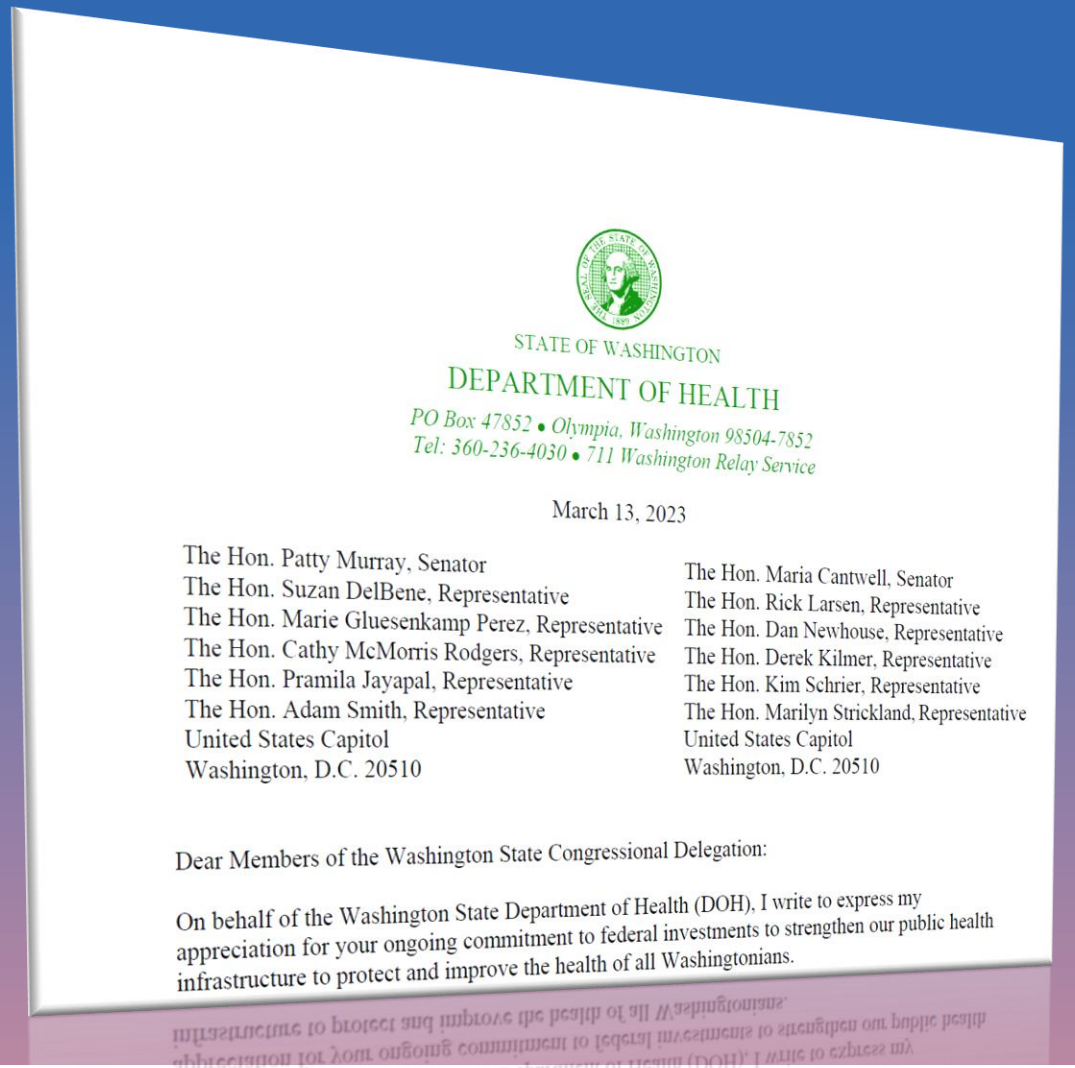
Public health system continue comprehensive monitoring of COVID-19 post-PHE

- **Hospitalizations** (primary focus)
- **Emergency department visits**
- **Deaths** (via death certificate data)
- **Test positivity** data (passive reporting)
- **Genomic** surveillance (national, wastewater, traveler)
- **Sentinel** surveillance (high-risk populations, settings, and outcomes)
- **Wastewater** surveillance
- **Vaccine effectiveness** studies
- **Post-COVID conditions (Long COVID)** studies

118th United States Congress

Appropriations



STATE OF WASHINGTON
DEPARTMENT OF HEALTH
PO Box 47852 • Olympia, Washington 98504-7852
Tel: 360-236-4030 • 711 Washington Relay Service

March 13, 2023

The Hon. Patty Murray, Senator
The Hon. Suzan DelBene, Representative
The Hon. Marie Gluesenkamp Perez, Representative
The Hon. Cathy McMorris Rodgers, Representative
The Hon. Pramila Jayapal, Representative
The Hon. Adam Smith, Representative
United States Capitol
Washington, D.C. 20510

The Hon. Maria Cantwell, Senator
The Hon. Rick Larsen, Representative
The Hon. Dan Newhouse, Representative
The Hon. Derek Kilmer, Representative
The Hon. Kim Schrier, Representative
The Hon. Marilyn Strickland, Representative
United States Capitol
Washington, D.C. 20510

Dear Members of the Washington State Congressional Delegation:

On behalf of the Washington State Department of Health (DOH), I write to express my appreciation for your ongoing commitment to federal investments to strengthen our public health infrastructure to protect and improve the health of all Washingtonians.

- Public Health Infrastructure and Capacity
- Data Modernization Initiative
- Domestic Preparedness

A NATIONAL BLUEPRINT FOR BIODEFENSE:

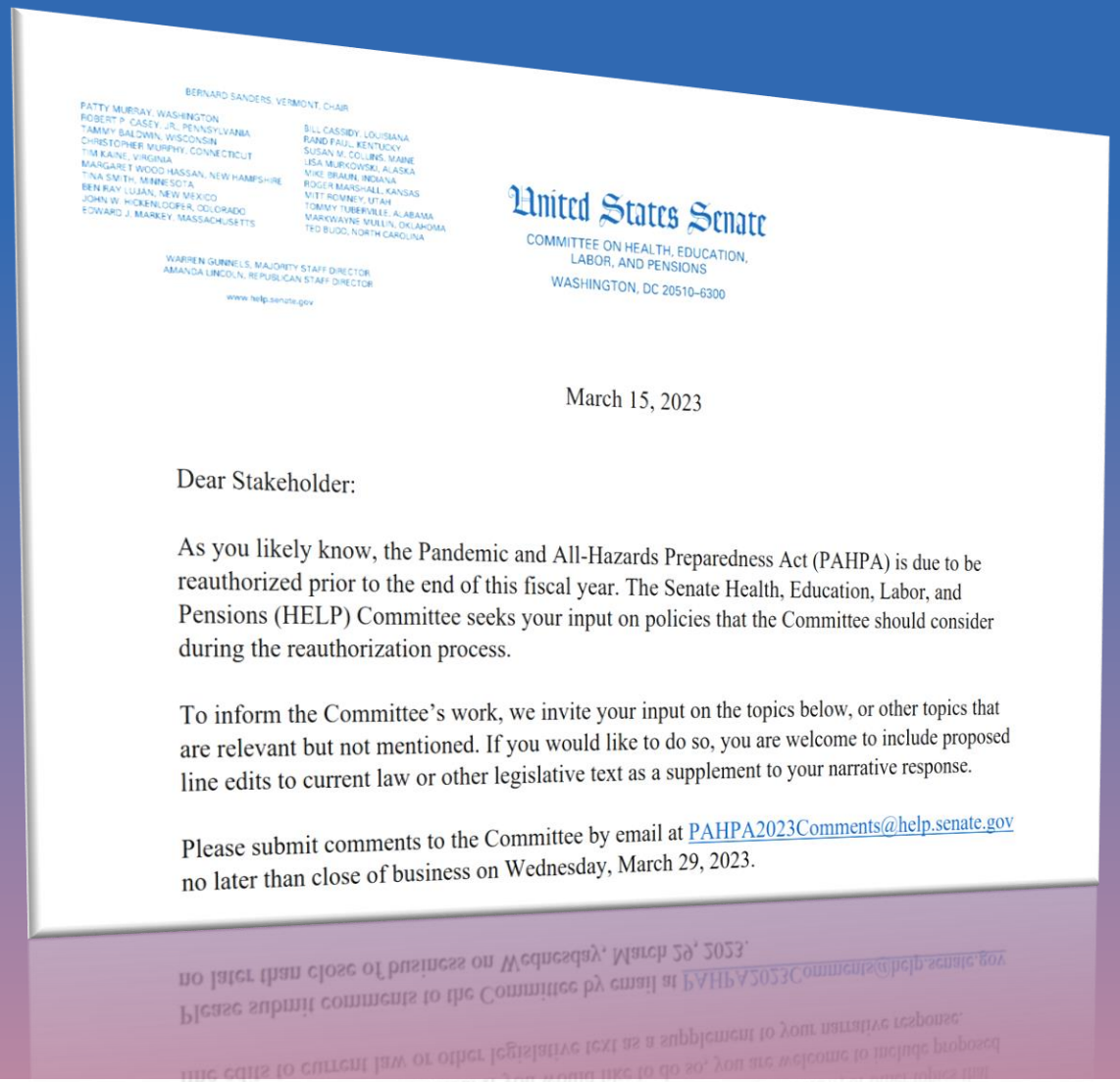
LEADERSHIP AND MAJOR REFORM NEEDED TO OPTIMIZE EFFORTS

REPORT OF THE BIPARTISAN COMMISSION ON BIODEFENSE

October 2015

BIPARTISAN COMMISSION ON BIODEFENSE

PAHPA Reauthorization



BERNARD SANDERS, VERMONT, CHAIR

PATTY MURRAY, WASHINGTON
ROBERT P. CASEY, JR., PENNSYLVANIA
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CHRISTOPHER MURPHY, CONNECTICUT
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LISA MURKOWSKI, ALASKA
MIKE BRAUN, INDIANA
ROGER MARSHALL, KANSAS
MITT ROMNEY, UTAH
TOMMY TUBERVILLE, ALABAMA
MARKWAYNE MULLIN, OKLAHOMA
TED BUDD, NORTH CAROLINA

WARREN GUNNELS, MAJORITY STAFF DIRECTOR
AMANDA LINCOLN, REPUBLICAN STAFF DIRECTOR

www.help.senate.gov

United States Senate

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS
WASHINGTON, DC 20510–6300

March 15, 2023

Dear Stakeholder:

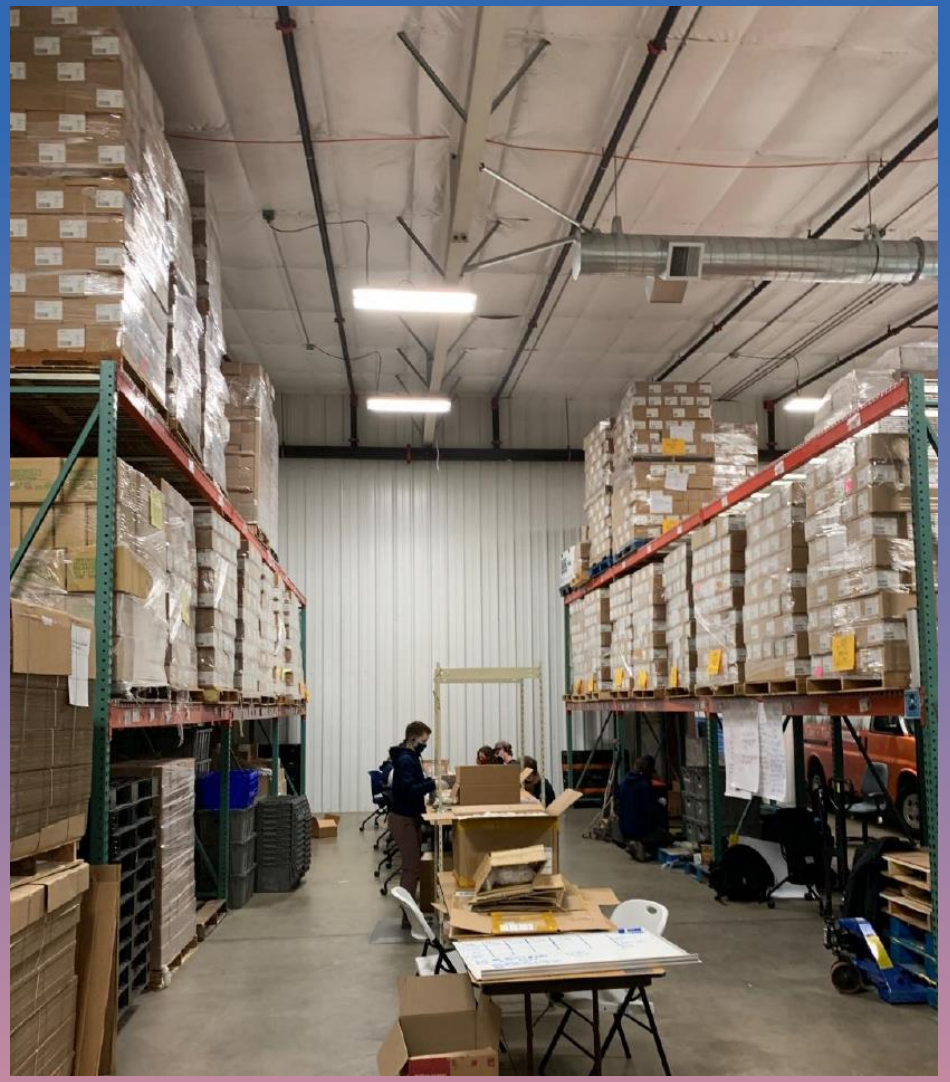
As you likely know, the Pandemic and All-Hazards Preparedness Act (PAHPA) is due to be reauthorized prior to the end of this fiscal year. The Senate Health, Education, Labor, and Pensions (HELP) Committee seeks your input on policies that the Committee should consider during the reauthorization process.

To inform the Committee's work, we invite your input on the topics below, or other topics that are relevant but not mentioned. If you would like to do so, you are welcome to include proposed line edits to current law or other legislative text as a supplement to your narrative response.

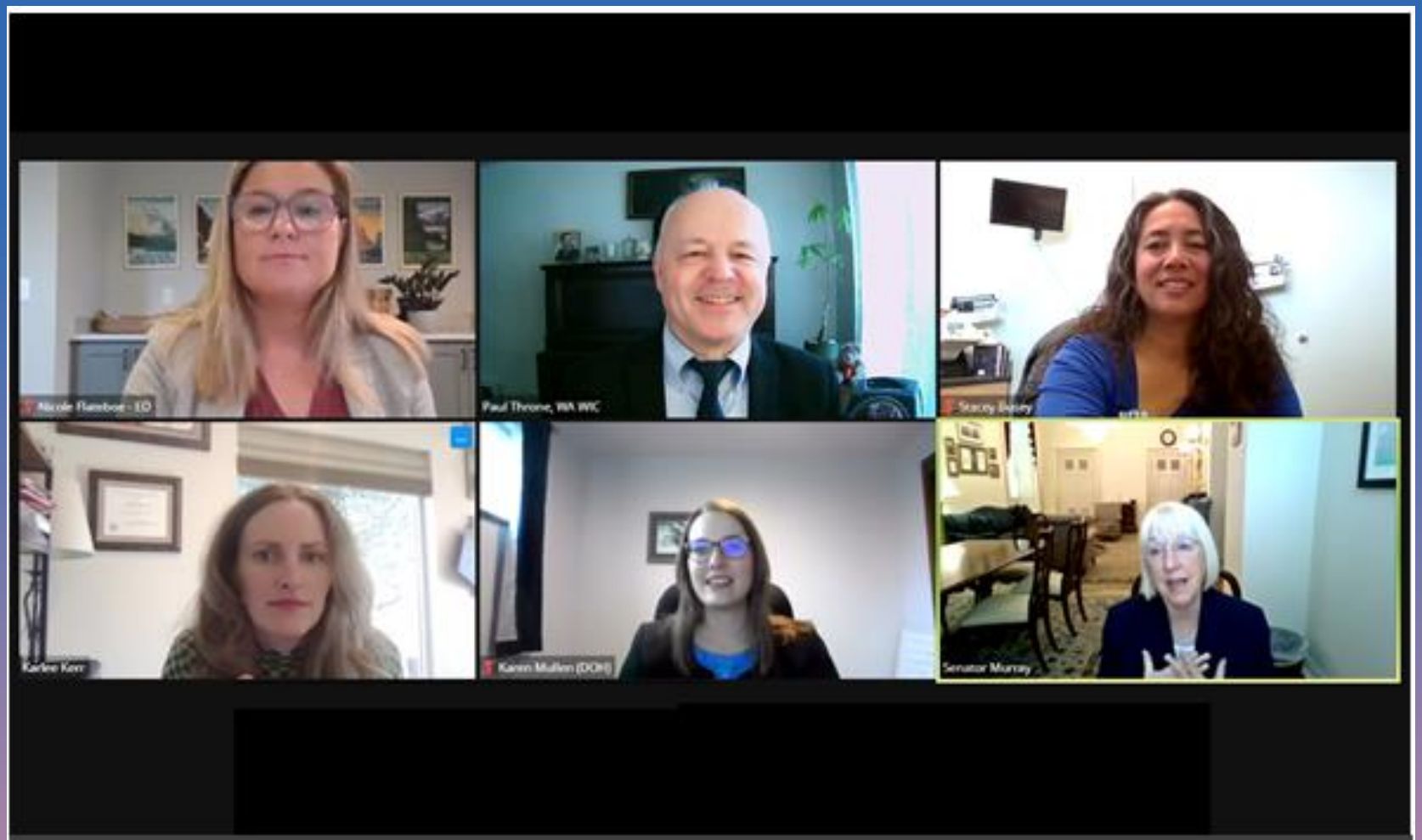
Please submit comments to the Committee by email at PAHPA2023Comments@help.senate.gov no later than close of business on Wednesday, March 29, 2023.

- This year's PAHPA reauthorization will build upon steps taken by lawmakers to bolster national defense against pandemics or biothreats.
- DOH shared comments with Senate HELP Committee in response to this request for information.

Washington State Medical Logistics Center



Washington State Nutrition Programs



From left to right: Nicole Flateboe, Paul Throne, Stacey Busey, Karlee Kerr, Karen Mullen, and Patty Murray discussed issues facing the WIC program, staff, and participants.

Washington State Nutrition Programs

Program	Who can use it	Benefits	Where Participants can Redeem Benefits
Women Infants and Children Program (WIC) 	• Pregnant participants • Breastfeeding and postpartum participants • Infants • Children 1-5 years Eligibility: • Household income below 185% of poverty level • Adjunctive eligibility, such as Medicaid, TANF, and SNAP. • About 200,000 participants	Food Package: • Fresh or frozen fruits and vegetables • Baby Food • Beans/Peas/Lentils • Breakfast Cereal • Cheese, Eggs • Fish – Canned • Dairy, Soy • Peanut Butter • Whole Grain Bread, Rice, Pasta Other Benefits: • Nutrition education • Breastfeeding support • Health screening • Referrals	• Participating Grocery Stores • Coming summer 2024: Online Ordering with Walmart
WIC Farmers Market Nutrition Program (FMNP) 	WIC participants (except infants) • 35,173 participants in 2022 season • $440,076 in food benefits	• $28 of benefits for use at Farmers Markets and Farm stands from participating WIC clinics each year. • Coming 2023: WIC Fruit and Vegetable Cash Value Benefits at Farmers Markets and Farm Stores • Local, fresh and unprocessed fruits, vegetables and cut herbs • Local means grown in Washington and in bordering counties in Idaho and Oregon • Season runs June 1-, Oct 31	• Participating Farmers Markets • Participating Farm Stores • Coming 2023: Participants can use Fruit and Vegetable Cash Value Benefits at Participating Farmers Markets and Farm Stores

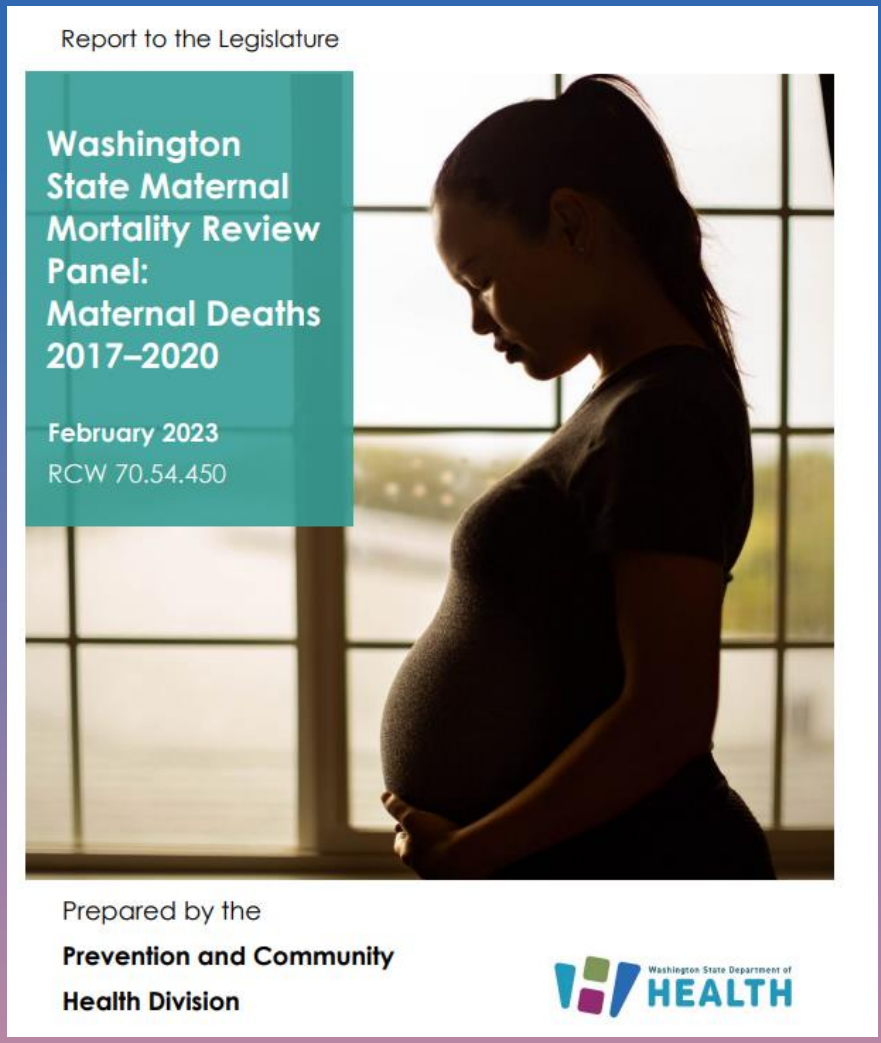
Washington State Nutrition Programs

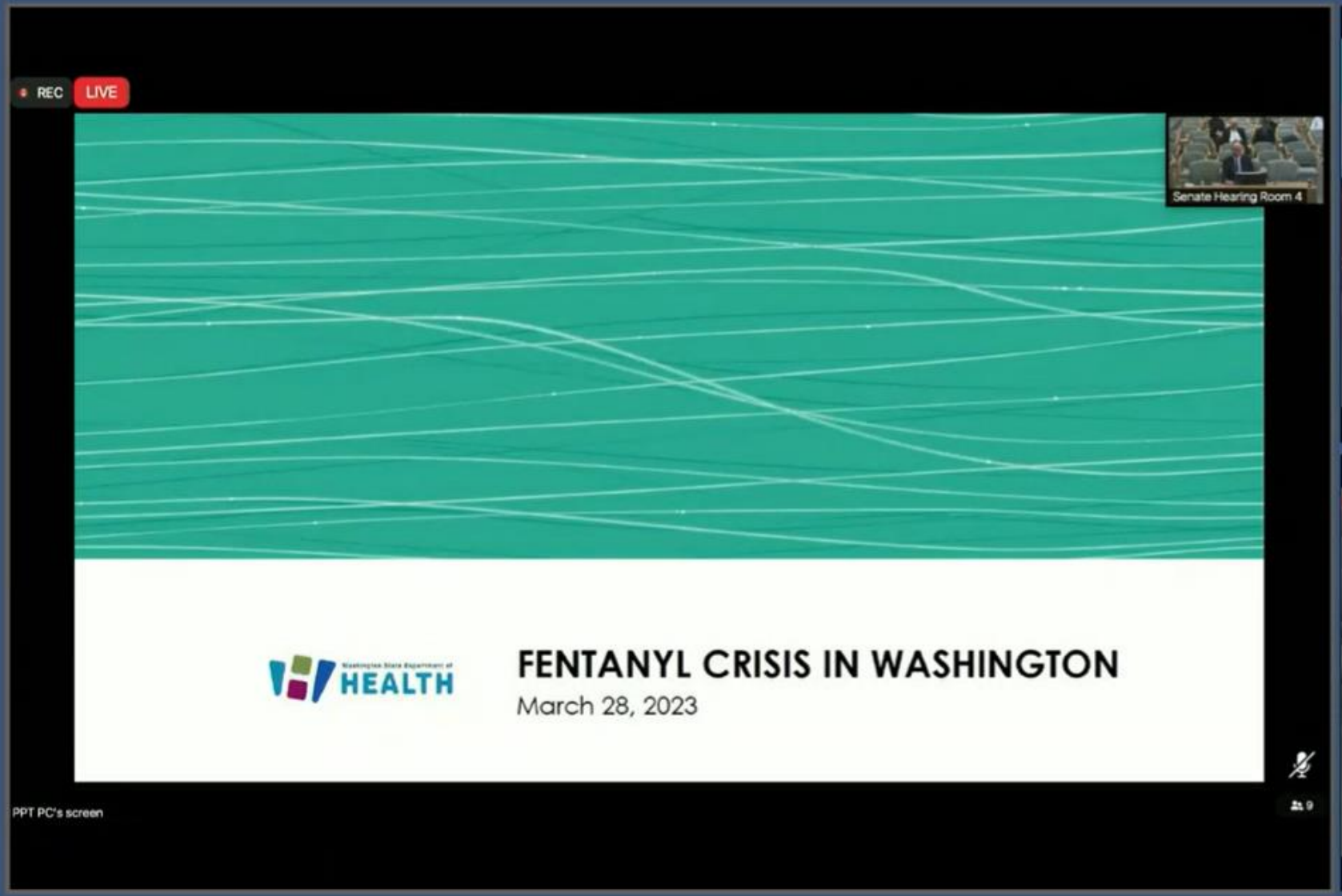
Program	Who can use it	Benefits	Where Participants can Redeem Benefits
SNAP Market Match	Anyone who has a SNAP/EBT card.	At participating Farmers Markets, get $1 SNAP Market Match for every $1 EBT (up to $25 per day). Spend the match on: • Fresh fruits, vegetables, and herbs • Mushrooms • Seeds and plants that produce food • SNAP Market Match dollars expire at the end of the year.	• At 123 Farmers Markets, Mobile Markets, and Farm Stands
SNAP Produce Match	Anyone who has a SNAP/EBT card.	Use $10 SNAP/EBT to buy qualifying fruits and vegetables and get $5 coupon for the next trip. Spend the coupon on : • Fruits and vegetables that are fresh and frozen with no added sugar, salt, or fat. • SNAP Produce Match coupons expire one month after they are issued.	• Participating Grocery Stores, currently: • Albertsons • Fiesta Foods • Amazon Fresh (online available) • Safeway (online available) • Community Food Co-op • Chimacum Corner Farmstand • The Food Co-op • Skagit Valley Food Co-op • Seatac International Market • Sophiya Mini Market
Fruit and Vegetable Prescriptions	Eligible participants: Have or are at-risk of developing a diet-related chronic condition; and screen positive for food insecurity	• Participant receives $250 in fruit and vegetable vouchers over 6 months ($10 per week).	• Any Safeway Store in Washington • There are 11 different health care systems currently distributing fruit and vegetable prescriptions in 50 clinics across Washington.

68th Washington State Legislature

Maternal Mortality Review Panel Report

- Submitted to the legislature as required every three years
- **Maternal Mortality Review Panel** review of deaths
- From **pregnancy** through **1 year postpartum**
- **Inequities**, **disparities**, and **contributing factors**
- **Recommendations** from **2017–2020** maternal deaths
- **Actions** for **policy**, **perinatal care**, and **agencies**





Tuesday, 28 March 2023 08:35:26 AM

Senate Health & Long Term Care

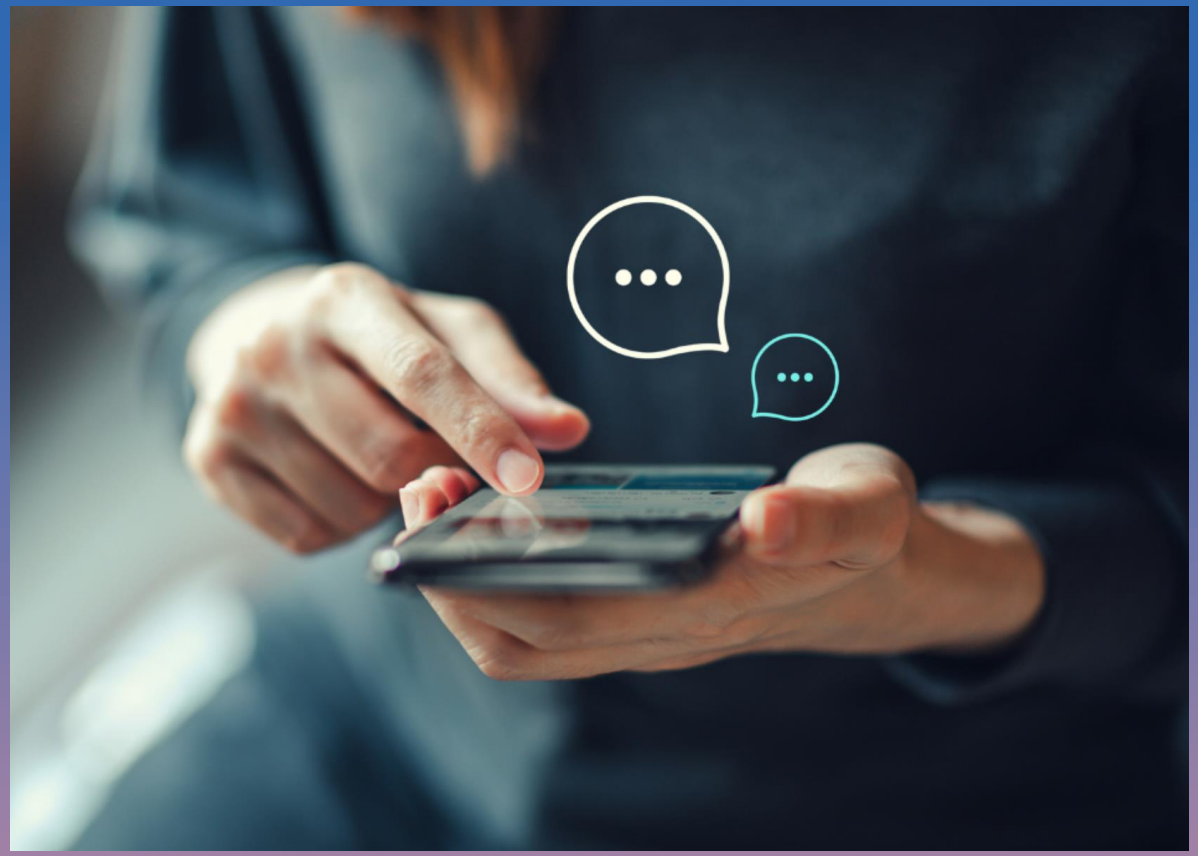
March 28, 2023, 8:00 am - Senate Hearing Rm 4 and Virtual

Workforce

- 4 New Health Professions
- 4 New Compacts
- Expanded Scopes

Behavioral Health

- 988 Crisis System
  - HB 1134 – Implementing the 988 crisis response system
  - SB 5120 – 23-hour Crisis relief centers
- Reducing Barriers to Licensure
  - HB 1724



Public Health and Safety

- HB 1470 – Private Detention Centers
- SB 5367 – Products containing THC
- SB 5536 Controlled Substances
- SB 5263 – Psilocybin
- HB 1335 – Doxxing

House and Senate Budgets

- **Foundational Public Health Services (FPHS)**
  - Senate - Increases base funding by 50 M/year
    - 23 M one time – FHPS specified for Data Systems
  - House – Increases base funding by 50 M/year
    - No specific appropriations
  - Both budgets use a mix of GFS and Vape Tax Revenue to reach 50 M/year
  - Brings the total ongoing biennial FPHS investment to approxitely 324 Million
- **School Rule Proviso**

Next Steps

- Sine Die – April 23
- Governor has 20 days after the end of Session to sign bills - including the Budget
- Budget effective July 1

Transforming Our Public Health System Together

1. **We are following a roadmap to unwind the public health emergency as we move beyond emergency response to COVID-19. Our public health system will continue comprehensive monitoring of COVID-19 post-PHE.**

2. **US Congress is deliberating on reauthorization of foundational legislation to modernize and strengthen emergency preparedness (PAHPA) and nutrition programs (Farm Bill), as well as critical annual investments in our nation.**

3. **Washington State Legislature is deliberating on bills to expand our health workforce and behavioral health capacity, as well as continue vital investments in foundational public health services.**

Going farther together

Washington State Department of
HEALTH

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Visit www.doh.wa.gov

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@Ushahmd

GOVERNOR'S INTERAGENCY COUNCIL ON HEALTH DISPARITIES

APRIL 12, 2023

PRESENTERS

Jessica Zinda & Victor Rodriguez, Redesign Co-leads

LinhPhụng Huỳnh & Grace Cohen, Council Staff

OVERVIEW

- Council background
- Past efforts
- Council redesign

CREATION

In 2006, Senator Rosa Franklin—the first African American woman elected to the WA State Senate (1993)—championed a bill intended to **eliminate health disparities among people of color and women** in Washington State.

Council authority, responsibilities, and membership are outlined in state law (RCW 43.20.270 - 43.20.280).

AUTHORITY

- Create a state action plan for eliminating health disparities.
- Create statewide policy that measures and addresses social determinants of health as well as contributing factors of health.
- Understand how state government actions reduce/contribute to health disparities.
- Recommend initiatives for improving the availability of culturally and linguistically appropriate health literature and interpretative services.

MEMBERSHIP

- 3 Community Members
- Governor's Office of Indian Affairs
- Commission on African American Affairs
- Commission on Asian Pacific American Affairs
- Commission on Hispanic Affairs
- Dept of Agriculture
- Dept of Children, Youth, and Families
- Dept of Commerce
- Dept of Health
- Health Care Authority
- State Board of Health
- Dept of Ecology
- K-12 Education (OSPI)
- Dept of Social and Health Services
- Workforce Training & Education Coordinating Board

PARTNERSHIP

The State Board of Health:

- Provides staffing and assistance to the Council
- Has a seat on the Council
- Conducts Health Impact Reviews in collaboration with the Council
- Shares a commitment to health equity
- May endorse Council recommendations

PAST RECOMMENDATION AREAS

- Education & early learning
- Health insurance coverage
- Healthcare workforce
- Specific health conditions
- Behavioral health
- Reproductive health access
- Poverty reduction
- Disaggregated data
- Culturally and linguistically appropriate services (CLAS)
- Environmental justice
- Equity in state government
- Community engagement
- Task Force projects

Access the Council's State Action Plan and past reports online.

REDESIGN

The Health Disparities Council is reviewing and recommending updates to our statute to incorporate 17 years of work
and learning addressing health disparities in Washington State.

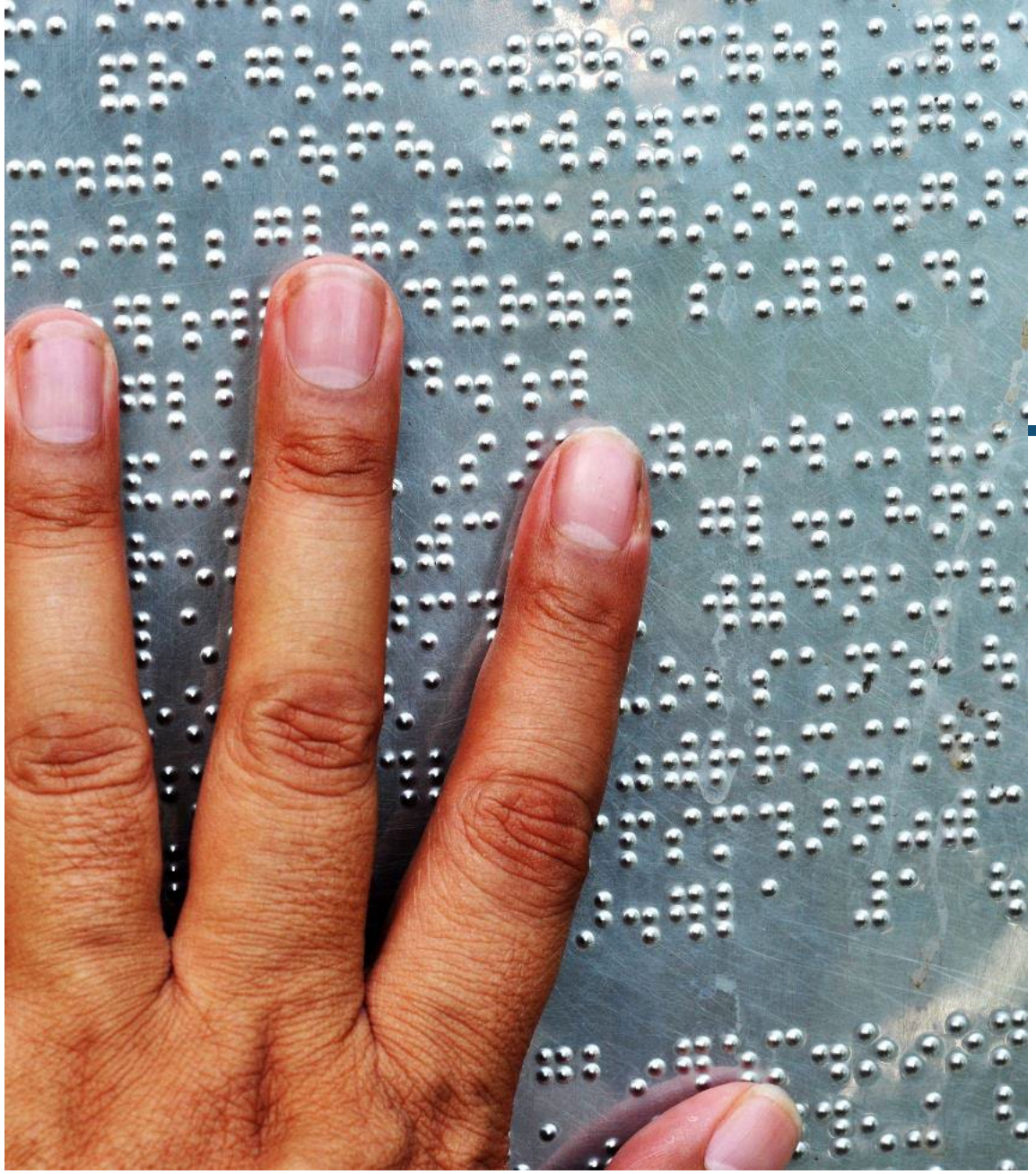
The Council will be guided by our vision and operating principles.

"We don't have many chances to redesign or reimagine like this.

We should commit to the joy in this.

This is a privilege to dream and imagine..."

- Ben Danielson, Council Chair



Foundational Truths

- Racism is a public health crisis.
- The COVID-19 pandemic has worsened conditions for communities.
- Community holds inherent power.
- There are many dimensions to health and wellbeing.
- We are interconnected.

Areas of Statute

Intent	What the state hopes to achieve.
Purpose	Reason for being, including our main role and the need(s) we must address.
Power & Responsibilities	How we operate and the channels we use to achieve our purpose, make impact, and exert influence. Interaction with key partners. Accountability measures.
Deliverables	Products we must deliver, to whom, and the frequency.
Structure	Group classification, membership, subcommittees, etc.
Staffing	Staffing level and roles dedicated to our operation.
Funding	Funding level and source(s) to achieve our purpose and sustain efforts.

Redesign Workshops

"Working in solidarity so everyone has meaningful opportunity to achieve their full potential."

- Public Participant

Draft Intent & Purpose Statement (English/Spanish)

Proposed intent: "It is the intent of the Washington State Legislature to advance health equity, wellbeing, and social justice through creating social, economic, and environmental conditions where all individuals and communities are free from racism and other forms of oppression and have full access to the social determinants of health, so they can be the healthiest version of themselves."

Areas of Exploration

- Change the narrative around health
- Health is a right
- Health equity benefits all of us
- Health equity requires racial equity
- Advance justice and restoration
- Support communities in building power and becoming more connected and resilient
- Support partners and enhance accountability
- Fully equip the Council and its members

"Our vision for change, our vision for Washington, our vision for health equity should be rooted in joy because ultimately, that's a critical indicator of a good quality of life—that we can experience joy in meaningful ways."

- Victor Rodriguez, Council Vice Chair

STAY CONNECTED

- Health Disparities Council website
  - Our Work
  - Action Plans and Reports
- Upcoming public meeting: Wednesday, May 10, 2023

www.healthequity.wa.gov Facebook/WAHealthEquity Twitter/WAHealthEquity

THANK YOU

HEALTH EQUITY
Governor's Interagency Council on Health Disparities

To request this document in an alternate format, please contact the Washington State Board of Health at 360-236-4110 or wsboh@sboh.wa.gov. TTY users can dial 711.

WASHINGTON STATE BOARD OF HEALTH

Date: April 12, 2023

To: Washington State Board of Health Members

From: Dimyana Abdelmalek, Board Member

Subject: Briefing/Update – Newborn Screening, Ornithine Transcarbamylase Deficiency (OTCD), Chapter 246-650 WAC

Background and Summary:

The State Board of Health (Board) has the authority under RCW 70.83.050 to adopt rules for screening Washington-born infants for hereditary conditions. Chapter 246-650 WAC is the Board's rule for newborn screening in Washington. WAC 246-650-010 defines the conditions, and WAC 246-650-020 lists the conditions on the state's required newborn screening panel.

Ornithine Transcarbamylase Deficiency (OTCD) is an inherited condition with a rapid onset that can result in significant morbidity and mortality if not detected and treated early.[1,2] OTCD is a urea cycle disorder that causes ammonia to accumulate in the blood, affecting the liver and other body systems. Newborn screening, resulting in possible early diagnosis, is essential to improve the quality of life for infants and their families and reduce infant mortality.

In 2021, the Board convened a technical advisory committee (TAC) to consider adding OTCD to the state's newborn screening panel. At its July 7, 2021, meeting, the TAC voted to include OTCD as a condition for screening. The Board discussed the TAC's recommendations at its October 13, 2021, meeting and voted to proceed with rulemaking to consider rules that would allow for screening of OTCD in the newborn screening program.

The Board filed a CR-101, Preproposal Statement of Inquiry, on February 4, 2022, to initiate rulemaking for chapter 246-650 WAC. Since the CR-101 filing, the Department of Health's (Department) Newborn Screening Program requested a fee increase from the legislature to add OTCD to the screening panel. The Board and Department have not been able to move forward with rulemaking, as authorization from the legislature (additional funding approved in the budget) is necessary to increase the fee to cover costs associated with including a new condition on the panel.

I have invited Molly Dinardo, Board Staff, to provide a brief overview of OTCD and an update on the Department's funding request for OTCD.

(continued on the next page)

Washington State Board of Health
April 12, 2023, Meeting Memo

Staff
Molly Dinardo

To request this document in an alternate format or a different language, please contact the Washington State Board of Health at 360-236-4110 or by email at wsboh@sboh.wa.gov. TTY users can dial 711.

PO Box 47990 • Olympia, WA 98504-7990
360-236-4110 • wsboh@sboh.wa.gov • sboh.wa.gov

1. Health Resources and Services Administration. Ornithine transcarbamylase deficiency | Newborn Screening. Last Updated December 2022. Accessed March 29, 2023. https://newbornscreening.hrsa.gov/conditions/ornithine-transcarbamylase-deficiency
2. National Center for Advancing Translational Sciences. Ornithine transcarbamylase deficiency - About the Disease - Genetic and Rare Diseases Information Center. Accessed March 29, 2023. https://rarediseases.info.nih.gov/diseases/8391/ornithine-transcarbamylase-deficiency

Washington State Board of Health

Update – Newborn Screening, Ornithine Transcarbamylase Deficiency (OTCD) Rulemaking

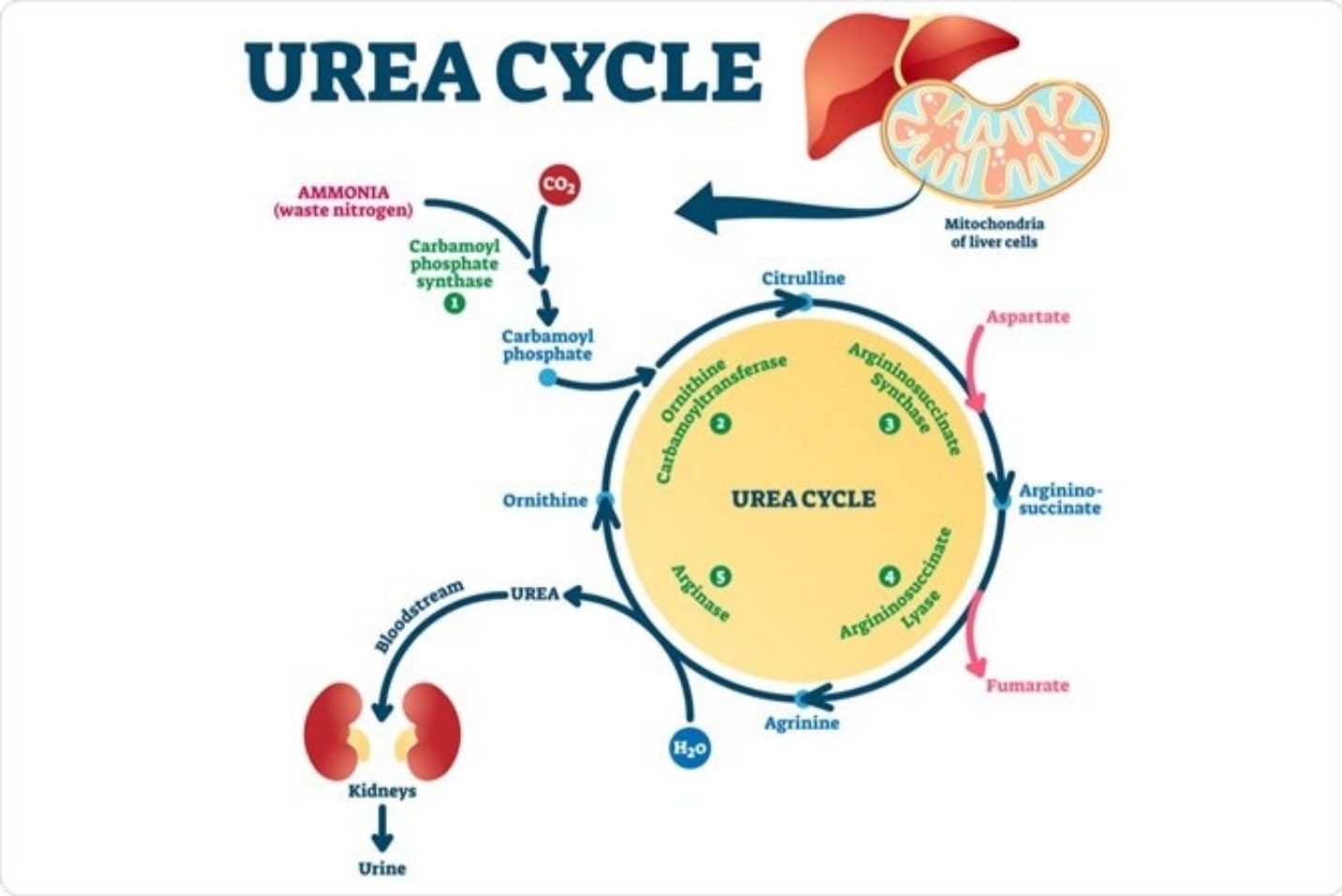
April 12, 2023

Molly Dinardo, MPH (she/her)

Policy Advisor, State Board of Health (SBOH)

What is OTCD?

- An inherited urea cycle disorder
- Prevents the body's ability to get rid of ammonia
- High levels of ammonia are toxic to the brain and nervous system and can lead to:
  - Tiredness/Sluggishness
  - Sepsis-like symptoms
  - Comas
  - Developmental delays
  - Death



Source: News Medical, The Urea Cycle Step-by-Step

OTCD as a Condition for Chapter 246-650 WAC

2020

- OTCD brought to the Board for consideration

2021

- Technical advisory committee (TAC) convened and voted to include OTCD as a condition for screening
- Board reviewed TAC recommendations and voted to proceed with rulemaking

2022

- CR-101 filed to initiate rulemaking
- Department submitted budget request to increase the newborn screening fee

2023 – Status of Funding Request and Next Steps

- Funding not included in the FY 2023-2025 Governor's, Senate, or House proposed budgets
- Legislative session is scheduled to end on April 23 – we will update the Board at that point
- Rulemaking to be put on hold until additional funding is available

Questions?

Thank You!

WASHINGTON STATE BOARD OF HEALTH

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TTY users can dial 711

Ornithine Transcarbamylase Deficiency (OTCD) Overview

Washington State Department of Health Newborn Screening Technical Advisory Committee
June 16, 2021

ABOUT THE CONDITION

The urea cycle is the body's way to get rid of ammonia, a toxic byproduct of our normal body processes. Ornithine transcarbamylase deficiency (OTCD) is an inherited urea cycle disorder in which the body cannot remove the ammonia waste. It is the most common of all urea cycle disorders.

Ammonia is formed when the body breaks down proteins from food. Ornithine transcarbamylase is one of the enzymes needed in this process. Normally, ammonia is excreted through the urine. When a baby cannot make any or enough of that enzyme, it can lead to a toxic build-up of ammonia in the body called hyperammonemia.

Levels of severity and onset of the disorder vary. Being an X-linked recessive condition, males are more affected than females (prevalence is about 1:56,000 boys). Affected males often develop severe early-onset symptoms and can die in the first week of life. Females are less likely to be affected and can be considered carriers of the disorder, although carriers can present mild symptoms of OTCD.

SYMPTOMS

Excess ammonia is toxic to the brain and nervous system. It can result in neurodevelopmental delay, intellectual disability, and death. The severity of OTCD is dependent on enzymatic compromise and the degree of hyperammonemia.

Early-onset symptoms can include lethargy, failure to thrive during the first week of life, and hyperammonemic coma with sepsis-like symptoms. Developmental delay and hyperammonemia crises can be experienced by survivors.

Males and females with late-onset OTCD can have high elevations of ammonia later in life. Symptoms can include confusion, lethargy, migraine, abdominal pain, vomiting, failure to thrive, psychiatric symptoms, and autism-like symptoms. Some patients can experience hyperammonemic crisis and death.

DIAGNOSIS

OTCD can be diagnosed through the testing of blood for amino acids and urine for organic acids. Genetic testing can be used to confirm diagnosis. There is good genotype/phenotype correlation, meaning the severity of outcomes relates to the specific genetic variant in the baby. The absence of hyperammonemia rules out urea cycle disorders.

TREATMENT

The goal of treatment is to prevent excess ammonia in order to avoid hyperammonemic episodes. Treatment can include a low protein diet, amino acid support, vitamin and mineral supplementation and medication, such as nitrogen scavengers, to improve the excretion of nitrogen waste. Dialysis is effective in decreasing ammonia levels if there is resistance to first line medication. Liver transplants can cure OTCD and normalize ammonia levels, though there are risks with surgery, post-operative complications and the patient requires life-long use of immunosuppressants.

PREPROPOSAL STATEMENT OF INQUIRY

CR-101 (October 2017)
(Implements RCW 34.05.310)
Do **NOT** use for expedited rule making

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OFFICE OF THE CODE REVISER
STATE OF WASHINGTON
FILED

DATE: February 04, 2022
TIME: 7:10 AM

WSR 22-05-012

Agency: State Board of Health

Subject of possible rule making: Chapter 246-650 WAC, Newborn Screening. The Washington State Board of Health (Board) is considering adding ornithine transcarbamylase defiency (OTCD) to the list of mandatory conditions for newborn screening conducted by the Department of Health (Department).

Statutes authorizing the agency to adopt rules on this subject: RCW 70.83.050 and RCW 70.83.020

Reasons why rules on this subject may be needed and what they might accomplish: OTCD is a severe condition with rapid onset that can result in significant morbidity and mortality if not detected and treated early. OTCD is a urea cycle disorder which causes ammonia to accumulate in the blood, affecting the liver and other body systems. Newborn screening, resulting in possible early diagnosis is essential to improve quality of life for infants and their families, and reduce infant mortality.

Identify other federal and state agencies that regulate this subject and the process coordinating the rule with these agencies: None

Process for developing new rule (check all that apply):

- ☐ Negotiated rule making
- ☐ Pilot rule making
- ☐ Agency study
- ☒ Other (describe) Collaborative; the Board convened with the Department, a technical advisory committee of multi-disciplinary members to assess OTCD against a set of criteria for inclusion on the newborn screening panel. The Board discussed the committee's recommendations and voted to proceed with rulemaking to consider rules that would allow for screening for OTCD in the newborn screening program.

Interested parties can participate in the decision to adopt the new rule and formulation of the proposed rule before publication by contacting:

	(If necessary)
Name: Samantha Pskowski	Name:
Address: PO Box 47990, Olympia, WA 98504-7990	Address:
Phone: (360) 789-2358	Phone:
Fax: N/A	Fax:
TTY: 711	TTY:
Email: samantha.pskowski@sboh.wa.gov	Email:
Web site: https://sboh.wa.gov/Rulemaking/CurrentRulesandActivity/NewbornScreeningOTCD	Web site:
Other:	Other:

Additional comments: To be added to the listserv for notifications regarding this rulemaking, email Samantha.pskowski@SBOH.wa.gov with the subject line "Newborn Screening - OTCD." For more information, please view the website at https://sboh.wa.gov/Rulemaking/CurrentRulesandActivity/NewbornScreeningOTCD

Date: 002/03/2022	**Signature:** 
Name: Michelle A. Davis	
Title: Executive Director	

WASHINGTON STATE BOARD OF HEALTH

Date: April 12, 2023

To: Washington State Board of Health Members

From: Umair A. Shah, MD, MPH, Secretary of Health

Subject: Emergency Rulemaking for On-Site Sewage Systems, WAC 246-272A-0110—Proprietary Treatment Products and Supply Chain Shortages

Background and Summary:

By memo dated June 1, 2022, the Washington Department of Health (Department) requested an emergency rule to address supply chain shortages associated with on-site sewage system proprietary treatment products regulated under WAC 246-272A-0110. At its meeting on June 8, 2022, the State Board of Health (Board) adopted an emergency rule to address the issue and staff filed the rule on June 15, 2022, as WSR 22-13-101.

Subsequently, at the Board meeting on October 12, 2022, the Department updated the Board and requested that a second emergency rule be filed. The Board adopted a second emergency rule, which was filed on October 13, 2022, as WSR 22-21-070. On January 9, 2023, the Department again updated the Board and requested that a third emergency rule be filed when the second emergency rule expires. The Board adopted a third emergency rule and filed it on February 10, 2023, as WSR 23-05-055.

Today, the Department is asking the Board to adopt a fourth emergency rule to allow retrofits and maintenance of proprietary treatment products with comparable components during continued supply chain shortages or similar manufacturing disruptions to avoid public health risks associated with poor system performance. The following information further explains the Department's emergency rule request, concurrent rulemaking on the full chapter, and implementation status of the emergency rule.

Under RCW 43.20.050, the Board has rulemaking authority for on-site sewage systems with design flows less than three thousand five hundred gallons per day. The Board's rules, chapter 246-272A WAC, set comprehensive standards for the siting, design, installation, use, care, and management of these small on-site sewage systems. The Department and local health jurisdictions jointly administer the rules.

Under RCW 34.05.350, the Board may adopt emergency rules when it finds that emergency adoption of a rule is necessary for the preservation of public health, safety, or general welfare, and that observing the time requirements of notice and opportunity to comment upon adoption of a permanent rule would be contrary to the public interest. Emergency rules are effective for 120 days. Identical or substantially similar emergency

(continued on the next page)

rules may be adopted in sequence if conditions have changed or the agency is actively undertaking the appropriate procedures to adopt the rule as a permanent rule.

In 2018, the Board filed a CR-101, Preproposal Statement of Inquiry, WSR 18-06-082, to initiate permanent rulemaking and update the on-site sewage system rules. That rulemaking is still underway and is expected to conclude in 2023. Amending WAC 246-272A-0110 to address supply chain shortages associated with on-site sewage system proprietary treatment products fits within the existing CR-101 and staff are working to include it in the permanent rulemaking as previously directed.

The on-site sewage system rules require installation of on-site sewage systems that are approved by the Department for use in Washington and that are designed to provide adequate treatment of sewage on the properties they serve. This includes the use of proprietary or trademarked technologies that are properly tested, approved, and registered for use in the state based on the Board's rules.

Homeowners, service providers, and regulators are continuing to experience supply chain shortages and other manufacturing disruptions that are affecting the maintenance and repair of proprietary systems currently in use as well as the installation of new systems. This is due mainly to the shortage of a specific product used in many proprietary systems—a disinfecting ultraviolet light manufactured by Salcor Inc.—as well as other parts and components that continue to be in short supply and are integral to the performance of these on-site sewage systems.

The shortage of replacement parts and components threatens system maintenance and public health and safety due to poor system performance. Failure to maintain on-site sewage systems easily and properly can also impede system inspections associated with property-transfer transactions.

There are thousands of on-site sewage systems in Washington that use the Salcor disinfecting ultraviolet light, and many types of proprietary products serve properties with challenging site conditions such as small lots, poor soils, and proximity to surface waters that compound the public health risks associated with the existing manufacturing disruptions.

Jeremy Simmons, Manager of the Department's On-Site Wastewater Management Program, will explain the Department's request for this fourth emergency rule to continue to allow manufacturers of registered proprietary treatment products to replace system components that are unavailable due to manufacturing disruptions with comparable components that will not negatively impact performance, treatment, operation, or maintenance of the original registered product. He will also update the Board on activity to date reviewing and approving these component-replacement requests from manufacturers. Given the possibility of continuing or future shortages, staff will continue to research this issue and address it in the permanent on-site sewage system rulemaking.

Recommended Board Actions:

The Board may wish to consider and amend, if necessary, the following motion:

The Board directs staff to file a fourth CR-103E, Emergency Rulemaking Order, upon expiration of the third emergency rule, filed as WSR 23-05-055, to amend WAC 246-272A-0110 to help ensure on-site sewage system proprietary treatment products continue to function properly without negatively impacting treatment, operation, or maintenance during supply chain shortages or other manufacturing disruptions.

Staff

Stuart Glasoe

To request this document in an alternate format or a different language, please contact the Washington State Board of Health at 360-236-4110 or by email at wsboh@sboh.wa.gov. TTY users can dial 711.

PO Box 47990 • Olympia, WA 98504-7990
360-236-4110 • wsboh@sboh.wa.gov • sboh.wa.gov

STATE OF WASHINGTON
DEPARTMENT OF HEALTH
OFFICE of ENVIRONMENTAL HEALTH and SAFETY
PO Box 47824, Olympia, WA 98504
(360) 236-3330 ● 711 Washington Relay Service

June 1, 2022

TO: Michelle Davis, Executive Director
State Board of Health

FROM: Todd Phillips, Director
Office of Environmental Health and Safety

SUBJECT: Emergency rule request, WAC 246-272A-0110, Proprietary treatment products - Certification and registration.

The Department of Health (department) requests the State Board of Health adopt an emergency rule to allow on-site sewage systems proprietary treatment products to be operated and maintained with the best components available during an ongoing supply chain shortage.

WAC 246-272A-0110, requires manufacturers of proprietary treatment products used in on-site sewage systems to test their products with the National Science Foundation (NSF) and register their products with the department based on the NSF test results before the product is allowed to be permitted or installed in Washington. This allows the department to ensure that products used in on-site sewage systems can provide the appropriate level of treatment needed to protect public health and the environment such as such as drinking water sources and shellfish sites. Proprietary treatment products are required to be installed and operated as they were tested and registered to ensure they continue to perform as needed. Supply chain disruptions have occasionally made this requirement difficult for manufacturers and owners to comply with, particularly in recent years.

Some manufacturers have incorporated disinfecting ultraviolet (UV) light systems into their products to achieve higher treatment performance required for sensitive sites. These disinfecting UV light systems require routine maintenance that requires replacement supplies. Salcor Inc., the manufacturer of a disinfecting UV light system incorporated into several proprietary treatment products sold and currently in use in Washington, has recently ceased operation. This has created a sudden shortage of Salcor supplies that are needed for operation and maintenance for on-site sewage systems currently in operation. Exact numbers are unavailable, but we know there are several thousand on-site sewage systems using Salcor products in Washington.

Without these supplies, the on-site sewage systems that use Salcor products do not operate as registered and may not completely treat sewage. This may impact sensitive sites near to these on-site sewage systems. It is also currently preventing home sales when maintenance of these devices is noted on home inspections for property transfers because replacement parts are unavailable. New construction is likewise impacted as many active or pending permits include on-site sewage systems using Salcor products. There are other manufacturers of disinfecting UV light systems that can be substituted into the proprietary treatment products that use Salcor products.

The request for an emergency rule is intended to allow manufacturers to make a written request to substitute components of a registered product's construction in cases of a demonstrated supply chain shortage or similar manufacturing disruptions that may impact installations, operation, or maintenance. The request must include information that demonstrates the substituted component will not negatively impact performance or diminish the effect of the treatment, operation, and maintenance of the original registered product. This is a short-term solution that will provide appropriate public health and environmental protections while limiting negative impacts to home sales and construction. A long-term solution will be investigated and developed for incorporation into the permanent rulemaking while this emergency rule is in effect.

Respectfully,

Todd Phillips, R.S.
Director, Office of Environmental Health & Safety

AMENDATORY SECTION (Amending WSR 05-15-119, filed 7/18/05, effective 9/15/05)

WAC 246-272A-0110 Proprietary treatment products—Certification and registration. (1) Manufacturers shall register their proprietary treatment products with the department before the local health officer may permit their use.

(2) To qualify for product registration, manufacturers desiring to sell or distribute proprietary treatment products in Washington state shall:

(a) Verify product performance through testing using the testing protocol established in Table I and register their product with the department using the process described in WAC 246-272-0120;

(b) Report test results of influent and effluent sampling obtained throughout the testing period (including normal and stress loading phases) for evaluation of constituent reduction according to Table II;

(c) Demonstrate product performance according to Table III. All ((~~thirty-day~~)) 30-day averages and geometric means obtained throughout the test period must meet the identified threshold values to qualify for registration at that threshold level; and

(d) For registration at levels A, B, and C verify bacteriological reduction according to WAC 246-272A-0130.

(3) Manufacturers verifying product performance through testing according to the following standards or protocols shall have product testing conducted by a testing facility accredited by ANSI:

(a) ANSI/NSF Standard 40—Residential Wastewater Treatment Systems;

(b) NSF Standard 41: Non-Liquid Saturated Treatment Systems;

(c) NSF Protocol P157 Electrical Incinerating Toilets - Health and Sanitation; or

(d) Protocol for bacteriological reduction described in WAC 246-272A-0130.

(4) Manufacturers verifying product performance through testing according to the following standards or protocols shall have product testing conducted by a testing facility meeting the requirements established by the Testing Organization and Verification Organization, consistent with the test protocol and plan:

(a) EPA/NSF—Protocol for the Verification of Wastewater Treatment Technologies; or

(b) EPA Environmental Technology Verification Program protocol for the Verification of Residential Wastewater Treatment Technologies for Nutrient Reduction.

(5) Treatment levels used in these rules are not intended to be applied as field compliance standards. Their intended use is for establishing treatment product performance in a product testing setting under established protocols by qualified testing entities.

(6) Manufacturers may make written application to the department to substitute components of a registered product's construction in cases of supply chain shortage or similar manufacturing disruptions that may impact installations, operation, or maintenance. The application must include a report stamped, signed, and dated by a professional engineer that demonstrates the substituted component will not negatively impact performance or diminish the effect of the treatment, operation, and maintenance of the original registered product. The department's

approval of the substituted component is in effect until it is rescinded by the department.

TABLE I

Testing Requirements for Proprietary Treatment Products	
Treatment Component/ Sequence Category	**Required Testing Protocol**
Category 1 Designed to treat sewage with strength typical of a residential source when septic tank effluent is anticipated to be equal to or less than treatment level E.	ANSI/NSF 40— Residential Wastewater Treatment Systems (protocols dated between July 1996 and the effective date of these rules)
Category 2 Designed to treat high-strength sewage when septic tank effluent is anticipated to be greater than treatment level E. (Such as at restaurants, grocery stores, mini-marts, group homes, medical clinics, residences, etc.)	EPA/NSF Protocol for the Verification of Wastewater Treatment Technologies/ EPA Environmental Technology Verification (April 2001)
Category 3 Black water component of residential sewage (such as composting and incinerating toilets).	NSF/ANSI Standard 41: Non-Liquid Saturated Treatment Systems (September 1999) NSF Protocol P157 Electrical Incinerating Toilets - Health and Sanitation (April 2000)
Total Nitrogen Reduction in Categories 1 & 2 (Above)	Protocol for the Verification of Residential Wastewater Treatment Technologies for Nutrient Reduction/EPA Environmental Technology Verification Program (November, 2000)

TABLE II

Test Results Reporting Requirements for Proprietary Treatment Products	
Treatment Component/Sequence Category	**Testing Results Reported**
Category 1 Designed to treat sewage with strength typical of a residential source when septic tank effluent is anticipated to be equal to or less than treatment level E.	Report test results of influent and effluent sampling obtained throughout the testing period for evaluation of constituent reduction for the parameters: $CBOD_5$, and TSS:

Test Results Reporting Requirements for Proprietary Treatment Products	
	□ Average □ Standard Deviation □ Minimum □ Maximum □ Median □ Interquartile Range □ 30-day Average (for each month) For bacteriological reduction performance, report fecal coliform test results of influent and effluent sampling by geometric mean from samples drawn within ((~~thirty-day~~)) 30-day or monthly calendar periods, obtained from a minimum of three samples per week throughout the testing period. See WAC 246-272A-0130. Test report must also include the individual results of all samples drawn throughout the test period.
Category 2 Designed to treat high-strength sewage when septic tank effluent is anticipated to be greater than treatment level E. (Such as at restaurants, grocery stores, mini-marts, group homes, medical clinics, residences, etc.)	Report all individual test results and full test average values of influent and effluent sampling obtained throughout the testing period for: $CBOD_5$, TSS and O&G. Establish the treatment capacity of the product tested in pounds per day for $CBOD_5$.
Category 3 Black water component of residential sewage (such as composting and incinerating toilets).	Report test results on all required performance criteria according to the format prescribed in the NSF test protocol described in Table I.
Total Nitrogen Reduction in Categories 1 & 2 (Above)	Report test results on all required performance criteria according to the format prescribed in the test protocol described in Table I.

TABLE III

Product Performance Requirements for Proprietary Treatment Products						
Treatment Component/Sequence Category	**Product Performance Requirements**					
Category 1 Designed to treat sewage with strength typical of a residential source when septic tank effluent is anticipated to be equal to or less than treatment level E.	**Treatment System Performance Testing Levels**					
	Level	**Parameters**				
		$CBOD_5$	**TSS**	**O&G**	**FC**	**TN**
	A	10 mg/L	10 mg/L	——	200/100 ml	——
	B	15 mg/L	15 mg/L	——	1,000/100 ml	——
	C	25 mg/L	30 mg/L	——	50,000/100 ml	——
	D	25 mg/L	30 mg/L	——	——	——
	E	125 mg/L	80 mg/L	20 mg/L	——	——
	N	——	——	——	——	20 mg/L
	Values for Levels A - D are 30-day values (averages for $CBOD_5$, TSS, and geometric mean for FC.) All 30-day averages throughout the test period must meet these values in order to be registered at these levels. Values for Levels E and N are derived from full test averages.					
Category 2 Designed to treat high-strength sewage when septic tank effluent is anticipated to be greater than treatment level E.	All of the following requirements must be met:					

Product Performance Requirements for Proprietary Treatment Products	
Treatment Component/Sequence Category	**Product Performance Requirements**
(Such as at restaurants, grocery stores, mini-marts, group homes, medical clinics, residences, etc.)	(1) All full test averages must meet Level E; and (2) Establish the treatment capacity of the product tested in pounds per day for $CBOD_5$.
Category 3 Black water component of residential sewage (such as composting and incinerating toilets).	Test results must meet the performance requirements established in the NSF test protocol.
Total Nitrogen Reduction in Categories 1 & 2 (Above)	Test results must establish product performance effluent quality meeting Level N, when presented as the full test average.

March 2023

On-site Sewage Systems – Emergency Rule

WAC 246-272A-0110

Emergency Rule Summary and Product-Component Approvals

The State Board of Health (Board) adopted an emergency rule on June 8, 2022 to allow manufacturers of registered proprietary treatment products to replace components of their products that are not available due to supply chain shortages or similar manufacturing disruptions with like components that will not negatively impact performance, treatment, operation, or maintenance of the original registered product. As directed by the Board, the emergency rule amendment will be considered for incorporation into the permanent rulemaking that is currently underway.

To-date, four companies have received department approval to substitute the Salcor 3G UV lamp, a disinfecting ultraviolet lamp, as summarized in the table below.

Company	Registered Product	Component to be Substituted	Substitution Component(s)	Approved Treatment Levels
Bio-Microbics	MicroFAST series with Salcor 3G	Salcor 3G UV Unit	Norweco AT 1500 UV & Jet Illumi-jet 952 & 952 Retrofit Kit	Treatment Level A Treatment Level B
Delta	Whitewater DF with Salcor 3G	Salcor 3G UV Unit	Norweco AT 1500 UV & Jet Illumi-jet 952 & 952 Retrofit Kit	Treatment Level A Treatment Level B
Delta	ECOPOD - N with Salcor 3G	Salcor 3G UV Unit	Norweco AT 1500 UV & Jet Illumi-jet 952 & 952 Retrofit Kit	Treatment Level A Treatment Level B
Enviro-Flo	NuWater B 500 with Salcor 3G	Salcor 3G UV Unit	Jet Illumi-jet 952 & 952 Retrofit Kit	Treatment Level B
Enviro-Flo	NuWater BNR 500 / BNR 600 with Salcor 3G	Salcor 3G UV Unit	Jet Illumi-jet 952 & 952 Retrofit Kit	Treatment Level A Treatment Level B
Jet	Model J-500 with Salcor 3G	Salcor 3G UV Unit	Jet Illumi-jet 952 & 952 Retrofit Kit	Treatment Level A Treatment Level B

These approvals allow replacement of the Salcor 3G UV lamp on several individual product lines as listed on the List of Registered On-site Treatment and Distribution Products for Washington State.

Link to emergency rule:
Proprietary Treatment Products Emergency Rule | Washington State Department of Health
Emergency Rule OSS Proprietary Treatment Products - CR103 (wa.gov)

Link to permanent rule making:
On-site Sewage System Rule Revision | Washington State Department of Health

For more information, contact Jeremy Simmons, Program Manager at (360) 236-3346.

CODE REVISER USE ONLY

RULE-MAKING ORDER
EMERGENCY RULE ONLY

CR-103E (December 2017)
(Implements RCW 34.05.350 and 34.05.360)

Agency: State Board of Health

Effective date of rule:

Emergency Rules

☒ Immediately upon filing.

☐ Later (specify)

Any other findings required by other provisions of law as precondition to adoption or effectiveness of rule?

☐ Yes ☒ No If Yes, explain:

Purpose: The State Board of Health (board) adopted an emergency rule regarding substitute components of registered products as part of the certification and registration of proprietary treatment products used in on-site sewage systems. The original emergency rule was filed on June 15, 2022 (WSR 22-13-101). Emergency rules have been filed continuously thereafter with the most recent filing on February 10, 2023 (WSR 23-05-055). Only one change has been made to the amendments since the filing of the original emergency rule. This emergency rule is being adopted without change of the previous emergency rule.

This fourth emergency rules amends WAC 246-272A-0110 to allow manufacturers to make a written request to the Department of Health (department) to substitute components of a registered product's construction in cases of a demonstrated supply chain shortage or similar manufacturing disruptions that may impact installations, operation, or maintenance. The request must include information that demonstrates the substituted component will not negatively impact performance or diminish the effect of the treatment, operation, and maintenance of the original registered product. The emergency rule will also allow manufacturers of registered proprietary treatment products to replace components of their products that are not available due to supply chain shortages or similar manufacturing disruptions with like components, as long as the components will not negatively impact performance, treatment, operation, or maintenance of the original registered product.

The current rule require manufacturers of proprietary treatment products used in on-site sewage systems to test their products with the National Science Foundation (NSF) and register their products with the department based on the NSF test results before the product is allowed to be permitted or installed in Washington. Without the emergency rule, the current rule would impede home sales when maintenance of proprietary products has not been completed as noted on home inspections for property transfers because replacement parts with NSF registration are unavailable. New construction is likewise impacted as many active or pending permits include on-site sewage systems using Salcor products. Salcor manufactures a disinfecting ultraviolet (UV) light system incorporated into several proprietary treatment products used in Washington State. There are other manufacturers of disinfecting UV light systems that can be substituted into proprietary treatment products in place of Salcor products. Salcor was sold and the new owner is working with NSF to get their products approved but this process will take several months. In order to continue to protect the public's health, safety, and welfare, it is necessary to adopt a fourth emergency rule to allow the department to consider written requests from manufacturers of proprietary treatment products for substitutes to proprietary treatment product components so their systems will be able to function properly without negatively impacting treatment, operation or maintenance during supply chain shortages. To

date, three manufacturers have received department approval to substitute the Salcor 3G UV lamp with an alternate UV lamp.

In 2018, the board filed a CR-101, Preproposal Statement of Inquiry (WSR 18-06-082), to initiate permanent rulemaking and update the on-site sewage system rules. That rulemaking is still underway and is expected to conclude in 2023. As directed by the board at the June 8, 2022 meeting, the emergency rule amendment will be considered for incorporation into the permanent rulemaking that is currently underway.

Citation of rules affected by this order:
New: None
Repealed: None
Amended: WAC 246-272A-0110
Suspended: None

Statutory authority for adoption: RCW 43.20.050 (3)

Other authority:

EMERGENCY RULE

Under RCW 34.05.350 the agency for good cause finds:

☒ That immediate adoption, amendment, or repeal of a rule is necessary for the preservation of the public health, safety, or general welfare, and that observing the time requirements of notice and opportunity to comment upon adoption of a permanent rule would be contrary to the public interest.

☐ That state or federal law or federal rule or a federal deadline for state receipt of federal funds requires immediate adoption of a rule.

Reasons for this finding: : The board finds that in order to protect the public's health, safety, and welfare it is necessary to adopt the emergency rule to amend WAC 246-272A-0110 to allow the department to consider written request from manufacturers of proprietary treatment products to substitute a proprietary treatment product component so their systems may continue to function properly without negatively impacting performance or diminish the effect of the treatment, operation, or maintenance during supply chain shortages.

Note: If any category is left blank, it will be calculated as zero. No descriptive text.

Count by whole WAC sections only, from the WAC number through the history note. A section may be counted in more than one category.

The number of sections adopted in order to comply with:

Federal statute:	New	0	Amended	0	Repealed	0
Federal rules or standards:	New	0	Amended	0	Repealed	0
Recently enacted state statutes:	New	0	Amended	0	Repealed	0

The number of sections adopted at the request of a nongovernmental entity:

New 0 Amended 0 Repealed 0

The number of sections adopted on the agency's own initiative:

New 0 Amended 1 Repealed 0

The number of sections adopted in order to clarify, streamline, or reform agency procedures:

New 0 Amended 0 Repealed 0

The number of sections adopted using:

Negotiated rule making:	New	0	Amended	0	Repealed	0
Pilot rule making:	New	0	Amended	0	Repealed	0
Other alternative rule making:	New	0	Amended	1	Repealed	0

Date Adopted:	**Signature:**
Name: Michelle Davis, MPA	
Title: Executive Director Washington State Board of Health	

Board Authority

RCW 43.20.050

Powers and duties of state board of health—Rule making—Delegation of authority—Enforcement of rules.

(1) The state board of health shall provide a forum for the development of public health policy in Washington state. It is authorized to recommend to the secretary means for obtaining appropriate citizen and professional involvement in all public health policy formulation and other matters related to the powers and duties of the department. It is further empowered to hold hearings and explore ways to improve the health status of the citizenry.

In fulfilling its responsibilities under this subsection, the state board may create ad hoc committees or other such committees of limited duration as necessary.

(2) In order to protect public health, the state board of health shall:

(a) Adopt rules for group A public water systems, as defined in RCW 70A.125.010, necessary to assure safe and reliable public drinking water and to protect the public health. Such rules shall establish requirements regarding:

(i) The design and construction of public water system facilities, including proper sizing of pipes and storage for the number and type of customers;

(ii) Drinking water quality standards, monitoring requirements, and laboratory certification requirements;

(iii) Public water system management and reporting requirements;

(iv) Public water system planning and emergency response requirements;

(v) Public water system operation and maintenance requirements;

(vi) Water quality, reliability, and management of existing but inadequate public water systems; and

(vii) Quality standards for the source or supply, or both source and supply, of water for bottled water plants;

(b) Adopt rules as necessary for group B public water systems, as defined in RCW 70A.125.010. The rules shall, at a minimum, establish requirements regarding the initial design and construction of a public water system. The state board of health rules may waive some or all requirements for group B public water systems with fewer than five connections;

(c) Adopt rules and standards for prevention, control, and abatement of health hazards and nuisances related to the disposal of human and animal excreta and animal remains;

(d) Adopt rules controlling public health related to environmental conditions including but not limited to heating, lighting, ventilation, sanitary facilities, and cleanliness in public facilities including but not limited to food service establishments, schools, recreational facilities, and transient accommodations;

(e) Adopt rules for the imposition and use of isolation and quarantine;

(f) Adopt rules for the prevention and control of infectious and noninfectious diseases, including food and vector borne illness, and rules governing the receipt and

conveyance of remains of deceased persons, and such other sanitary matters as may best be controlled by universal rule; and

(g) Adopt rules for accessing existing databases for the purposes of performing health related research.

(3) The state board shall adopt rules for the design, construction, installation, operation, and maintenance of those on-site sewage systems with design flows of less than three thousand five hundred gallons per day.

(4) The state board may delegate any of its rule-adopting authority to the secretary and rescind such delegated authority.

(5) All local boards of health, health authorities and officials, officers of state institutions, police officers, sheriffs, constables, and all other officers and employees of the state, or any county, city, or township thereof, shall enforce all rules adopted by the state board of health. In the event of failure or refusal on the part of any member of such boards or any other official or person mentioned in this section to so act, he or she shall be subject to a fine of not less than fifty dollars, upon first conviction, and not less than one hundred dollars upon second conviction.

(6) The state board may advise the secretary on health policy issues pertaining to the department of health and the state.

[**2021 c 65 § 37**; **2011 c 27 § 1**; **2009 c 495 § 1**; **2007 c 343 § 11**; **1993 c 492 § 489**; **1992 c 34 § 4**. Prior: **1989 1st ex.s. c 9 § 210**; **1989 c 207 § 1**; **1985 c 213 § 1**; **1979 c 141 § 49**; **1967 ex.s. c 102 § 9**; **1965 c 8 § 43.20.050**; prior: (i) **1901 c 116 § 1**; **1891 c 98 § 2**; RRS § 6001. (ii) **1921 c 7 § 58**; RRS § 10816.]

WASHINGTON STATE BOARD OF HEALTH

Date: April 12, 2023

To: Washington State Board of Health Members

From: Socia Love-Thurman, Board Member

Subject: Petition – Chapter 246-650 WAC, Newborn Screening, Request to add Arginase 1 Deficiency (ARG1-D)

Background and Summary:

The Administrative Procedures Act (RCW 34.05.330) allows any person to petition a state agency to request the adoption, amendment, or repeal of any rule. Upon receipt of a petition, the agency has sixty days to either (1) deny the petition in writing, stating the reasons and, as appropriate, offer other means for addressing the concerns raised by the petitioner, or (2) accept the petition and initiate rulemaking.

On March 29, 2023, the Washington State Board of Health (Board) received a rulemaking petition requesting to amend chapter 246-650 WAC to add Arginase 1 deficiency (ARG1-D) as a condition for newborn screening. The petition states that "a diagnosis [of ARG1-D] at birth would allow for more immediate treatment to slow down and prevent severe brain damage from occurring with affected newborns rather than waiting until symptoms appear at a later age."

ARG1-D is a rare and inherited metabolic disease that prevents the body from correctly breaking down the amino acid arginine, an enzyme present in the blood.[1,2] Arginase is one of six enzymes responsible for breaking down arginine and is part of an essential process in the body called the urea cycle.[1,3] The urea cycle helps remove ammonia from the body, a waste product used to process protein. If the arginase enzyme isn't working properly, the body can't break down arginine and get rid of ammonia through the urea cycle. Irregularities in the urea cycle may cause levels of ammonia in the blood to increase.[1,2,4] If levels of ammonia become too high, it has toxic effects and can cause serious damage to the nervous system and other parts of the body.

Symptoms of ARG1-D include seizures, muscle stiffness, difficulty eating, vomiting, and trouble breathing.[1,2] People with ARG1-D might also experience delays in both physical and cognitive development, loss of developmental milestones, and intellectual disabilities. According to the Health Resources and Services Administration (HRSA) website, over 30 states currently screen for ARG1-D or argininemia in their newborn screening panel as either a core or secondary condition.[5] ARG1-D is listed as a secondary condition on the Federal Recommended Uniform Screening Panel (RUSP). In addition, Washington's newborn screening lab currently runs the ARG1-D blood testing for babies born in Idaho.[6,7]

(continued on the next page)

Washington State Board of Health
April 12, 2023, Meeting Memo

The Board has the authority under RCW 70.83.050 to adopt rules for screening Washington-born infants for hereditary conditions. WAC 246-650-010 defines the conditions, and WAC 246-650-020 lists the conditions on the state's required newborn screening panel.

The Board has a process it follows when considering new conditions to include in the state's newborn screening panel. To determine which conditions to include in the panel, the Board may convene an advisory committee to evaluate candidate conditions using guiding principles and an established set of criteria. Before an advisory committee is convened, there should be sufficient scientific evidence available to apply the Board's criteria for inclusion. This may require a preliminary review.

I have invited Molly Dinardo, Board Staff, and John Thompson, Director of the Department of Health's Newborn Screening Program, to provide an overview of the Board's process for adding a condition to the panel, the petition request, and a brief overview of ARG1-D.

Recommended Board Actions:

The Board may wish to consider one of the following motions:

The Board declines the petition for rulemaking to add ARG1-D as a condition for newborn screening in Chapter 246-650 WAC, but directs staff to work with the Department of Health to perform a preliminary review of the condition for inclusion in WAC 246-650-020 and then report back to the Board so the Board can determine whether to establish a technical advisory committee to evaluate ARG1-D against the Board's criteria for adding conditions to the newborn screening rule.

OR

The Board declines the petition for rulemaking to add ARG1-D as a condition for newborn screening in Chapter 246-650 WAC, but directs staff to work with the Department of Health to move forward with convening a technical advisory committee to evaluate ARG1-D using the Board's process and criteria to evaluate conditions for inclusion in WAC 246-650-020 and then make a recommendation to the Board.

OR

The Board accepts the petition for rulemaking to amend Chapter 246-650 WAC to add Arginase 1 deficiency (ARG1-D) as a condition for newborn screening. The Board directs staff to notify the requestor of its decision and to file a CR-101, Preproposal of Inquiry, under its authority in RCW 70.83.050.

Staff

Molly Dinardo

To request this document in an alternate format or a different language, please contact the Washington State Board of Health at 360-236-4110 or by email at wsboh@sboh.wa.gov. TTY users can dial 711.

PO Box 47990 • Olympia, WA 98504-7990
360-236-4110 • wsboh@sboh.wa.gov • sboh.wa.gov

1. Health Resources and Services Administration (HRSA). Arginase deficiency | Newborn Screening. Published December 2022. Accessed March 29, 2023. https://newbornscreening.hrsa.gov/conditions/arginase-deficiency
2. National Institutes of Health National Library of Medicine. Arginase deficiency: MedlinePlus Genetics. Accessed March 29, 2023. https://medlineplus.gov/genetics/condition/arginase-deficiency/
3. Arginase 1 Deficiency (ARG1D) Foundation. What is Arginase 1 Deficiency? ARG1D. Published January 2023. Accessed March 29, 2023. https://arg1d.org/
4. National Center for Advancing Translational Sciences, Genetic and Rare Diseases Information Center (GARD). Arginase deficiency. Published February 2023. Accessed March 29, 2023. https://rarediseases.info.nih.gov/diseases/5840/arginase-deficiency
5. Newborn Screening in Your State | Newborn Screening. Accessed March 29, 2023. https://newbornscreening.hrsa.gov/your-state
6. Dried Blood Spot and CCHD Newborn Screening | Idaho Department of Health and Welfare. Accessed March 31, 2023. https://healthandwelfare.idaho.gov/services-programs/children-families/dried-blood-spot-and-cchd-newborn-screening
7. Washington State Department of Health. Newborn Screening. Washington State Department of Health. Accessed March 31, 2023. https://doh.wa.gov/you-and-your-family/infants-and-children/newborn-screening

PETITION FOR ADOPTION, AMENDMENT, OR REPEAL OF A STATE ADMINISTRATIVE RULE

Print Form

In accordance with RCW 34.05.330, the Office of Financial Management (OFM) created this form for individuals or groups who wish to petition a state agency or institution of higher education to adopt, amend, or repeal an administrative rule. You may use this form to submit your request. You also may contact agencies using other formats, such as a letter or email.

The agency or institution will give full consideration to your petition and will respond to you within 60 days of receiving your petition. For more information on the rule petition process, see Chapter 82-05 of the Washington Administrative Code (WAC) at http://apps.leg.wa.gov/wac/default.aspx?cite=82-05.

CONTACT INFORMATION *(please type or print)*

Petitioner's Name: Christine Zahn

Name of Organization: Arginase 1 Deficiency https://arg1d.org

Mailing Address: 9803 49th Ave SW

City: Seattle State: WA Zip Code: 98136

Telephone: 253 332-1864 Email: christinelzahn@gmail.com info@arg1d.org

COMPLETING AND SENDING PETITION FORM

- Check all of the boxes that apply.
- Provide relevant examples.
- Include suggested language for a rule, if possible.
- Attach additional pages, if needed.
- Send your petition to the agency with authority to adopt or administer the rule. Here is a list of agencies and their rules coordinators: http://www.leg.wa.gov/CodeReviser/Documents/RClist.htm.

INFORMATION ON RULE PETITION

Agency responsible for adopting or administering the rule: WSBOH New Born Screening

☐ **1. NEW RULE - I am requesting the agency to adopt a new rule.**

☐ The subject (or purpose) of this rule is: _____

☐ The rule is needed because: _____

☐ The new rule would affect the following people or groups: _____

☒ **2. AMEND RULE - I am requesting the agency to change an existing rule.**

List rule number (WAC), if known: 246-650 WAC

☒ I am requesting the following change: We request that Argininemia/Arginase 1 Deficency be added to the list of newborn screening requirements for all infants born in the State of Washington.

☒ This change is needed because: A diagnosis at birth would allow for immediate treatment to slow down/prevent severe brain damage from occuring with affected newborns rather than waiting

☒ The effect of this rule change will be: Will improve the quaity of life and save these babies from the progressively debilitating symtoms that occur when undiagnosed or misdiagnosed.

☐ The rule is not clearly or simply stated: _____

☐ **3. REPEAL RULE - I am requesting the agency to eliminate an existing rule.**

List rule number (WAC), if known: _____

(Check one or more boxes)

☐ It does not do what it was intended to do.

☐ It is no longer needed because: _____

☐ It imposes unreasonable costs: _____

☐ The agency has no authority to make this rule: _____

☐ It is applied differently to public and private parties: _____

☐ It conflicts with another federal, state, or local law or rule. List conflicting law or rule, if known: _____

☐ It duplicates another federal, state or local law or rule. List duplicate law or rule, if known: _____

☐ Other (please explain): _____

Supplemental Materials for Arginase 1 Deficiency (ARG1-D) Petition

- Letter from Petitioner
- Newborn Screening (NBS) Dr. Angela Sun, Criteria Questions and Answers
    - Responses from Dr. Angela Sun, Biochemical Geneticist at Seattle Children's Hospital, regarding ARG1-D and the Washington State Board of Health's (WSBOH) newborn screening criteria
- ARG-1D Gene Review, Dr. Angela Sun
    - National Institutes of Health (NIH), National Library of Medicine, National Center for Biotechnology Information (NCBI) Bookshelf Gene Review. Sun A, Crombez EA, Wong D. Arginase Deficiency. 2004 Oct 21 [Updated 2020 May 28]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1159/
- ARG1-D Publications
    - Crombez, E. A., & Cederbaum, S. D. (2005). Hyperargininemia due to liver arginase deficiency. Molecular genetics and metabolism, 84(3), 243-251.
    - Diaz, G. A., Bechter, M., & Cederbaum, S. D. (2023). The role and control of arginine levels in arginase 1 deficiency. Journal of Inherited Metabolic Disease, 46(1), 3-14.
    - Huang, Y., Sharma, R., Feigenbaum, A., Lee, C., Sahai, I., Russo, R. S., ... & Salazar, D. (2021). Arginine to ornithine ratio as a diagnostic marker in patients with positive newborn screening for hyperargininemia. Molecular genetics and metabolism reports, 27, 100735.
    - Therrell, B. L., Currier, R., Lapidus, D., Grimm, M., & Cederbaum, S. D. (2017). Newborn screening for hyperargininemia due to arginase 1 deficiency. Molecular Genetics and Metabolism, 121(4), 308-313.
- Family Testimonies
    - Tanja and Willow's Story
    - Jackson's Story
    - Brandy and Landon's Story
    - Alex and Josh's Story
    - Angela and Isaiah's Story
    - Vanessa and Brie's Story
    - Lincoln's Story

March 31, 2023

Letter from Christine Zahn in support of testing for Arginase 1 Deficiency at newborn screening in Washington State.

My name is Christine Zahn. I am the Director of the Arginase 1 Deficiency Foundation. I am also the grandmother to Willow, an 11-year-old girl diagnosed at the age of 4 years, 11 months with the very rare genetic disorder of Argininemia also known as Arginase 1 Deficiency (ARG1D). It was not until Willow was 3 years of age that she started showing symptoms of spasticity, seizures, and failure to thrive. My perfectly beautiful granddaughter was no longer growing or gaining weight. She could not walk without stumbling and falling. She started having numerous seizures, often 30-50 in a day.

Had Willow, through the very simple heel prick blood test at newborn screening (NBS) shown elevated arginine we would have been alerted that there was potentially something wrong. Instead, Willow's arginine levels rose steadily through her early years of life crossing the brain barrier and injuring her brain. This lack of diagnosis at an early age has left Willow and her care-taking family with lifelong medical issues, medical bills and special needs at a very high cost both emotionally and financially. It's hard to not think about the difference an early diagnosis would have made in Willow's life.

While this may be a very rare disorder, it's a bit surprising how many families we have met that share a similar story with a late diagnosis. Many of the families we know that were diagnosed as toddlers or even later in life will have lifelong medical issues. Sadly, some of the families with late diagnosis are very medically complex needing around the clock care, ports for feeding tubes and medication and many have lost their ability to walk. I am sure there are probably even more children that are misdiagnosed or not diagnosed at all.

Included with our Petition and support from Dr. Sun and Dr. Cedarbaum are stories from many of our families. Each of these families felt it was important to share what living with an ultrarare metabolic disorder is like. As a group of people and a foundation we know the importance of newborn screening and the impact it has made on our loved ones. We ask that Washington State, and all States require testing for Arginase 1 Deficiency for all newborns.

A few facts about Arginase 1 Deficiency and newborn screening:

- Recommended Uniform Screening Panel (RUSP) already lists Arginase 1 Deficiency/Argininemia as an approved secondary NBS.
- Only 17 States including Washington State do not test for Arginase 1 Deficiency - 33 States test for Arginase 1 Deficiency.
- Interestingly Washington State runs the NBS for Idaho which includes testing for Arginase 1 Deficiency.
- Arginase 1 Deficiency rarely has an acute onset so that there is more than sufficient time to institute therapy before any symptoms appear.

The following comments regarding WSBOH criteria for testing are provided by Angela Sun, MD. (Biochemical Genetics, Genetics, Non-Malignant Transplant Program)
On staff at Seattle Children's since August 2012.

Criteria for Testing

Available Screening Technology.
The technology is tandem mass spectrometry, which measures amino acids in newborn dried blood spots. Tandem MS is already being used for NBS conditions such as PKU and MSUD (maple syrup urine disease), so this is easy. Adding arginase deficiency would not require developing, validating, and implementing a new lab test.

Diagnostic Testing and Treatment available.
Biochemical and genetic testing are widely available to confirm the diagnosis. Treatment includes a protein restricted diet, supplementation of essential amino acids with medical formulas, and in some cases, ammonia scavenging medications. In the future, it is possible that enzyme replacement therapy will be available.

Prevention Potential and Medical Rationale - The newborn identification of the condition allows early diagnosis and intervention:

Important considerations:
There is sufficient time between birth and onset of irreversible harm to allow for diagnosis and intervention.

- The symptoms of arginase deficiency appear gradually in the first few years of life. Unlike other urea cycle disorders, infants with arginase deficiency do not present in the first few days of life with catastrophic hyperammonemia, though they can have episodes of hyperammonemia later in life. Therefore, there is ample time between birth and the onset of symptoms to allow for diagnosis and initiation of treatment.

The benefits of detecting and treating early onset forms of the condition (within 1 year of life) balance the impact of detecting late onset forms of the condition.

- There is a spectrum of clinical severity in arginase deficiency. Regardless of severity, most affected individuals have onset of symptoms in the first few years of life. Unlike other conditions on the NBS such as X-linked adrenoleukodystrophy and Pompe disease where patients may not have symptoms until the 4th or 5th decade of life, arginase deficiency does not have this long, asymptomatic period. Furthermore, all patients are started on treatment immediately after diagnosis, whereas those with Pompe disease may not require treatment for decades.

Newborn screening is not appropriate for a condition that only presents in adulthood.

- See above. This is a moot point. That being said, whenever we start NBS for a disease, we end up finding the really mild patients that in the past never came to clinical presentation. We could look into the experience of other states that are already screening for arginase deficiency.

Public Health Rationale: Nature of the condition justifies population based screening rather than risk-based screening of other approaches.

- Arginase deficiency is underdiagnosed as the symptoms can be nonspecific (toe walking, seizures, developmental delay). It is often misdiagnosed as cerebral palsy. Because it is a rare disease, some patients may carry this misdiagnosis their entire life. Only those with access to specialists receive further work-up. Importantly, patient outcomes are improved when treatment is started earlier in life, but the treatment cannot be initiated if the correct diagnosis is not made. Therefore, population-based screening with a cost effective, sensitive and specific laboratory assay is a better diagnostic approach for this disorder.

Cost-benefit/Cost-effectiveness: The outcome outweighs the costs of screening. All outcomes, both positive and negative, need to be considered in the analysis. Important considerations to be included in economic analyses include:

- Cost benefit analysis is complicated. I don't think this would add much cost to the NBS since we are already doing tandem MS. Dr. Cederbaum's paper has some more info here.

Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023.

Arginase Deficiency

Synonyms: ARG1 Deficiency, Arginase-1 Deficiency, Hyperargininemia

Angela Sun, MD
Seattle Children's Hospital;
University of Washington
Seattle, Washington
Email: angela.sun@seattlechildrens.org

Eric A Crombez, MD
Ultragenyx Pharmaceutical Inc
Novato, California
Email: ecrombez@ultragenyx.com

Derek Wong, MD
University of California Los Angeles Medical Center
Los Angeles, California
Email: dawong@mednet.ucla.edu

Initial Posting: October 21, 2004; Last Update: May 28, 2020.

Estimated reading time: 25 minutes

Summary

Clinical characteristics. Arginase deficiency in untreated individuals is characterized by episodic hyperammonemia of variable degree that is infrequently severe enough to be life threatening or to cause death. Most commonly, birth and early childhood are normal. Untreated individuals have slowing of linear growth at age one to three years, followed by development of spasticity, plateauing of cognitive development, and subsequent loss of developmental milestones. If untreated, arginase deficiency usually progresses to severe spasticity, loss of ambulation, complete loss of bowel and bladder control, and severe intellectual disability. Seizures are common and are usually controlled easily. Individuals treated from birth, either as a result of newborn screening or having an affected older sib, appear to have minimal symptoms.

Diagnosis/testing. The diagnosis of arginase deficiency is established in a proband with suggestive clinical and/or biochemical findings and confirmed by identification of biallelic pathogenic variants in *ARG1* or, in limited instances, by failure to detect arginase enzyme activity (usually <1% of normal) in red blood cell extracts.

Management. *Treatment of manifestations:* Management should closely mirror that for urea cycle disorders, except that individuals with arginase deficiency are not as likely to have episodes of hyperammonemia; if present, such episodes respond to conservative management (e.g., intravenous fluid administration). Treatment should involve a team coordinated by a metabolic specialist. Routine outpatient management includes restriction of dietary protein and consideration of oral nitrogen-scavenging drugs (in those who have chronic or recurrent hyperammonemia). Treatment of an acutely ill (comatose and encephalopathic) individual requires: rapid reduction of plasma ammonia concentration; use of pharmacologic agents (sodium benzoate and/or sodium phenylbutyrate/phenylacetate) to promote excretion of excess nitrogen through alternative pathways; and introduction of calories supplied by carbohydrates and fat to reduc catabolism and the amount of excess nitrogen in the diet while avoiding overhydration and resulting cerebral edema. Standard treatment for seizures, spasticity, developmental delay / intellectual disability, and joint contractures. In thos with persistent hepatic synthetic function abnormalities, fresh-frozen plasma should be considered prior to surgical procedures. In the rare instance of progression to hepatic fibrosis and cirrhosis, liver transplantation can be considered.

Prevention of primary manifestations: Maintenance of plasma arginine concentration as near normal as possible through restriction of dietary protein and use of oral nitrogen-scavenging drugs as necessary to treat hyperammonemia. Liver transplantation eliminates hyperargininemia and presumably the risk for hyperammonemia but is rarely necessary in arginase deficiency.

Surveillance: Regular follow up at intervals determined by age and degree of metabolic stability. Assessment of metabolic control (plasma ammonia, amino acid profile, and nutritional labs) at least monthly for the first year of life and as determined by a metabolic specialist after the first year of life; guanidinoacetate and liver function tests every six to 12 months; monitoring of growth and developmental progress at each visit.

Agents/circumstances to avoid: Valproic acid (exacerbates hyperammonemia).

Evaluation of relatives at risk: Plasma quantitative amino acid analysis, molecular genetic testing (if the family-specific pathogenic variants are known), or enzymatic testing in all sibs (especially younger ones) of a proband to allow early diagnosis and treatment of those found to be affected.

Pregnancy management: In general, affected pregnant women should continue dietary protein restriction and ammonia-scavenging medications (after an appropriate benefit/risk calculation) based on their clinical course before pregnancy.

Other: Immunizations on the usual schedule; appropriate use of antipyretics as indicated (ibuprofen preferred over acetaminophen).

Genetic counseling. Arginase deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Heterozygotes (carriers) are asymptomatic. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the *ARG1* pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Scenario 1. Abnormal newborn screening (NBS) result

- NBS for arginase deficiency is primarily based on quantification of the analyte arginine on dried blood spots.
- Arginine values above the cutoff reported by the screening laboratory are considered positive and require follow-up biochemical testing (see **Preliminary laboratory findings** below).
- If these studies support the diagnosis of arginase deficiency, additional testing is required to establish the diagnosis (see Establishing the Diagnosis).

Note: (1) Some infants with arginase deficiency may have follow-up arginine levels in the normal range, and thus infants who continue to have elevated arginine-to-ornithine ratios and arginine toward the upper limit of normal should undergo additional diagnostic testing (see Establishing the Diagnosis) [Author, personal observation]. (2) Arginase deficiency is currently a secondary condition on the Recommended Uniform Screening Panel. Thus, not all states will screen for and detect newborns with arginase deficiency.

Scenario 2. Symptomatic individual with either atypical findings or untreated arginase deficiency resulting from any of the following:

- NBS not performed

- False negative NBS result
- Caregivers not compliant with recommended treatment following a positive NBS result

Supportive but nonspecific clinical findings and preliminary laboratory findings can include the following.

Clinical findings

- Slowing of linear growth at age one to three years
- Development of spasticity in the lower extremities
- Plateauing of cognitive development
- Loss of developmental milestones
- Seizures

Preliminary laboratory findings

- **Plasma quantitative amino acid analysis.** Elevation of plasma arginine concentration three- to fourfold the upper limit of normal is highly suggestive of the diagnosis. Plasma arginine elevation is the primary means of ascertainment.

  Note: Up to twofold the upper limit of normal may be seen in infants who do not have arginase deficiency and who are otherwise normal.
- **Plasma ammonia concentration.** Elevation of plasma ammonia concentration may be intermittent. Acute hyperammonemia (plasma ammonia concentration >150 µmol/L) is uncommon.
- **Urinary orotic acid concentration.** Although urinary orotic acid concentration is often elevated, it is not a primary screen for this disorder.

  Note: Because elevations of these metabolites individually are not entirely specific to arginase deficiency, follow-up testing is required to establish or rule out the diagnosis of arginase deficiency (see Establishing the Diagnosis).

Establishing the Diagnosis

The diagnosis of arginase deficiency **is established** in a proband with suggestive clinical and/or biochemical findings and confirmed by identification of biallelic pathogenic variants in *ARG1* (see Table 1) or, in limited instances, by failure to detect arginase enzyme activity (usually <1% of normal) in red blood cell extracts. Because of its relatively high sensitivity, *ARG1* molecular genetic testing is the preferred confirmatory test for arginase deficiency.

Note: Enzyme assay can be helpful if two pathogenic variants are not found on molecular genetic testing.

Molecular Genetic Testing Approaches

Scenario 1. Abnormal newborn screening (NBS) result. When NBS results and other laboratory findings suggest the diagnosis of arginase deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ARG1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; depending on the method used, exon or whole-gene deletions/duplications may not be detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: In individuals of French Canadian ancestry, the c.57+1G>A founder variant may be tested for first.

- **A multigene panel** that includes *ARG1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Scenario 2. Symptomatic individual with atypical findings or untreated arginase deficiency (resulting from NBS not performed or false negative NBS result):

- If arginase deficiency is suspected, single-gene testing or a multigene panel may be performed (see Scenario 1).
- When the diagnosis of arginase deficiency has not been considered, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1.

Molecular Genetic Testing Used in Arginase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ARG1	Sequence analysis [3]	>98% [4]
	Gene-targeted deletion/duplication analysis [5]	<2% [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Diez-Fernandez et al [2018]; data derived from Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Three single or multiexon deletions have been reported [Korman et al 2004, Wang et al 2012, Diez-Fernandez et al 2018].

Measurement of Red Blood Cell Arginase Enzyme Activity

Most affected individuals have no detectable arginase enzyme activity (usually <1% of normal) in red blood cell extracts.

Note: (1) Although arginase is stable, a control sample should be obtained and treated identically if the cells are to be shipped to a distant site. (2) Liver and red blood cell arginase activity correlate well; therefore, it is not necessary to perform a liver biopsy when enzyme activity can be measured from a blood sample.

Clinical Characteristics

Clinical Description

To date, more than 260 individuals with arginase deficiency have been identified [Uchino et al 1995; De Deyn et al 1997; Crombez & Cederbaum 2005; Schlune et al 2015; Huemer et al 2016; Therrell et al 2017; Diez-Fernandez et al 2018; Chandra et al 2019; Author, personal observation]. The following description of the phenotypic features associated with this condition is based primarily on individuals with severe disease. It should be noted that a phenotypic spectrum exists, and mildly affected individuals exhibit less severe features. Individuals treated from birth (as a result either of newborn screening or of having an affected older sib) appear to have minimal symptoms [Cederbaum et al 2004].

Growth and feeding. Most commonly, growth at birth and through early childhood is normal.

- At age one to three years, linear growth slows and eventually the majority of affected children demonstrate growth deficiency, which persists if arginase deficiency goes untreated.
- Microcephaly is common and is congenital in some cases.
- Feeding issues may develop, leading to inadequate nutrition. Some require a supplemental feeding tube.

Cognitive development. Initially, cognitive development in infancy and early childhood is normal.

- Starting at age one to three years, previously normal cognitive development slows or stops and the child begins to lose developmental milestones.
- If untreated, arginase deficiency usually progresses to severe intellectual disability with accompanying neurologic findings (see **Neurologic features** below).
- Full scale IQ in adults is in the 70s, and about half are able to live independently, though they experience significant memory and fine motor deficits [Waisbren et al 2016]. Mildly affected individuals and those treated early in life may be able to hold a job.
- Some children are more severely affected cognitively, whereas others have more severe spasticity and secondary joint contractures.

Neurologic features. In untreated individuals, progressive neurologic signs typically include the development of severe spasticity with loss of ambulation and complete loss of bowel and bladder control.

- **Spasticity.** Between 80% and 90% of affected individuals develop spasticity of the lower extremities [Huemer et al 2016, Chandra et al 2019].
  - Spastic diplegia typically appears between ages two and four years and is often misdiagnosed as cerebral palsy.
  - Severe spasticity can lead to joint contractures and lordosis.
- **Seizures** occur in 60%-75% of affected individuals and are usually controlled easily by anti-seizure medication [Huemer et al 2016, Chandra et al 2019]. Generalized tonic-clonic seizures are the most common seizure type.
- **Brain imaging** often reveals cortical atrophy. Other parts of the nervous system including basal ganglia, cerebellum, medulla, and spinal cord are largely spared [De Deyn et al 1997].

Hyperammonemia. Unlike the other eight primary urea cycle disorders (see Urea Cycle Disorders Overview), arginase deficiency rarely results in elevated plasma ammonia concentration in the newborn period.

- Episodic hyperammonemia of variable degree may occur during illness but is rarely severe enough to be life threatening, although death has been reported.
- Hyperammonemia presents with vomiting, lethargy, and altered mental status but in some cases is asymptomatic and only recognized if blood ammonia is obtained during an acute illness.
- Older individuals may present with postoperative encephalopathy.

Liver disease. Hepatic dysfunction, if present, is usually mild, manifesting as transaminitis, prolonged coagulation time, and in some cases hepatomegaly. Affected individuals typically do not have bleeding problems from prolonged coagulation time. Rarely, neonatal cholestatic jaundice has been reported [Braga et al 1997, Gomes Martins et al 2010], and cirrhosis can occur. Some adults have developed hepatocellular carcinoma.

Other. Some affected females experience symptomatic hyperammonemia during menstrual cycles. These individuals may require abortive therapy (see Management, Prevention of Primary Manifestations).

Prognosis. While data are not available, the vast majority of affected individuals appear to survive and live long (albeit handicapped) lives.

Genotype-Phenotype Correlations

Genotype-phenotype correlations indicate that the amount of residual enzyme activity modulates the phenotype [Diez-Fernandez et al 2018]. Severe disease is associated with:

- Homozygosity or compound heterozygosity for predicted loss-of-function variants such as c.466-2A>G, c.77delA, c.263_266delAGAA, and c.647_648ins32;
- Missense changes such as p.Ile8Lys or p.Gly106Arg when homozygous or in combination with another severe allele.

Prevalence

Arginase deficiency is one of the rarest urea cycle defects. Its incidence has been estimated at between 1:350,000 and 1:1,000,000; the true incidence in nonrelated populations is unknown.

Arginase deficiency is pan ethnic but may be more common among French Canadians due to a pathogenic founder variant [Uchino et al 1995] (see Table 9).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ARG1*.

Differential Diagnosis

Hyperammonemia. Arginase is the sixth and final enzyme of the eight known steps in the urea cycle. See Urea Cycle Disorders Overview for approaches to distinguish:

- Other causes of hyperammonemia from a urea cycle disorder; and
- The differences between the urea cycle disorders themselves.

Spasticity. Arginase deficiency may be misdiagnosed as static spastic diplegia (cerebral palsy). See Hereditary Spastic Paraplegia Overview. It should be noted that arginase deficiency is one of the few treatable causes of spastic diplegia [Prasad et al 1997].

***ARG2*.** A second arginase gene is known (*ARG2*), but no human deficiency state has been identified and it is not clear that elevated plasma arginine would be a part of such a deficiency.

CAT-2. A new metabolic disorder in the human cationic amino acid transporter-2 has been proposed. The biochemical profile includes high levels of arginine, ornithine, and lysine in both blood and urine. The one described affected individual presented with an abnormal newborn screen for arginase deficiency [Yahyaoui et al 2019].

Management

No consensus clinical management guidelines for arginase deficiency have been published. However, general guidelines for the management of urea cycle disorders are available [Häberle et al 2019].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with arginase deficiency, the following evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2.

Recommended Evaluations Following Initial Diagnosis in Individuals with Arginase Deficiency

Evaluation	Comment
Obtain plasma ammonia, amino acid profile, guanidinoacetate, & liver function tests. [1]	Consultation w/metabolic physician / biochemical geneticist
Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consultation w/metabolic dietitian • Consider eval for gastric tube placement in those unable to meet nutritional needs orally.
Developmental assessment	Consider referral to developmental pediatrician.
Neurologic eval	Consider referral to neurologist if spasticity is present or seizures are suspected.
Musculoskeletal eval	To assess for secondary joint contractures & lordosis. Consider referral to rehabilitation medicine.

1. Albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, prothrombin time (PT), and partial thromboplastin time (PTT).

Treatment of Manifestations

The management of individuals with arginase deficiency should closely mirror that described in the Urea Cycle Disorders Overview, with one caveat: individuals with arginase deficiency are less prone to episodes of

hyperammonemia and when present, hyperammonemia is more likely to respond to conservative management such as intravenous fluid administration. However, the individual who is comatose and encephalopathic is at high risk for severe brain damage and should be treated accordingly. Arginine supplementation is obviously contraindicated.

Table 3.

Routine Outpatient Management in Individuals with Arginase Deficiency

Principle	Treatment	Consideration/Other
Restriction of dietary protein [1]	• At least half of dietary protein from natural (complete) sources • Supplementation w/arginine-free essential amino acid formula	• Protein requirement varies by age. Ideally, affected person should be on the minimum protein intake needed to maintain protein biosynthetic function, growth, & normal plasma amino acid concentrations. • Dietary modification does not lead to normalization of plasma arginine concentration but does cause improvement of some clinical symptoms.
Administration of oral nitrogen-scavenging drugs	Sodium benzoate • 250 mg/kg/day Sodium phenylbutyrate • ≤250 mg/kg/day if <20 kg • 5 g/m^2/day if >20 kg	• Medications to be taken in = amts w/each meal or feeding (i.e., 3-4x/day) [2] • Not all affected individuals require nitrogen scavengers. Use only for chronic or recurrent hyperammonemia.

1. The goal should be maintenance of plasma arginine concentration as near normal as possible.
2. Häberle et al [2019], Urea Cycle Disorders Consortium

Table 4.

Acute Outpatient Management in Individuals with Arginase Deficiency

Manifestation/Concern	Treatment	Consideration/Other
Mildly ↑ catabolism [1]	• Carbohydrate supplementation orally or by feeding tube • ↓ natural protein intake [2]	Trial of outpatient treatment at home for 12-48 hrs w/assessments for clinical changes [3]
Fever	Administration of antipyretics (acetaminophen, ibuprofen) if temperatures rises >38.5°C	
Occasional vomiting	Antiemetics	

1. Fever; vomiting, diarrhea, dehydration
2.

Some centers advocate reducing natural protein intake to zero or to 50% of the normal prescribed regimen for short periods (24-48 hours) in the outpatient setting during intercurrent illness.

3. Alterations in mentation/alertness, fever, and enteral feeding tolerance with any new or evolving clinical features should be discussed with the designated center of expertise for inherited metabolic diseases.

Table 5.

Acute Inpatient Management in Individuals with Arginase Deficiency

Manifestation/Concern	Treatment	Consideration/Other
Hyperammonemia (mild to moderate)	Increase caloric intake: • IV fluids w/≥10% dextrose at 1-1.5x maintenance rate [1] • Protein-free oral formula, e.g., Mead Johnson PFD or Ross Formula ProPhree®	Complete restriction of protein should not exceed 24-48 hrs, as depletion of essential amino acids may result in endogenous protein catabolism & nitrogen release. Transition patients from parenteral to enteral feeds as soon as possible.
Hyperammonemia (severe)	Same as above, plus nitrogen scavengers: • Enteral: Sodium benzoate, sodium phenylbutyrate, or glycerol phenylbutyrate • IV: Sodium phenylacetate & sodium benzoate (Ammonul®)	
	Consider intralipids for additional calories or TPN if affected person is unable to tolerate enteral feeds for > few days.	If affected person is unable to hydrate orally, consider placement of NG tube. Avoid overhydration, which can result in cerebral edema. [2]
	Dialysis [3]	It is rare for persons w/arginase deficiency to require dialysis. The ammonia level & clinical status determine need for dialysis.

TPN = total parenteral nutrition

1. High parenteral glucose plus insulin can be used acutely to diminish catabolism.
2. The duration of cerebral edema correlates with poor neurologic outcome.
3. Treatment of choice to most rapidly decrease serum ammonia concentration. The method employed depends on the affected person's circumstances.

Table 6.

Management of Other Complications in Individuals with Arginase Deficiency

Manifestation/Concern	Treatment	Consideration/Other
Seizures	Standard ASM depending on seizure type [1]	Referral to neurologist
Spasticity	Consider a trial of Botox®.	
	Orthotics, walkers, wheelchairs, & other durable medical equipment	Referral to rehabilitation medicine
Persistent hepatic synthetic function abnormalities [2]	• In most cases, only clinical monitoring is necessary. • W/more severe coagulopathy, FFP is administered prior to surgical procedures.	Referral to hematologist for severe cases
Hepatic fibrosis & cirrhosis	Liver transplantation	This is a rare complication.
Joint contractures	• Physical therapy • Tendon release procedures	Referral to orthopedist if severe

ASM = anti-seizure medication; FFP = fresh-frozen plasma

1. Valproic acid should be avoided (see Agents/Circumstances to Avoid).
2. Particularly elevated prothrombin time

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Developmental Disability / Intellectual Disability Management Issues

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the United States, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the United States, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine if any changes are needed.

- Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
- PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
- As a child enters teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Prevention of Primary Manifestations

The treatment goal is maintenance of plasma arginine concentration as near normal as possible through restriction of dietary protein intake, supplementation with arginine-free essential amino acid formula, and use of nitrogen-scavenging drugs as needed to treat hyperammonemia. Liver transplantation eliminates hyperargininemia and presumably the risk for hyperammonemia but (in contrast to other urea cycle disorders) is rarely necessary in arginase deficiency; see also Table 3.

Prevention of Secondary Complications

Table 7.

Prevention of Secondary Manifestations in Individuals with Arginase Deficiency

Manifestation/ Situation	Prevention	Considerations/Other
Hyperammonemic episodes	Ongoing education of affected persons & caregivers re natural history, maintenance & emergency treatment, prognosis, & risks of acute encephalopathic crises	Written protocols for maintenance & emergency treatment should be provided to parents, primary care providers/pediatricians, & teachers & school staff. [1, 2]
	Treatment protocols & provision of emergency letters or cards to incl guidance for care in the event of illness	Emergency letters/cards should be provided summarizing key information & principles of emergency treatment for arginase deficiency & containing contact information for the primary treating metabolic center.
	MedicAlert® bracelets/pendants, or car seat stickers	

Manifestation/ Situation	Prevention	Considerations/Other
	Adequate supplies of specialized dietary products (protein-free formulas; medication required for maintenance & emergency treatment) should always be maintained at home.	For any planned travel or vacations, consider contacting a center of expertise near the destination prior to travel dates.

1. Essential information including written treatment protocols should be provided *before* inpatient emergency treatment may be needed.
2. Parents or local hospitals should immediately inform the designated metabolic center if: (1) temperature is >38.5°C; (2) vomiting/diarrhea or other symptoms of intercurrent illness develop; or (3) new neurologic symptoms occur.

Surveillance

Regular follow up at intervals determined by age and degree of metabolic stability is recommended (see Table 8).

Table 8.

Recommended Surveillance for Individuals with Arginase Deficiency

Manifestation/Monitoring	Evaluation	Frequency
Assessment of metabolic control	Plasma ammonia, amino acid profile, & nutritional monitoring labs	At least 1x/mo for 1st yr of life; thereafter per metabolic specialist
	Guanidinoacetate	Every 6-12 mos
Poor growth	Monitor growth	At each visit
Developmental delay	Monitor developmental milestones	At each visit in those age <18 yrs
	Neuropsychological testing using age-appropriate standardized assessment batteries	As needed
Neurologic deterioration [1]	Neurologic eval	At each visit [2]
Persistent hepatic synthetic function abnormalities	Liver function tests [3]	Every 6-12 mos
Quality of life	Standardized quality of life assessment tools for affected persons & parents/caregivers	As needed

1. Developmental stagnation and/or regression; seizures; spasticity; development of joint contractures
2. Referral to neurologist, orthopedist, and/or physical therapist as indicated
3. Albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, prothrombin time (PT), and partial thromboplastin time (PTT).

Agents/Circumstances to Avoid

Valproic acid should be avoided as it exacerbates hyperammonemia in urea cycle defects and other inborn errors of metabolism [Scaglia & Lee 2006].

Evaluation of Relatives at Risk

Because the age of onset of arginase deficiency is delayed beyond the newborn period and the manifestations can vary, the genetic status of all sibs of a proband (especially the younger ones) should be clarified so that morbidity can be reduced by early diagnosis and treatment in those who are affected. Testing methods can include any one of the following:

- Plasma quantitative amino acid analysis
- Molecular genetic testing (if the family-specific *ARG1* pathogenic variants are known)
- Analysis of enzymatic activity in red blood cells

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

The authors are not aware of any instance in which pregnancy has been reported in a woman with arginase deficiency.

Prior to and During Pregancy

To achieve metabolic control that will enable normal fetal growth and development, affected pregnant women should generally continue dietary protein restriction and ammonia-scavenging medications (after an appropriate benefit/risk calculation) based on their clinical course before pregnancy.

- Protein restriction during pregnancy is challenging given the complications that commonly arise during pregnancy (i.e., nausea, vomiting, anorexia).
- Due to increased protein and energy requirements in pregnancy and, oftentimes, difficulty with compliance, weekly to every two-week monitoring of plasma amino acids and ammonia is recommended, especially in the first and third trimester, and close monitoring immediately after delivery.
- Plasma amino acid levels can help guide quick adjustments to diet in order to achieve normal plasma amino acid profiles that prevent catabolism and hyperammonemia while allowing for normal fetal growth and development.

Fetal Outcomes

There are no well-controlled epidemiologic studies of the fetal effects of sodium benzoate, phenylacetate, or phenylbutyrate during human pregnancy, although there are several case reports.

Redonnet-Vernhet et al [2000] reported a woman with symptomatic ornithine transcarbamylase (OTC) deficiency who was treated with sodium benzoate during the first 11 weeks of gestation and was subsequently transitioned to sodium phenylbutyrate for the remainder of pregnancy. She delivered a healthy female, who at age two years continued to do well.

Lamb et al [2013] reported another woman with symptomatic OTC who was treated throughout pregnancy with sodium benzoate (4 g/4x/day), sodium phenylbutyrate (2 g/4x/day) and arginine (300 mg/4x/day) who delivered a healthy, unaffected male who was doing well at age six weeks.

Ho et al [2019] are the first to document the use of sodium phenylbutyrate throughout two sequential pregnancies in a woman with HHH syndrome:

- In the first pregnancy sodium phenylbutyrate (5.5 g/4x/day) was used as maintenance therapy. This resulted in the delivery of a healthy female who was noted to have typical growth and development at age five years.

- In the second pregnancy, emergency treatment with Ammonul® (sodium phenylacetate/sodium benzoate) to manage hyperammonemic crisis (ammonia 295 µmol/L) was used in addition to maintenance therapy of sodium phenylbuterate (5 g/4x/day).

  Although the mother responded well to emergency treatment, the baby experienced intrauterine growth restriction and remained in the NICU due to prematurity and low birth weight. At age two years, the child exhibited speech delay and autism.

  How severe metabolic decompensation, elevated plasma ornithine, and/or side effects of sodium phenylbutyrate, phenylacetate, and/or benzoate may have contributed to the speech delay and/or autism is not known.

- Ho et al [2019] prefer and recommend the use of sodium benzoate if deemed medically necessary during pregnancy, but did not advise switching maintenance medications during pregnancy

Theoretic Concerns

Sodium benzoate has been reported to lead to malformations and neurotoxicity/nephrotoxicity in zebrafish larvae [Tsay et al 2007]. As a known differentiating agent, sodium phenylbutyrate also functions as a histone deacetylase inhibitor with potential teratogenicity, given its ability to alter gene expression in fetal mice [Di Renzo et al 2007]. Theoretically, the use of benzoate/phenylacetate and in particular sodium phenylbutyrate should be avoided during pregnancy, especially during the first trimester. The use of these medications should be carefully evaluated for each individual (benefit/risk ratio) in consultation with a metabolic genetics specialist.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

A clinical trial for enzyme replacement therapy using pegylated synthetic human arginase I is currently under way (Clinical Trials Identifier NCT03921541).

A variety of genomic therapies are under investigation including mRNA therapy [Asrani et al 2018, Truong et al 2019], *ARG1* gene editing [Lee et al 2016, Sin et al 2017], and viral-mediated gene therapy [Cantero et al 2016].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Other

Immunizations can be provided on the usual schedule.

Appropriate use of antipyretics is indicated. Ibuprofen is preferred over acetaminophen.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Arginase deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ARG1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Although most severely affected individuals have not reproduced, those who are successfully treated are likely to be fertile.
- Unless an individual with arginase deficiency has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ARG1*. Note: The rarity of the condition makes it unlikely that an unrelated reproductive partner of the proband whose ancestors do not come from a confined geographic area will be a carrier.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ARG1* pathogenic variant.

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk relatives requires prior identification of the *ARG1* pathogenic variants in the family.

Biochemical genetic testing. The normal mean red blood cell arginase enzyme activity is 100 times the lower limit of detection. Thus, most obligate carriers have been easily distinguished from normal. However, in at least one instance, a mother who was an obligate carrier tested in the mid- to normal range.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are under treatment for arginase deficiency, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. If both *ARG1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Biochemical genetic testing. If molecular genetic testing is not possible, prenatal testing for pregnancies at 25% risk may be possible by measuring arginase enzyme activity in fetal red blood cells obtained by percutaneous umbilical blood sampling after 18 weeks' gestation [Hewson et al 2003, Korman et al 2004].

Neither amniocytes nor chorionic villous cells have arginase enzyme activity and thus are unsuitable for prenatal diagnosis using biochemical testing.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  Arginase deficiency
- **Medical Home Portal**
  Arginase Deficiency
- **MedlinePlus**
  Arginase deficiency
- **National Urea Cycle Disorders Foundation**
  Phone: 626-578-0833
  Email: info@nucdf.org
  www.nucdf.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state
- **European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)**
  www.e-imd.org/en/index.phtml
- **Urea Cycle Disorder International Patient Registry**
  Phone: 626-578-0833
  Fax: 626-578-0823
  Email: coordinator@ucdparegistry.org

www.ucdregistry.org

- **Urea Cycle Disorders Consortium Registry**
  Children's National Medical Center
  Phone: 202-306-6489
  Email: jseminar@childrensnational.org
  www1.rarediseasesnetwork.org/cms/ucdc

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Arginase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ARG1	6q23.2	Arginase-1	ARG1 @ LOVD	ARG1	ARG1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B.

OMIM Entries for Arginase Deficiency (View All in OMIM)

207800	ARGININEMIA
608313	ARGINASE 1; ARG1

Molecular Pathogenesis

ARG1 encodes ARG1, which forms a homotrimer that requires manganese as a cofactor for catalytic activity and stability. Deficiency of arginase leads to accumulation of arginine and related, toxic compounds such as guanidinoacetate. The block in ureagenesis can lead to hyperammonemia although this is not common as arginase is the last (most distal) enzyme in the urea cycle.

Mechanism of disease causation. Loss-of-function variants cause arginase deficiency.

Table 9.

Notable *ARG1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000045.3	c.57+1G>A		French Canadian founder variant [Uchino et al 1995]

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000045.3 NP_000036.2	c.61C>T	p.Arg21Ter	Common variant in Turkey [Diez-Fernandez et al 2018]
	c.401C>T	p.Thr134Ile	Common variant in Brazil [Diez-Fernandez et al 2018]
	c.703G>A	p.Gly235Arg	Common variant in China [Diez-Fernandez et al 2018]
	c.23T>A	p.Ile8Lys	Severe variants [Diez-Fernandez et al 2018]
	c.77delA	p.Gly27AlafsTer5	
	c.263_266delAGAA	p.Lys88ArgfsTer45	
	c.316G>C	p.Gly106Arg	
NM_000045.3	c.466-2A>G		
	c.647_648ins32		

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Angela Sun is a specialist in biochemical genetics and an Associate Professor of Pediatrics at the University of Washington and Seattle Children's Hospital.

Eric Crombez is a specialist in biochemical genetics. He was formerly co-director, with Dr Stephen Cederbaum, of the Urea Cycle Disorders Consortium site at UCLA and is now at Shire HGT in Cambridge, MA.

Derek Wong is Associate Clinical Professor of Pediatrics at UCLA. He is the Director of the Urea Cycle Disorders Consortium site at UCLA, and is the Head of Biochemical Genetics.

Author History

Stephen Cederbaum, MD; University of California Los Angeles (2004-2020)
Eric Crombez, MD (2004-present)
Angela Sun, MD (2020-present)
Derek Wong, MD (2004-present)

Revision History

- 28 May 2020 (ma) Comprehensive update posted live
- 28 August 2014 (me) Comprehensive update posted live
- 9 February 2012(me) Comprehensive update posted live
- 5 October 2010 (cd) Revision: deletion/duplication analysis available clinically

- 1 September 2009 (me) Comprehensive update posted live
- 30 June 2008 (cd) Revision: sequence analysis and prenatal testing available for *ARG1* mutations
- 13 February 2007 (me) Comprehensive update posted live
- 21 October 2004 (me) Review posted live
- 2 March 2004 (sc) Original submission

References

Literature Cited

Asrani KH, Cheng L, Cheng CJ, Subramanian RR. Arginase I mRNA therapy - a novel approach to rescue arginase 1 enzyme deficiency. RNA Biol. 2018;15:914–22. [PMC free article: PMC6161738] [PubMed: 29923457]

Braga AC, Vilarinho L, Ferreira E, Rocha H. Hyperargininemia presenting as persistent neonatal jaundice and hepatic cirrhosis. J Pediatr Gastroenterol Nutr. 1997;24:218–21. [PubMed: 9106111]

Cantero G, Liu XB, Mervis RF, Lazaro MT, Cederbaum SD, Golshani P, Lipshutz GS. Rescue of the functional alterations of motor cortical circuits in arginase deficiency by neonatal gene therapy. J Neurosci. 2016;36:6680–90. [PMC free article: PMC4916246] [PubMed: 27335400]

Cederbaum SD, Yu H, Grody WW, Kern RM, Yoo P, Iyer RK. Arginases I and II: do their functions overlap? Mol Genet Metab. 2004;81 Suppl 1:S38–44. [PubMed: 15050972]

Chandra SR, Christopher R, Ramanujam CN, Harikrishna GV. Hyperargininemia experiences over last 7 years from a tertiary care center. J Pediatr Neurosci. 2019;14:2–6. [PMC free article: PMC6601119] [PubMed: 31316636]

Crombez EA, Cederbaum SD. Hyperargininemia due to liver arginase deficiency. Mol Genet Metab. 2005;84:243–51. [PubMed: 15694174]

De Deyn PP, Marescau B, Qureshi IE, Cederbaum SD, Lambert M, Cerone R, Chamoles N, Specola N, Leonard JV, Gatti R, Kang SS, Mizutani N, Rezvani I, Snyderman SE, Terheggen HG, Yoshino M, Appel B, Martin JJ, Beaudet AL, Vilarinho L, Hirsch E, Jakobs K, van der Knaap MS, Naito H, Pickut BA, Shapira SK, Fuchshuber A, Roth B, Hylan K. Hyperargininemia: a treatable inborn error of metabolism? In: De Deyn PP, Marescau B, Qureshi IA, Mori A, eds. *Guanidino Compounds in Biology and Medicine II.* London, UK: John Libbey; 1997:53-69.

Diez-Fernandez C, Rüfenacht V, Gemperle C, Fingerhut R, Häberle J. Mutations and common variants in the human arginase 1 (ARG1) gene: impact on patients, diagnostics, and protein structure considerations. Hum Mutat. 2018;39:1029–50. [PubMed: 29726057]

Di Renzo F, Broccia ML, Giavini E, Menegola E. Relationship between embryonic histonic hyperacetylation and axial skeletal defects in mouse exposed to the three HDAC inhibitors apicidin, MS-275, and sodium butyrate. Toxicol Sci. 2007;98:582–8. [PubMed: 17517827]

Gomes Martins E, Santos Silva E, Vilarinho S, Saudubray JM, Vilarinho L. Neonatal cholestasis: an uncommon presentation of hyperargininemia. J Inherit Metab Dis. 2010;33 Suppl 3:S503–6. [PubMed: 21229317]

Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, Mandel H, Martinelli D, Pintos-Morell G, Santer R, Skouma A, Servais A, Tal G, Rubio V, Huemer M, Dionisi-Vici C. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. J Inherit Metab Dis. 2019;42:1192–1230. [PubMed: 30982989]

Hewson S, Clarke JT, Cederbaum S. Prenatal diagnosis for arginase deficiency: a case study. J Inherit Metab Dis. 2003;26:607–10. [PubMed: 14605507]

Ho B, MacKenzie J, Walia J, Geraghty M, Smith G, Nedvidek J, Guerin A. Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome in pregnancy: considerations for management and review of the literature. JIMD Rep. 2019;46:28–34. [PMC free article: PMC6498866] [PubMed: 31240152]

Huemer M, Carvalho DR, Brum JM, Ünal Ö, Coskun T, Weisfeld-Adams JD, Schrager NL, Scholl-Bürgi S, Schlune A, Donner MG, Hersberger M, Gemperle C, Riesner B, Ulmer H, Häberle J, Karall D. Clinical phenotype, biochemical profile, and treatment in 19 patients with arginase 1 deficiency. J Inherit Metab Dis. 2016;39:331–40. [PubMed: 27038030]

Korman SH, Gutman A, Stemmer E, Kay BS, Ben-Neriah Z, Zeigler M. Prenatal diagnosis for arginase deficiency by second-trimester fetal erythrocyte arginase assay and first-trimester ARG1 mutation analysis. Prenat Diagn. 2004;24:857–60. [PubMed: 15565656]

Lamb S, Yi Ling Aye C, Murphy E, Mackillop L. Multidisciplinary management of ornithine transcarbamylase (OTC) deficiency in pregnancy: essential to prevent hyperammonemic complications. BMJ Case Rep. 2013;2013:bcr2012007416. [PMC free article: PMC3604418] [PubMed: 23283608]

Lee PC, Truong B, Vega-Crespo A, Gilmore WB, Hermann K, Angarita SA, Tang JK, Chang KM, Wininger AE, Lam AK, Schoenberg BE, Cederbaum SD, Pyle AD, Byrne JA, Lipshutz GS. Restoring ureagenesis in hepatocytes by CRISPR/Cas9-mediated genomic addition to arginase-deficient induced pluripotent stem cells. Mol Ther Nucleic Acids. 2016;5:e394. [PMC free article: PMC5155330] [PubMed: 27898091]

Prasad AN, Breen JC, Ampola MG, Rosman NP. Argininemia: a treatable genetic cause of progressive spastic diplegia simulating cerebral palsy: case reports and literature review. J Child Neurol. 1997;12:301–9. [PubMed: 9378897]

Redonnet-Vernhet I, Rouanet F, Pedespan JM, Hocke C, Parrot F. A successful pregnancy in a heterozygote for OTC deficiency treated with sodium phenylbutyrate. Neurology. 2000;54:1008. [PubMed: 10691008]

Scaglia F, Lee B. Clinical, biochemical, and molecular spectrum of hyperargininemia due to arginase I deficiency. Am J Med Genet C Semin Med Genet. 2006;142C:113–20. [PMC free article: PMC4052756] [PubMed: 16602094]

Schlune A, Vom Dahl S, Häussinger D, Ensenauer R, Mayatepek E. Hyperargininemia due to arginase I deficiency: the original patients and their natural history, and a review of the literature. Amino Acids. 2015;47:1751–62. [PubMed: 26123990]

Sin YY, Price PR, Ballantyne LL, Funk CD. Proof-of-concept gene editing for the murine model of inducible arginase-1 deficiency. Sci Rep. 2017;7:2585. [PMC free article: PMC5451454] [PubMed: 28566761]

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. [PMC free article: PMC7497289] [PubMed: 32596782]

Therrell BL, Currier R, Lapidus D, Grimm M, Cederbaum SD. Newborn screening for hyperargininemia due to arginase 1 deficiency. Mol Genet Metab. 2017;121:308–13. [PubMed: 28659245]

Truong B, Allegri G, Liu XB, Burke KE, Zhu X, Cederbaum SD, Häberle J, Martini PGV, Lipshutz GS. Lipid nanoparticle-targeted mRNA therapy as a treatment for the inherited metabolic liver disorder arginase deficiency. Proc Natl Acad Sci U S A. 2019;116:21150–59. [PMC free article: PMC6800360] [PubMed: 31501335]

Tsay HJ, Wang YH, Chen WL, Huang MY, Chen Y. treatment with sodium benzoate leads to malformation of zebrafish larvae. Neurotoxicol Teratol. 2007;29:562–9. [PubMed: 17644306]

Uchino T, Snyderman SE, Lambert M, Qureshi IA, Shapira SK, Sansaricq C, Smit LME, Jakobs C, Matsuda I. Molecular basis of phenotypic variation in patients with argininemia. Hum Genet. 1995;96:255–60. [PubMed: 7649538]

Waisbren SE, Gropman AL, Batshaw ML, et al. Improving long term outcomes in urea cycle disorders-report from the Urea Cycle Disorders Consortium. J Inherit Metab Dis. 2016;39:573–84. [PMC free article: PMC4921309] [PubMed: 27215558]

Wang J, Zhan H, Li FY, Pursley AN, Schmitt ES, Wong LJ. Targeted array CGH as a valuable molecular diagnostic approach: experience in the diagnosis of mitochondrial and metabolic disorders. Mol Genet Metab. 2012;106:221–30. [PubMed: 22494545]

Yahyaoui R, Blasco-Alonso J, Benito C, Rodríguez-García E, Andrade F, Aldámiz-Echevarría L, Muñoz-Hernández MC, Vega AI, Pérez-Cerdá C, García-Martín ML, Pérez B. A new metabolic disorder in human cationic amino acid transporter-2 that mimics arginase 1 deficiency in newborn screening. J Inherit Metab Dis. 2019;42:407–13. [PubMed: 30671984]

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Minireview

Hyperargininemia due to liver arginase deficiency

Eric A. Crombez[a], Stephen D. Cederbaum[a,b,c,d,*]

[a] Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[b] Department of Psychiatry, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[c] Department of Human Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[d] Mental Retardation Research Center, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

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Abstract

The urea cycle is a series of six reactions necessary to rid the body of the nitrogen generated by the metabolism, primarily of amino acids, from the diet or released as the result of endogenous protein catabolism. Arginase is the sixth and final enzyme of this cycle. Arginase catalyzes the conversion of arginine to urea and ornithine, the latter recycled to continue the cycle. Hyperargininemia due to arginase deficiency is inherited in an autosomal recessive manner and gene for arginase, designated AI, has been cloned. Unlike the other urea cycle enzymes, a second gene encoding arginase, with similar structural properties and enzyme characteristics, exists and has been named Arginase II (AII). Comprehensive histories and physical examinations confirm a strikingly uniform clinical picture and one notably different from patients with other urea cycle disorders. This condition rarely presents in the neonatal period and first symptoms typically present in children between 2 and 4 years of age. First symptoms are often neurologically based. If untreated, symptoms are progressive with a gradual loss of developmental milestones. With adherence to a dietary and drug regimen, a favorable outcome can be expected, with cessation of further neurological deterioration and in some instances, of improvement. This article summarizes the clinical course of selected patients who represent the full spectrum of presentations of arginase deficiency. In addition to the clinical characterization of this disorder; the biochemical, enzymatic, and molecular evidence of disease is summarized. Treatment and prenatal diagnosis are also discussed.

Keywords: Arginine; Arginase; Urea cycle; Treatment

Introduction

The urea cycle is a series of six reactions that have been recruited to rid the body of waste nitrogen (Fig. 1). Arginase is the sixth and final enzyme of this cycle and the most recently evolved; the others having been present for arginine biosynthesis in lower organisms [1]. Arginase catalyzes the conversion of arginine to urea and ornithine, the latter recycled to continue the cycle. The first three enzymes, *N*-acetyl-glutamate synthase (NAGS), carbamoyl phosphate synthase I (CPSI), and ornithine transcarbamylase (OTC) function inside of the mitochondria whereas the latter three, argininosuccinic acid synthase, argininosuccinic acid lyase, and arginase, act in the cytosol [1]. At least two transporters, for ornithine and citrulline (ORNTI) [2] and aspartate (citrin) [3] are also critical to the process. The waste nitrogen for this cycle is generated by the metabolism, primarily of amino acids, either ingested in the diet or released as the result of endogenous protein catabolism [1]. The liver is the only organ in the body to contain all of the enzymes needed for the function of the urea cycle.

Defects of all six steps of the urea cycle are known [1]. All may result in defective function of the cycle and in

* Corresponding author. Fax: +1 310 206 5431.
E-mail address: scederbaum@mednet.ucla.edu (S.D. Cederbaum).

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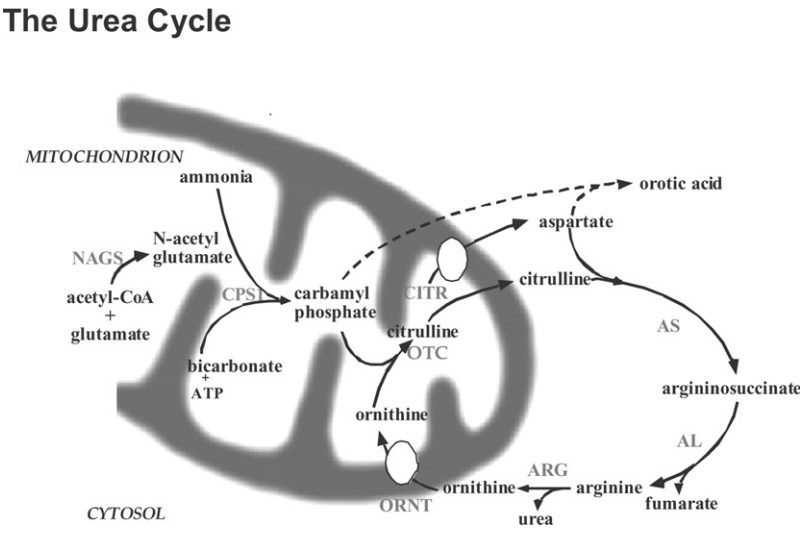

Fig. 1. The urea cycle. The six primary enzymatic steps of the urea cycle are shown in bold capital letters. NAGS, *N*-acetylglutamate synthase; CPSI, carbamylphosphate synthase; OTC, ornithine transcarbamylase; AS, argininosuccinic acid synthase; AL, argininosuccinic acid lyase; and ARG, arginase. ORNT and CITR are respectively, the ornithine and aspartate transporters. Their function is necessary for the movement of substrates in and out of the mitochondrion. Reprinted with permission from Tuchman and Bradshaw [47].

the accumulation of excess ammonia in the body, either continuously or intermittently, with resulting neurological damage, developmental delay, and mental retardation. Defects in any of the first five steps of the cycle have been reported to cause acute neonatal or acute intermittent hyperammonemia.

Hyperammonemia has infrequently been associated with arginase deficiency and presentation in the neonatal period is an uncommon event [4]. Ornithine transcarbamylase deficiency has the highest incidence of the six disorders and arginase and NAGS deficiencies have the lowest incidence. This is ascertained from the number and timing of the case reports, from a fairly comprehensive survey of urea cycle disorders in Japan [5] and from the screening of at least 7000 developmentally handicapped individuals in an institution for the mentally retarded in which no cases of arginase deficiency were ascertained [6]. The true incidence of arginase and NAGS deficiencies is unknown.

The first case of arginase deficiency was probably reported in 1965 by Peralta Serrano [7], but no comprehensive evaluation or enzymatic assay was done. The first family known to have this disorder was reported by Terheggen and associates in 1969 [10–13]. Subsequently, more than 30 cases have been reported in the literature and a larger number are known to our metabolic team and to DeDeyn et al. [8] who published a review in the proceedings of a conference on guanidino compounds, held in Montreal in 1994. The summary material in this article derives from our own extensive experience and the collective experience reflected in that article, encompassing professor DeDeyn's remarkable feat of having visited the majority of known patients in the world prior to that time. The disorder is inherited in an autosomal recessive manner with frequent instances of consanguinity. A pocket of increased frequency may occur amongst the French Canadian due to a well known bottleneck in the founder population of the lake region of northern Quebec province [9].

The gene for liver arginase, designated AI, was cloned in 1986 by Mori and co-workers [10] and ourselves [11,12] and we have subsequently defined a number of natural mutations in the gene [12–14]. Ash and co-workers [15] have crystallized rat liver arginase and have super-imposed the homologous human enzyme on the coordinates derived from the rat. In addition, the perturbation in protein structure and function caused by these mutations has been described [16]. Unlike the other urea cycle enzymes, a second gene encoding arginase, with similar structural properties and enzyme characteristics, exists and has been named Arginase II (AII) [17–20]. Arginase II is most abundantly expressed in kidney and prostate and is located in the mitochondrial matrix. It appears to be induced in AI deficiency and may mitigate the degree of hyperargininemia and hyperammonemia in this disease [21]. The function of AII is not well-defined or proven and is subject of intense study.

Clinical presentations and course

The patients whom we have seen represent the full spectrum of presentations. Thus we have chosen to report them as individuals.

Patient 1, now 13 years, was diagnosed at 4 years of age after presenting with growth failure starting at 2 years, gait abnormalities since 3 years, bilateral lower extremity spasticity, and a seizure disorder. Physical examination on presentation showed growth failure, decreased range of motion, increased tone, and extreme

hyperreflexia of the lower extremities. The deep tendon reflexes in the upper extremities were also increased, but to a lesser extent. There was no history or evidence of developmental delay. The newborn period and infancy was complicated by feeding intolerance, first with breast milk and then with many different formulas, possibly indicating protein intolerance. The patient has been below the 3‰ for height since 2 years of age, weight was initially at the 3‰ and has increased to the 10‰ since starting treatment. The patient was diagnosed with a seizure disorder at 4 years of age with generalized atypical spike and wave over the left frontal temporal region found on EEG. He had one episode of metabolic crisis requiring hospitalization associated with gastroenteritis at 6 years of age at which time he had encephalopathy with increased spasticity and transient hemiparesis and new cranial nerve deficits. Plasma ammonia peaked at 120 μg/dL and all new symptoms resolved within 36 h. Currently, his plasma arginine level, on a protein-limited diet with a limited amount of sodium benzoate, approximately 1/4 the recommended dose, is about three times the upper limit of normal. His muscle tone in the upper extremities is normal, as are his deep tendon reflexes. In the lower extremities he is hypertonic and spastic, the reflexes are excessive, and he has 1–2 beats of clonus at the ankles. The ankles cannot be brought to 90° with the floor and he is a little clumsy. He has never had hepatomegaly. This child has always been intellectually advanced and continues to excel in a traditional classroom. In the course of his care he was diagnosed with, "reactive spasticity" and received several botox treatments with a remarkable response. He has required no treatments for several years. His clinical condition is stabilizing or improved on therapy.

Patient 2, deceased at 22 years of age from cerebral edema with uncal herniation, presented at 2 years of age and was diagnosed at 5 years of age [22]. Irritability, frequent vomiting, and mild developmental delay marked the first 2 years of life. Physical examination on presentation showed increased tone, increased deep tendon reflexes, mild spasticity, hyperreflexia, and clonus in the lower extremities and hyperreflexia in the upper extremities. This patient had progressive deterioration with slow progressive loss of speech and general cognitive function until dietary therapy and sodium benzoate was started. Weight and height had always been much below the 3‰. This patient had moderate to severe mental retardation when treatment was started and management was difficult. This patient showed great behavioral difficulties even with ammonia and arginine levels within the normal range. The patient often refused his medication and would steal food. When diet and medications were carefully monitored the patient was able to maintain a very modest elevation of arginine. During periods of noncompliance ammonia levels were generally three times the upper limit of normal. The patient also presented with and continued with an uncontrolled generalized seizure disorder with approximate frequency of 1 seizure per month.

Patient 3, now 31 years, was diagnosed at 11 years after presenting with hyperammonemia, somnolence, and confusion [23]. Diet therapy and sodium benzoate were started at the time of diagnosis. At presentation he was below the 3‰ for both height and weight, there was some restricted motion at the ankles, increased tone in all extremities, and increased reflexes in the lower extremities. This patient was reported to reach all early developmental milestones on time until 8 years when his intellectual development began to slow. The patient was placed into and graduated from a school for children with learning disabilities. At 5 years, the patient reportedly became clumsy and would fall very easily; the patient was also noted to vomit frequently and began to self-select against high protein containing food. At 6 years this patient developed spastic diplegia and had his first surgery at 8 years for heel cord lengthening and was ambulatory without assistance until his mid-teenage years when he required the use of a walker due to the spasticity in his lower extremities. At 24 years the patient suffered a traumatic right lower extremity fracture, healed well, but never regained the same level of ambulation and is now predominantly wheelchair dependent. At 27 years the patient had surgery which involved bilateral adductor and hamstring releases and bilateral Achilles tendon releases. At present he is stable but noncompliant with both diet and sodium benzoate. The patient's care has also been complicated by depression that began around 15 years. He has never had a seizure. Physical examination is significant for short stature, hyperreflexia in both upper and lower extremities, spasticity of his lower extremities, hyperreflexic with cross adductor responses. He has flexion contractures in bilateral knees, hips, and feet. There is no hepatomegaly. He never had a second episode of hyperammonemia.

Patients 4 and 5 are siblings [24]. The first born is a female, now 42 years, diagnosed at 12 years after presenting with moderate to severe developmental delay and severe lower extremity spasticity. This patient had mild developmental delay first noticed at 4 years. Her development progressed until 6 years; she was bilingual, able to speak in sentences, and able to walk with assistance. She began to deteriorate to the point that at age 12 years she was unable to speak or stand. She also developed a seizure disorder at 8 years that is under reasonable control. At the time of presentation she was below the 3‰ for height, weight, and head circumference, she had episodic irritability, hyperreflexia, spasticity in the all extremities, and contractures of ankles and knees. At the age of 14 years she underwent bilateral adductor myotomies, obturator neurectomies, and Achilles tendon release. She was started on diet of essential amino acids excluding arginine at 16 years after

previously being treated with a protein-restricted diet. Sodium benzoate therapy was started at 18 years. After starting a modified diet she had some improvement in spasticity, toilet training, and language. At present remains in excellent control, is stable neurologically at a baseline maintained since starting a modified diet and has regained limited language skills. Exam is significant for atrophic lower extremities with severe weakness, moderate upper extremity strength, contractures of bilateral knees and ankles, and hyperreflexia in all extremities.

Her younger brother, deceased at 22 years from cerebral edema, was diagnosed at 6 years after an episode of coma with hepatomegaly. This patient had normal development until 3 years when he began to have difficulties walking. His development continued to deteriorate to the point that at 6 years he was unable to walk secondary to severe spasticity, contractures, and weakness. Exam at that time also showed height, weight, and head circumference below the 3‰, mild spasticity of the upper extremities with mild weakness, and hyperreflexia in all extremities. He also developed a seizure disorder at 7 years. He was started on a synthetic diet at 8 years after previous treatment with a low protein diet started at 6 years and was started on sodium benzoate at 11 years. His neurological status stabilized after starting a low protein diet and he showed marked improvement after starting a synthetic diet. Prior to death he was speaking in short phrases in both Spanish and English, was able to perform simple tasks and had limited ambulation. His death was due to hyperammonemia following aspiration pneumonia. He had suffered from bulbar paraparesis, a condition only partially improved by treatment.

Clinical characteristics

Both clinical case reports and the comprehensive examination by us and Dr. DeDeyn confirm a strikingly uniform clinical picture and one remarkably different from patients with other urea cycle disorders [4]. The condition rarely presents in the neonatal period and most patients are described as normal, or at the outer limits of normal, in early life. The first symptoms are often noted between 2 and 4 years of age and consist of clumsiness, tripping, falling, and diminished growth. If untreated, the symptoms are progressive, resulting into frank spasticity and a gradual loss of developmental milestones. Patient 4 was documented to be normal in development and bilingual at age 6 years and by age 12 years had progressed to the point of being alingual.

The most prominent physical findings are spastic paraparesis or paraplegia with lesser effects on the upper extremities, increased deep tendon reflexes, scissoring and cross adductor responses, toe walking, loss of intellectual milestones, poor growth, and seizures with EEG abnormalities. Many patients require heel cord lengthening and obdurator release, sometimes repeatedly. The growth which is normal for several years falls off and all patients are far below the 3‰ for height. Ataxia has been reported in patients, but if present, this is a minor finding. Brain imaging has revealed cerebral atrophy. Strikingly, the cerebellum appears unaffected and there is no impairment of hearing or vision. In general, peripheral nerve testing has been normal or nearly so.

A minority of patients have either persistent or intermittent episodes of irritability, nausea, poor appetite, and vomiting, sometimes progressing to lethargy. Many recover with symptomatic treatment with or without intervenous ammonia diverting drugs. A minority have presented with acute episodes of hyperammonemia which in general are less severe than those that occur with other urea cycle defects. Two of our own patients have died during episodes of acute hyperammonemia and we are aware of others who have suffered a similar fate.

Hepatomegaly is present during acute hyperammonemia episodes but is generally absent at other times. Liver cirrhosis was reported in at least one patient [25]. We have found persistent abnormalities in clotting studies in two patients [4,5], but neither was severe or symptomatic. The severe neurologic disease has led to a number of secondary skeletal abnormalities. One of our patients had episodes of seizures, coma or both associated with her menstrual periods. This was eliminated with hormonal suppression of ovarian cycling and ultimately by hysterectomy without oophorectomy [26].

Biochemical characteristics

The first patients were ascertained at a time when plasma amino acid determinations were more difficult and the first findings frequently were a urine amino acid pattern reminiscent of cystinuria, due to an overflow of the dibasic amino acids which shared a common kidney transport system [22,24,27–30]. Today, plasma amino acid determination in individuals with developmental delay or neurological difficulties would reveal an elevated level of arginine [24]. If the patients are chronically mildly hyperammonemic, glutamine levels may be elevated as well. Arginine levels were increased 5- to 15-fold and sometimes more [21] and proved to be relatively constant for most patients, barely responding to protein intake variation within a normal and growth sustaining range [24]. Orotic acid in the urine is frequently increased [21]. We and others have observed higher urea levels in these patients than in patients with other urea cycle defects and these levels have risen with increase protein intake (Table 1) [24]. Similarly, urinary urea excretion increases as the protein intake increases and

the plasma arginine remains unchanged [24]. This led us to propose the existence of a second form of arginase and this was subsequently proven.

Plasma ammonia levels are usually normal when arginase deficient patients are well, although glutamine levels may be increased [4]. Some patients have consistently mild elevations of ammonia and often are symptomatic as a result. The majority of patients have experienced one or more episodes of hyperammonemia and ammonia levels as high as 400 μM have been seen. Two patients for whom we cared, who subsequently died, had astoundingly high levels of ammonia (6000 μM) and plasma arginine had risen to 1500 μM or higher [21].

All patients studied had elevated levels of arginine in the cerebralspinal fluid and two we studied had a number of other amino acid elevations as well (Table 2) [24]. The basis for this is not understood, but levels improve with therapy. We and our colleagues recently reported a newborn with AI deficiency that succumbed after 3 days of age after ammonia levels, never higher than 194 μg/dL, were brought under control and normalized. In this patient, however, while the glutamine level in plasma was within normal limits (909 μmol/L; nl 332–1084) the glutamine level in CSF (9587 μmol/L; nl 385–771) was unprecedently high and is inferred to have caused the fatal neurotoxicity [31]. Such a disparity between ammonia levels and those of glutamine have been seen in other patients with urea cycle disorders and may indicate that ammonia may not be the best and only marker for the severity of the pathologic effects of urea cycle defects.

Guanidino compounds derived directly from arginine have been studied in many arginase deficient patients as a result of the painstaking efforts undertaken by Marescau et al. [4,32,33]. There was a general increase in the guanidino compounds synthesized from arginine. Creatinine was normal in all patients and creatine was elevated in some. It is not clear whether or not these perturbations contribute to the pathogenesis of this disorder. One patient has undergone testing for activity of the urea cycle by isotope dilution methods and was found to be deficient [34].

Table 1
Urea cycle and related amino acids in the plasma (mM) of pateints 4 and 5

	Protein intake[a]					Normal values[b]
	Patient 5			Patient 4		
	1.0	2.0	3.0	1.0	2.5	
Arginine	637	591	677	786	913	21–151
Citrulline	53	38	46	40	58	12–55
Ornithine	46	39	40	75	95	30–126
Lysine	127	86	80	87	194	83–237
Glutamine	392	440	451	556	607	415–694
Urea	13.5[c]	14.7	18.4	15.5	20.3	20–30

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[a] Protein intake in g/kg body weight/day. All specimens were collected 3 h after a meal containing 1/3 of the prescribed diet. (One fasting sample was not distinguishable from the postprandial one.)

[b] Dickinson et al. [7].

[c] Expressed as mg/dL.

Table 2
CSF amino acid levels (mg/dL) 2.5–3.0 g protein/kg/day (3 h pp)

Amino acid	Patient 4	Patient 5	Controls	X Normal
Arginine	1.71	1.21	0.35 ± 0.1	4
Citrulline	0.16	0.072	0.035 ± 0.14	
Ornithine	0.62	1.25	0.075 ± 0.024	10–20
Lysine	0.21	0.43	0.27 ± 0.1	
Aspartate	0.40	0.38	0.012 ± 0.007	30
Serine	1.82	1.99	0.40 ± 0.24	5
Glutamine	47.4	16.0	7.4 ± 2.1	2–6
Glycine	0.64	0.78	0.05 ± 0.01	15
Other amino acids				2–5

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Arginase activity in arginase AI deficient patients

Arginase activity is very low or absent in the red blood cells of all patients in whom it was tested. White blood cell arginase, and in one instance stratum corneum, enzyme levels were similarly diagnostic [24]. Arginase activity in the liver has been reported in a smaller number of patients. In each, it was reduced to 10% of normal or less [21,24,35–37]. This accords with independent enzymological and immunological studies suggesting substantial correlation between red blood cell and liver arginase.

Very early in the investigations of patients with arginase deficiency it became clear that there were some striking biochemical differences between arginase deficient patients and those with other urea cycle disorders. The patients infrequently had episodes of hyperammonemia, these episodes were usually self-limited when they occurred, the peak ammonia levels were rarely as high as in the other urea cycle disorders (even in what turned out to be patients with two nonsense mutations), and urea levels, always in the normal range, rose with increased protein intake [24]. The most likely explanation for this combination of findings, the existence of a second arginase activity, turned out to be correct.

Spector et al. [38] first observed augmented levels of arginase activity in kidney when liver arginase activity was greatly reduced. This has subsequently been confirmed by us in four other patients [31,37]. Levels of the second, mitochondrial arginase (AII) were elevated as much as 40-fold under conditions of extreme hyperammonemia and hyperargininemia (Table 3). In 1996, when AII was cloned, sequenced, and compared to AI, it was clear that the two arginases had a common ancestry, with the duplication in the parent gene having occurred at east 300 million years ago at the time of the evolution of amphibians [17–20].

Table 3
Arginase II activity in tissue extracts of hyperargininemic patients

Tissue	Normal	Activity (nmol/mg/30 min)		
		Patient 2	Patient 5	Patient[a]
Kidney	200 (350)	5192	8564	1430
Liver	300 (19,500)	334	532	980
Brain	50	492	N.D.	N.D.
Heart	N.D.	N.D.	N.D.	10
Spinal cord	N.D.	N.D.	N.D.	10

[a] Ref. [35].

From these data we have inferred that the higher or augmented levels of AII in baseline conditions and its further induction under conditions of higher plasma arginine and ammonia is responsible for the higher ureagenesis in AI deficiency. We infer further that the milder course of AI deficiency as compared with other urea cycle disorders is a result of this second isozyme.

Studies in the AI knockout mouse have so far not shed light on this issue [39]. The mouse which succumbs at 2 weeks with hyperammonemia may have a 2-fold induction of AII, levels which would not reach statistical significance. Moreover, the AI/AII double knockout does not increase the vulnerability further. Studies of arginase expression by in situ hybridization suggest that AI and not AII is the gene most prominently transcribed in utero [40]. AII expression in kidney only begins at birth. Thus AII may play a more prominent role in AI deficiency in the model as well when we can bring the knockout animals to weaning and beyond.

Pathology and pathogenesis of neurological disease

Liver biopsy during acute episodes has shown swollen hepatocytes without obvious abnormalities of lipid accumulation, mitochondrial derangement or biliary defects. This is consistent with the tendency of ammonia to cause hydropic and reversible changes in hepatocytes [37]. In a number of patients, chronic fibrosis and cirrhosis were seen. As noted previously, some of patients have had abnormalities of liver function consistent with the ongoing and permanent hepatic damage, whereas the elevated transaminase levels often return to normal between episodes [4]. Complete autopsies done in a number of patients have failed to reveal any consistent abnormalities or abnormalities that might be associated with the primary enzymatic defect [4,24]. Neuropathology has confirmed the cerebral atrophy found on imaging in those patients, but there were no specific abnormalities otherwise.

The pathogenesis of the neurologic disease is less clear. It is apparent that the intermittent or chronic elevation of blood ammonia underlies the episodic irritability, anorexia, and vomiting. With control of the ammonia levels these symptoms disappear. Similarly, we have observed acute psychosis during minor hyperammonemia in an older patient and this too regressed with control of ammonia levels. The extreme and progressive cerebral and motor neuron disease is clearly different from other urea cycles disorders, even those with recurrent acute or chronic hyperammonemia and clearly must relate in one or another way to the elevated arginine level. Whether it is arginine or one of its metabolites, such as guanidino compounds, is unclear [4,32,33]. Of the latter, α-keto-γ-guanidino valeric acid has been shown to cause seizures in rabbits. Similarly, arginine may be a precursor to glutamate or GABA and thus cause damage on an excitotoxic basis. Arginine is also a precursor of nitric oxide and elevated levels of arginine may cause greater synthesis of nitric oxide and oxidative damage. This may represent an important unexplored area of investigation and provide accessory approaches to the care of patients with this disorder. Marescau et al. [4] champion other guanidine compounds as the primary brain toxins.

Molecular studies

Uchino et al. [12] and Vockley et al. [13,14] have carried out mutation analysis in patients with arginase I deficiency. Nonsense mutations and small deletions were found in a large minority of the patients and were scattered randomly throughout the coding sequences. In contrast, the missense mutations were found exclusively in those residues that have been conserved in evolution and imply a critical role for these amino acids in the stability of catalytic function. Uchino et al. concluded that some correlation between mutations and disease severity existed, whereas Vockley et al. were less impressed in their series of patients. Vockley et al. [13] expressed the mutant proteins in an *Escherichia coli* expression system and demonstrated reduced activity in all cases save one. In that instance, the semi-conservative nature of the amino acid change and the evolutionary data predicted no loss of activity.

The human arginase missense mutations were superimposed on the crystal structure of rat liver arginase with which it shared 87% homology at the amino acid level. In each instance, in which a natural or a site directed mutant caused loss in activity, the crystal structure model predicted significant perturbation in the active site. No distortion in structure was seen with the neutral mutation. More recently, Kim et al. have isolated an alternatively spliced AI message which contained an eight amino acid insertion near the N-terminal region of the protein. This in frame 24 base insertion encoded a protein that was 10% as active as the wild type [41]. Again, the crystal structure predicted a lesser degree of active site perturbation than one would expect since the inserted amino acids lie on the external surface of the

protein in an area unlikely to impinge heavily on the active site or on the formation of the trimer. The effect of these changes on multimer formation is being studied.

Studies of red blood cells from AI deficient patients demonstrated that immunologically cross reacting material was absent from all but one patient who had normal arginase band after SDS–PAGE electrophoresis [23]. Thus both most missense and nonsense mutations had a destabilizing effect on the protein, presumably after it had been translated. What if any significance this may have is uncertain.

Treatment

Hyperargininemia is a favorable candidate for standard urea cycle therapy; limitation of natural protein intake, essential amino acid supplementation, and ammonia diversion to salvage pathways (Table 4) [20]. Arginase deficient patients are less prone to acute, uncontrolled hyperammonemia and may have no or only moderate levels of ammonia elevation on a diet containing natural foods. For those patients and families able to comply with the onerous regimen, treatment has been encouraging. At least one patient and possibly others, treated from birth with a protein limited diet and essential amino acids have no apparent defects in his 30's [42]. Another, younger individual, also treated from birth is doing similarly well [43]. Based on our own experience comprising more than 75 patient years, reasonable adherence to the treatment regimen is very likely to halt the disease progress, will relieve acute symptoms of ammonia and "arginine" toxicity, and will permit recovery of some lost functions over time. Unfortunately, only the minority of patients can adhere to a diet rigorous enough to get arginine levels into or near the normal range. In some of these patients, the spasticity of the legs may continue to progress, albeit at a very slow rate. The, "good news" is that successful treatment is unlikely to be undone by severe and brain-damaging episodes of intermittent hyperammonemia.

Prenatal diagnosis and newborn screening

The arginase AI gene is located at 6q23 and arginase deficiency is inherited as an autosomal recessive disorder [44]. The recurrence risk in subsequent births to the same parents is 25%. If the mutation(s) in the patient is known, prenatal diagnosis can be accomplished by mutation analysis in chorionic villous tissue or in amniotic fluid cells. Some years ago we demonstrated that AI is expressed in fetal red cells at 16–20 weeks of gestation and at levels comparable, albeit somewhat lower than postnatal levels [45]. Percutaneous umbilical blood sampling (PUBS) was recently used to predict a normal sibling to an arginase deficient patient [46], as well as an affected patient [42]. The ability to do prenatal diagnosis for a condition whose treatment from birth, although onerous, is successful raises an ethical issue. Some may find it unethical to terminate in such a circumstance, despite this being legal.

The advent of newborn screening by tandem mass spectrometry now allows for measurement of blood levels of arginine. We recently reported the diagnosis of a patient with arginase deficiency from a newborn blood spot [31]. An informal and unscientific poll of participants in a metabolic disease listserv resulted in the report of four more cases diagnosed on newborn screening and one that was missed. From this information it appears likely that many, if not most patients with this condition will be diagnosed prior to the onset of symptoms and the occurrence of permanent neurological injury. This is indeed good news for patients with this disorder, even if it means being sentenced to a life-long ascetic regimen.

Table 4
Treatment results for patient 4

Plasma parameter (mg/100 ml)	Control	Benzoate		Phenyl acetate	Both med	Normal diet both med	Normal values
		5 g/day	10 g/day	10 g/day			
Patient 4							
Arginine	6.49	4.95	2.98	1.95	1.82	5.89	0.37–2.63
Ornithine	0.42	0.48	0.40	0.41	0.39	0.33	0.39–1.67
Citrulline	0.33	0.29	0.15	0.10	0.046	0.13	0.21–0.97
Lysine	3.22	2.11	1.82	1.88	2.27	2.58	1.21–3.47
Glutamine	9.13	8.26	5.10	3.28	3.31	6.94	6.06–10.14
Urea	5.00	4.70	2.18	<1.00	3.50	6.48	20–40
Patient 5							
Arginine	7.81	6.27	3.29	1.83	1.90	4.93	0.37–2.63
Ornithine	0.46	0.39	0.43	0.38	0.35	0.43	0.39–1.67
Citrulline	0.51	0.32	0.16	0.10	0.075	0.23	0.21–0.97
Lysine	3.05	1.78	1.79	1.75	2.15	1.64	1.21–3.47
Glutamine	9.28	7.83	4.15	2.59	3.28	4.44	6.06–10.14
Urea	6.14	4.66	2.82	1.90	1.64	4.92	20–40

Summary

Hyperargininemia due to liver arginase deficiency is a treatable inborn error of the urea cycle. With adherence to the dietary and drug regimen, a favorable outcome can be expected, with cessation of further neurological deterioration and in some instances, of improvement. It appears that this favorable outcome is due, in part, to the augmented expression of a second arginase gene. The existence of this second locus provides a unique approach to treatment, if only expression could be greatly enhanced, especially in liver. Arginase deficiency is also a good candidate fore gene therapy, an approach that may be more distantly in the future.

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References

[1] S.W. Brusilow, A.L. Horwich, Urea cycle enzymes, in: C.R. Scriver, A.L. Beaudet, D. Valle, W.S. Sly, B. Vogelstein, B. Childs, K.W. Kinzler (Eds.), The Metabolic and Molecular Bases of Inherited Disease, eighth ed., McGraw-Hill, New York, 2001, pp. 1909–1963.

[2] J.A. Camacho, C. Obie, B. Biery, B.K. Goodman, C.A. Hu, S. Almashanu, G. Steel, R. Casey, M. Lambert, G.A. Mitchell, D. Valle, Hyperornithinaemia–hyperammonaemia–homocitrullinursyndrome syndrome is caused by mutations in a gene encoding a mitochondrial ornithine transporter, Nat. Genet. 22 (1999) 151–158.

[3] T. Saheki, K. Kobayashi, M. Iijima, M. Horiuchi, L. Begum, M.A. Jalil, M.X. Li, Y.B. Lu, M. Ushikai, A. Tabata, M. Moriyama, K.J. Hsiao, Y. Yang, Adult-onset type II citrullinemia and idiopathic neonatal hepatitis caused by citrin deficiency: involvement of the aspartate glutamate carrier for urea synthesis and maintenance of the urea cycle, Mol. Genet. Metab. 81 (Suppl. 1) (2004) S20–S26.

[4] B. Marescau, P.P. De Deyn, I.A. Qureski, et al., Guanidino compounds in hyperargininemia, in: P.P. De Deyn, B. Marescau, V. Stalon, I.A. Qureski (Eds.), Guanidino Compounds in Biology and Medicine, J. Libbey, London, 1992, pp. 363–371.

[5] N. Nagata, I. Matsuda, K. Oyanagi, Estimated frequency of urea cycle enzymopathies in Japan, Am. J. Med. Genet. 39 (1991) 228–229.

[6] E.W. Naylor, A.P. Orfanos, R. Guthrie, A simple screening test for arginase deficiency (hyperargininemia), J. Lab. Clin. Med. 89 (1977) 876–880.

[7] A. Peralta Serrano, Argininuria, convulsions and oligophrenia; a new inborn error of metabolism?, Rev. Clin. Esp. 97 (1965) 176–184.

[8] P.P. De Deyn, B. Marescau, I.A. Qureski, et al., Hyperargininemia: a treatable inborn error of metabolism, in: P.P. De Deyn, B. Marescau, I.A. Qureski, A. Mori (Eds.), Guanidino Compounds in Biology and Medicine, J. Libbey, London, 1997, pp. 53–69.

[9] I.A. Qureshi, J. Letarte, R. Ouellet, J. Larochelle, B. Lemieux, A new French-Canadian family affected by hyperargininemia, J. Inherit. Metab. Dis. 6 (1983) 179–182.

[10] Y. Haraguchi, M. Takiguchi, Y. Amaya, S. Kawamoto, I. Matsuda, M. Mori, Molecular cloning and nucleotide sequence of cDNA for human liver arginase, Proc. Natl. Acad. Sci. USA 84 (1987) 412–415.

[11] G.J. Dizikes, W.W. Grody, R.M. Kern, S.D. Cederbaum, Isolation of human liver arginase cDNA and demonstration of nonhomology between the two human arginase genes, Biochem. Biophys. Res. Commun. 141 (1986) 53–59.

[12] T. Uchino, S.E. Snyderman, M. Lambert, I.A. Qureshi, S.K. Shapira, C. Sansaricq, L.M. Smit, C. Jakobs, I. Matsuda, Molecular basis of phenotypic variation in patients with argininemia, Hum. Genet. 96 (1995) 255–260.

[13] J.G. Vockley, D.E. Tabor, R.M. Kern, B.K. Goodman, P.B. Wissmann, D.S. Kang, W.W. Grody, S.D. Cederbaum, Identification of mutations(D128G, H141L) in the liver arginase gene of patients with hyperargininemia, Hum. Mutat. 4 (1994) 150–154.

[14] J.G. Vockley, B.K. Goodman, D.E. Tabor, R.M. Kern, C.P. Jenkinson, W.W. Grody, S.D. Cederbaum, Loss of function mutations in conserved regions of the human arginase I gene, Biochem. Mol. Med. 59 (1996) 44–51.

[15] Z.F. Kanyo, L.R. Scolnick, D.E. Ash, D.W. Christianson, Structure of a unique binuclear manganese cluster in arginase, Nature 383 (1996) 554–557.

[16] D.E. Ash, L.R. Scolnick, Z.F. Kanyo, J.G. Vockley, S.D. Cederbaum, D.W. Christianson, Molecular basis of hyperargininemia: structure–function consequences of mutations in human liver arginase, Mol. Genet. Metab. 64 (1998) 243–249.

[17] J.G. Vockley, C.P. Jenkinson, H. Shukla, R.M. Kern, W.W. Grody, S.D. Cederbaum, Cloning and characterization of the human type II arginase gene, Genomics 38 (1996) 118–123.

[18] S.M. Morris Jr., D. Bhamidipati, D. Kepka-Lenhart, Human type II arginase: sequence analysis and tissue-specific expression, Gene 193 (1997) 157–161.

[19] T. Gotoh, T. Sonoki, A. Nagasaki, K. Terada, M. Takiguchi, M. Mori, Molecular cloning of cDNA for nonhepatic mitochondrial arginase(arginase II) and comparison of its induction with nitric oxide synthase in a murine macrophage-like cell line, FEBS Lett. 395 (1996) 119–122.

[20] R. Iyer, C.P. Jenkinson, J.G. Vockley, R.M. Kern, W.W. Grody, S. Cederbaum, The human arginases and arginase deficiency, J. Inherit. Metab. Dis. 21 (Suppl. 1) (1998) 86–100.

[21] W.W. Grody, R.M. Kern, D. Klein, A.E. Dodson, P.B. Wissman, S.H. Barsky, S.D. Cederbaum, Arginase deficiency manifesting delayed clinical sequelae and induction of a kidney arginase isozyme, Hum. Genet. 91 (1993) 1–5.

[22] S.D. Cederbaum, K.N. Shaw, M. Valente, Hyperargininemia, J. Pediatr. 90 (1977) 569–573.

[23] J. Bernar, R.A. Hanson, R. Kern, B. Phoenix, K.N. Shaw, S.D. Cederbaum, Arginase deficiency in a 12-year-old boy with mild impairment of intellectual function, J. Pediatr. 108 (1986) 432–435.

[24] S.D. Cederbaum, K.N. Shaw, E.B. Spector, M.A. Verity, P.J. Snodgrass, G.I. Sugarman, Hyperargininemia with arginase deficiency, Pediatr. Res. 13 (1979) 827–833.

[25] A.C. Braga, L. Vilarinho, E. Ferreira, H. Rocha, Hyperargininemia presenting as persistent neonatal jaundice and hepatic cirrhosis, J. Pediatr. Gastroenterol. Nutr. 24 (1997) 218–221.

[26] W.W. Grody, R.J. Chang, N.M. Panagiotis, D. Matz, S.D. Cederbaum, Menstrual cycle and gonadal steroid effects on symptom-

atic hyperammonaemia of urea-cycle-based and idiopathic aetiologies, J. Inherit. Metab. Dis. 17 (1994) 566–574.
[27] H.G. Terheggen, A. Schwenk, A. Lowenthal, M. van Sande, J.P. Colombo, Hyperargininemia with arginase deficiency. A new familial metabolic disease. II. Biochemical studies, Z Kinderheilkd 107 (1970) 313–323.
[28] H.G. Terheggen, A. Lowenthal, F. Lavinha, J.P. Colombo, Familial hyperargininemia, Arch. Dis. Child. 50 (1975) 57–62.
[29] S.E. Snyderman, C. Sansaricq, W.J. Chen, P.M. Norton, S.V. Phansalkar, Argininemia, J. Pediatr. 90 (1977) 563–568.
[30] E.W. Naylor, S.D. Cederbaum, Urinary pyrimidine excretion in arginase deficiency, J. Inherit. Metab. Dis. 4 (1981) 207–210.
[31] J.D. Picker, A.C. Puga, H.L. Levy, D. Marsden, V.E. Shih, U. Degirolami, K.L. Ligon, S.D. Cederbaum, R.M. Kern, G.F. Cox, Arginase deficiency with lethal neonatal expression: evidence for the glutamine hypothesis of cerebral edema, J. Pediatr. 142 (2003) 349–352.
[32] B. Marescau, P.P. De Deyn, A. Lowenthal, I.A. Qureshi, I. Antonozzi, C. Bachmann, S.D. Cederbaum, R. Cerone, N. Chamoles, J.P. Colombo, et al., Guanidino compound analysis as a complementary diagnostic parameter for hyperargininemia: follow-up of guanidino compound levels during therapy, Pediatr. Res. 27 (1990) 297–303.
[33] B. Marescau, P.P. De Deyn, I.A. Qureshi, M.E. De Broe, I. Antonozzi, S.D. Cederbaum, R. Cerone, N. Chamoles, R. Gatti, S.S. Kang, et al., The pathobiochemistry of uremia and hyperargininemia further demonstrates a metabolic relationship between urea and guanidinosuccinic acid, Metabolism 41 (1992) 1021–1024.
[34] B. Lee, H. Yu, F. Jahoor, W. O'Brien, A.L. Beaudet, P. Reeds, In vivo urea cycle flux distinguishes and correlates with phenotypic severity in disorders of the urea cycle, Proc. Natl. Acad. Sci. USA 97 (2000) 8021–8026.
[35] F. Scaglia, N. Brunetti-Pierri, S. Kleppe, J. Marini, S. Carter, P. Garlick, F. Jahoor, W. O'Brien, B. Lee, Clinical consequences of urea cycle enzyme deficiencies and potential links to arginine and nitric oxide metabolism, J. Nutr. 134 (Supp. 10) (2004) 2775S–2782S; discussion 2796S–2797S.
[36] V.V. Michels, A.L. Beaudet, Arginase deficiency in multiple tissues in argininemia, Clin. Genet. 13 (1978) 61–67.
[37] W.W. Grody, C. Argyle, R.M. Kern, G.J. Dizikes, E.B. Spector, A.D. Strickland, D. Klein, S.D. Cederbaum, Differential expression of the two human arginase genes in hyperargininemia. Enzymatic, pathologic, and molecular analysis, J. Clin. Invest. 83 (1989) 602–609.
[38] E.B. Spector, S.C. Rice, S.D. Cederbaum, Immunologic studies of arginase in tissues of normal human adult and arginase-deficient patients, Pediatr. Res. 17 (1983) 941–944.
[39] R.K. Iyer, P.K. Yoo, R.M. Kern, N. Rozengurt, R. Tsoa, W.E. O'Brien, H. Yu, W.W. Grody, S.D. Cederbaum, Mouse model for human arginase deficiency, Mol. Cell. Biol. 22 (2002) 4491–4498.
[40] H. Yu, R.K. Iyer, P.K. Yoo, R.M. Kern, W.W. Grody, S.D. Cederbaum, Arginase expression in mouse embryonic development, Mech. Dev. 115 (2002) 151–155.
[41] P.S. Kim, R.K. Iyer, K.V. Lu, H. Yu, A. Karimi, R.M. Kern, D.K. Tai, S.D. Cederbaum, W.W. Grody, Expression of the liver form of arginase in erythrocytes, Mol. Genet. Metab. 76 (2002) 100–110.
[42] S.E. Snyderman, C. Sansaricq, P.M. Norton, F. Goldstein, Argininemia treated from birth, J. Pediatr. 95 (1979) 61–63.
[43] P.P. De Deyn, B. Marescau, I.A. Qureshi, A. Mori, Guanidino Compounds: 2 eds., J. Libbey, London, 1997 pp. 71–76.
[44] R.S. Sparkes, G.J. Dizikes, I. Klisak, W.W. Grody, T. Mohandas, C. Heinzmann, S. Zollman, A.J. Lusis, S.D. Cederbaum, The gene for human liver arginase (ARG1) is assigned to chromosome band 6q23, Am. J. Hum. Genet. 39 (1986) 186–193.
[45] E.B. Spector, M. Kiernan, B. Bernard, S.D. Cederbaum, Properties of fetal and adult red blood cell arginase: a possible prenatal diagnostic test for arginase deficiency, Am. J. Hum. Genet. 32 (1980) 79–87.
[46] S. Hewson, J.T. Clarke, S. Cederbaum, Prenatal diagnosis for arginase deficiency: a case study, J. Inherit. Metab. Dis. 26 (2003) 607–610.
[47] M. Tuchman, M. Batshaw, Management of inherited disorders of ureagenesis, The Endocrinologist 12 (2002) 99–109.

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REVIEW

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The role and control of arginine levels in arginase 1 deficiency

George A. Diaz[1] | Mark Bechter[2] | Stephen D. Cederbaum[3]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA

[2]Aeglea BioTherapeutics, Inc., Austin, TX, USA

[3]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Correspondence
Stephen D. Cederbaum, Intellectual and Developmental Disabilities Research Center, University of California, Los Angeles, 635 Charles E Young Drive South, Los Angeles, CA 90095-7332, USA.
Email: scederbaum@mednet.ucla.edu

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Abstract

Arginase 1 Deficiency (ARG1-D) is a rare urea cycle disorder that results in persistent hyperargininemia and a distinct, progressive neurologic phenotype involving developmental delay, intellectual disability, and spasticity, predominantly affecting the lower limbs and leading to mobility impairment. Unlike the typical presentation of other urea cycle disorders, individuals with ARG1-D usually appear healthy at birth and hyperammonemia is comparatively less severe and less common. Clinical manifestations typically begin to develop in early childhood in association with high plasma arginine levels, with hyperargininemia (and not hyperammonemia) considered to be the primary driver of disease sequelae. Nearly five decades of clinical experience with ARG1-D and empirical studies in genetically manipulated models have generated a large body of evidence that, when considered in aggregate, implicates arginine directly in disease pathophysiology. Severe dietary protein restriction to minimize arginine intake and diversion of ammonia from the urea cycle are the mainstay of care. Although this approach does reduce plasma arginine and improve patients' cognitive and motor/mobility manifestations, it is inadequate to achieve and maintain sufficiently low arginine levels and prevent progression in the long term. This review presents a comprehensive discussion of the clinical and scientific literature, the effects and limitations of the current standard of care, and the authors' perspectives regarding the past, current, and future management of ARG1-D.

KEYWORDS

arginase deficiency, guanidino compounds, hyperargininemia, inborn error of metabolism, urea cycle disorder

Synopsis

ARG1-D is a distinct urea cycle disorder with a progressive neurologic phenotype. This review presents a comprehensive discussion of evidence from genetically manipulated mouse models and observations from clinical practice that implicate high arginine levels directly in disease pathophysiology.

1 | INTRODUCTION

Arginase 1 Deficiency (ARG1-D) is a rare, progressive inborn error of metabolism that results in persistent hyperargininemia and debilitating cognitive, neurologic, and mobility impairments.[1,2] These clinical impairments consistently manifest in patients with ARG1-D, although with varying age of onset and rate of progression.[2,3] Although ARG1-D shares some clinical characteristics with other urea cycle disorders (UCDs), there are several distinct biochemical and clinical features of ARG1-D that suggest a unique mechanism driving development and progression of disease manifestations. Neurotoxic effects of elevated levels of arginine and arginine metabolites, as well as a mechanistic role of chronic hyperargininemia in the development and progression of neurologic manifestations have long been proposed,[4–10] and are supported by both empirical studies and clinical evidence discussed here.

1.1 | Arginase 1 deficiency is a distinct urea cycle disorder

The urea cycle comprises six consecutive enzymatic reactions and two transporters in the liver that detoxify ammonia through conversion into urea, which is excreted through the kidneys. Under normal conditions, arginase 1 hydrolyzes arginine into ornithine and urea in the final step of the cycle. Mutations in the *ARG1* gene lead to impaired or absent arginase 1 activity and, as a direct effect of defective metabolism, intracellular hepatic arginine accumulates at levels approximately 50-fold higher than normal (Figure 1).[11] This excess arginine is released to the plasma and subsequently accumulates in other organs (including brain and cerebrospinal fluid [CSF]),[8,12] as a result of arginine being readily transported and maintained in an equilibrium between different tissues and plasma.[13–15] Elevated levels of arginine and arginine-derived guanidino compounds, putative neurotoxins generated through downstream enzymatic pathways external to the urea cycle,[8,11,12,16–18] are well-documented in the plasma/serum and CSF of patients with ARG1-D as well as rodent models of this multisystem disorder.[1,4,8]

Biochemically, markedly elevated plasma arginine is the most readily apparent feature of ARG1-D. Normal plasma arginine levels range from 40 to 115 μmol/L[19] but are typically >300 μmol/L in ARG1-D and often much higher[20]; levels >10-fold normal have been reported. In contrast, arginine levels are low in other UCDs because of upstream metabolic abnormalities that diminish endogenous arginine production—in fact, arginine supplementation is indicated for all UCDs other than ARG1-D.[20] In most UCDs, hyperammonemia is a common and potentially life-threatening complication. Hyperammonemic episodes, often severe, may occur throughout life and can cause encephalopathy, neurocognitive sequelae, or even death. Symptomatic hyperammonemia and hyperammonemic crisis are comparatively less common in ARG1-D, probably because upstream ammonia detoxification processes (through activity of

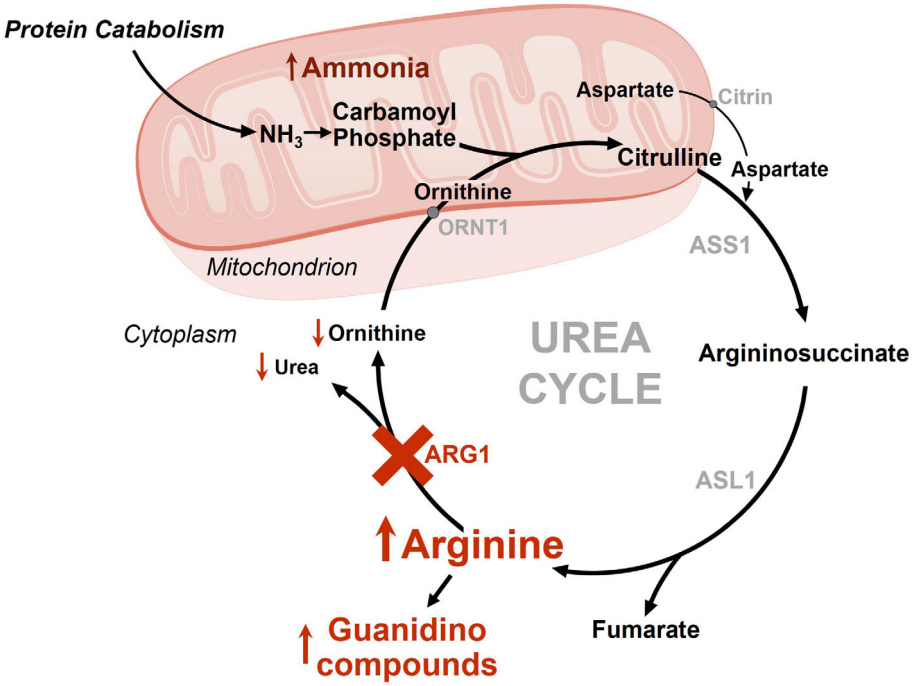

FIGURE 1 Urea Cycle Dysfunction in Arginase 1 Deficiency. Loss of arginase 1 enzymatic activity results in pathologic accumulation of arginine, decreased levels of its urea cycle products (ornithine and urea), and increased levels of guanidino compounds. ARG1, arginase 1; ASL1, argininosuccinate lyase; ASS1, argininosuccinate synthetase 1; ORNT1, ornithine transporter 1. Adapted with permission from Blair NF, Cremer PD, and Tchan MC. *Pract Neurol.* 2015;15:45–48. doi:10.1136/practneurol-2014-000916

enzymes preceding arginase 1 in the urea cycle) remain intact.[20,21]

The importance of hyperammonemia in most other UCDs is reflected in their management and clinical course, wherein early manifestations of the more complete enzyme deficiencies become apparent in the first days or weeks of life and commonly involve signs and symptoms driven by ammonia accumulation (e.g., cerebral edema, lethargy, anorexia, hypothermia, neurologic posturing, seizures, and coma). Cases of severe neonatal/infantile hyperammonemia in ARG1-D have been described but are uncommon.[22–26] Instead, the classic phenotype of ARG1-D involves insidious onset with manifestations developing typically in the first years of life and worsening progressively over time at variable rates; newborns typically appear healthy.[2,17,27–29] The clinical profile of ARG1-D includes seizures, developmental delay, and cognitive impairment as common manifestations. Unlike other UCDs, however, developmental delay and cognitive impairment in ARG1-D are progressive. Furthermore, spastic diplegia is a hallmark clinical feature of ARG1-D that differentiates this disorder from other UCDs, with its pathogenesis distinct from the known toxic effects of ammonia.[20,21,30] Patients with ARG1-D exhibit progressive spasticity that predominantly affects the lower limbs and worsens in severity and impact over time. As a result, these patients may initially stumble and appear clumsy, develop gait abnormalities and mobility impairments, and eventually lose the ability to walk independently.[17,29] Based on this clinical profile, ARG1-D is uniquely recognized among UCDs as a clinical mimic of cerebral palsy and hereditary spastic paraplegia.[31–34]

The pathophysiologic profile of ARG1-D strongly suggests that elevated arginine, rather than hyperammonemia, plays the key role in development and progression of manifestations.[2,4,28] Plasma arginine levels may be within or near the normal range in the immediate postnatal period, when infants appear phenotypically normal.[30] Furthermore, progression of manifestations with increasing duration of disease suggests a cumulative effect of persistently high arginine.[35,36] Clinical recognition of the importance of plasma arginine levels in ARG1-D is reflected in current management guidelines.[20] Treatment of other UCDs is focused on reducing risk of hyperammonemia and addressing acute hyperammonemic episodes,[20] but, as noted previously, hyperammonemia is less of a concern in ARG1-D. Preventing symptomatic hyperammonemia does not prevent progression or improve long-term outcomes in these patients. Instead, current guidelines for ARG1-D management focus on lowering plasma arginine, and specifically recommend maintaining plasma arginine levels at <200 μmol/L or as low as possible (aiming for the upper reference range).[20]

1.2 | Empirical studies implicate arginine in development and progression of ARG1-D manifestations

Multiple mouse models support a key role of arginine accumulation in ARG1-D pathophysiology. These animals demonstrate markedly elevated plasma arginine and guanidino compounds that lead to phenotypic abnormalities consistent with disease manifestations observed in patients with ARG1-D, including failure to thrive, seizures, spasticity, gait abnormalities, and mobility impairment.[37–42]

The most extensively characterized *Arg1* knockout model, first described by Iyer et al., was developed through replacement of *Arg1* exon 4 (the active site) with a neomycin resistance gene by homologous recombination that results in a total lack of liver arginase 1.[37] These mice are phenotypically indistinguishable from wild-type littermates at birth and appear to behave normally for the first 10–12 days of life. Onset of hyperargininemia and hyperammonemia is followed by weight loss, central nervous system dysfunction (which manifests as gait instability, tremor, ataxia, lethargy, decerebrate posture, and seizure-like activity), encephalopathy, liver pathology, metabolic crisis, and death. Plasma arginine levels are approximately four-fold greater in these animals than wild-type comparators and rise to >10-fold normal levels during metabolic crisis. As expected, hyperargininemia is accompanied by marked increases in guanidino compounds in the serum as well as in the brain.[39,41,42] These mice ultimately succumb to severe hyperammonemia at approximately 14–21 days of life. The biochemical and phenotypic abnormalities stemming from arginine accumulation in these mice have been recapitulated in 2 different conditional adult-onset knockout mouse models generated using tamoxifen-inducible Cre-Lox mice with floxing of *Arg1* exons 7 and 8.[40,43] As is characteristic of the exon 4–targeted *Arg1* knockouts, the adult-onset models demonstrate hyperargininemia upon tamoxifen induction and ensuing signs of physical, neuromotor, and behavioral abnormalities such as growth disparity, weight loss, hunched body posture, difficulty standing, gait abnormalities (e.g., instability, staggering, irregular steps, and shortened stride length), and progressive ataxia.[40,43] Also like the exon 4–targeted knockouts, both inducible models follow a rapid course of metabolic disruption, including increased arginine, guanidino compounds, and ammonia, among other perturbations, as well as lethal hyperammonemia within 2–3 weeks.[40,43] A consistent observation across all three models is that hyperargininemia is established by the time that phenotypic abnormalities become apparent, suggesting that the phenotype may be biochemically driven by accumulation of arginine and arginine metabolites resulting from

hepatic *Arg1* disruption.[37,40,43] This hypothesis is further supported by a recent characterization of another genetic mouse model that lacks expression of *Arg1* in neural cells only.[44] Although small decreases were noted in the volume of two brain structures involved in motor activity of these neural-specific knockouts, others were unchanged and their gait was largely unaltered compared with wild-type controls. Assessment of blood amino acids revealed that arginine levels were also unchanged in mice lacking neural expression of *Arg1*. The striking contrast between this genetically manipulated model and the global or liver-specific *Arg1* knockouts led the authors to two important conclusions: (1) that hyperargininemia and neurologic manifestations of ARG1-D are driven by the toxic metabolic environment that results from loss of hepatic arginase 1, and (2) that reducing arginine levels in the blood represents the best chance to avoid neurologic manifestations.[44]

Restoration of *Arg1* in transgenic mouse models of ARG1-D has provided further evidence of a key role of arginine in disease manifestations, as pioneered by Gerald Lipshutz's group at UCLA. In an early proof-of-concept study, the exon 4–targeted *Arg1* knockout mice[37] were treated with *Arg1* gene transfer delivered using an adeno-associated viral (AAV) vector administered on the second day of life.[38] Whereas all untreated knockouts died within 24 days, AAV-treated mice (i.e., those with hepatic arginase 1 restored) demonstrated normal plasma arginine levels, less-severe hyperammonemia, improved weight gain, and prolonged survival with 89% alive through >8 months. Results of a detailed characterization of the biochemical, neuromotor, and neurobehavioral phenotype of knockout mice with AAV-mediated restoration of *Arg1* also supports this hypothesis.[39] Brain development at 4 months was similar between treated knockouts and wild-type littermates, with no abnormalities or lesions evident in key brain structures such as olfactory bulbs, cerebral cortex, basal ganglia, hippocampus, thalamus, cerebellum, or pons. A battery of functional assessments revealed no differences in exploratory activity, cerebellar function, spatial learning, or behavioral responses, or in body posture, tremor, locomotor activity, gait, grip strength, or righting reflexes. Notably, normal brain development and neurologic phenotype were observed in the context of reversal of metabolic abnormalities. By 3 weeks after AAV-mediated gene transfer, brain and serum levels of arginine were normalized or below control levels. Furthermore, serum guanidino compounds, which were markedly elevated in untreated knockout mice, were decreased to near-normal levels in sera and brain tissue of treated knockouts.[39]

The prominent, progressive spasticity observed in patients with ARG1-D and the analogous neuromotor abnormalities observed in *Arg1*-deficient mice prompted further investigations of the motor cortex in untreated knockout mice and knockouts with AAV-mediated *Arg1* hepatic gene therapy.[41,45] Altered circuitry in the motor cortex was observed in untreated knockouts at postnatal day 15 (after development of hyperargininemia) with decreased dendritic arborization, decreased numbers of excitatory and inhibitory synapses, and abnormal synaptic transmission, suggesting a potential arginine-driven neural mechanism of motor dysfunction in ARG1-D.[45] Neuronal structure and cortical circuitry were virtually normal in knockout mice with neonatal *Arg1* restoration.[45] In a second study, microarray expression analysis in untreated *Arg1* knockouts suggested abnormalities in myelinating oligodendrocytes that were supported by evidence of marked subcortical dysmyelination in key motor structures including the corpus callosum and caudate putamen.[41] Compared with wild-type mice, the *Arg1*-deficient mice had fewer myelinated axons in the motor cortex, pyramidal tract, and corticospinal tract, as well as decreased thickness of the myelin sheath where myelination was evident; axonal degeneration and decreased dendritic complexity were also observed. Among the knockouts receiving AAV treatment at postnatal day 2, myelinated axon density, oligodendrocyte wrapping of axons, and axonal integrity were largely normal, indicating prevention of neural abnormalities through restoration of functional arginase 1 and normalization of plasma arginine.[41] The results of these studies implicate arginine levels, rather than residual or induced brain arginase 1 or 2. Wild-type mice express only low levels of arginase 1 and arginase 2 confined to specific brain areas. Furthermore, there is little to no increase in brain arginase 2 in *Arg1* knockout animals, and little to no increase in brain arginase 1 in genetically corrected *Arg1* knockouts. Finally, in a more recent mouse model also spearheaded by the Lipshutz group, a lipid nanoparticle carrying human *Arg1* mRNA was administered intermittently to constitutive *Arg1* knockout mice to restore their hepatic arginase 1 activity.[46] Normalization of plasma arginine and reductions in guanidino compounds were achieved in the mice receiving lipid nanoparticle/*Arg1* mRNA compared with untreated knockouts and wild-type controls; these biochemical changes were associated with a dramatic recovery of myelin density, increased myelin sheath thickness, and normal growth and survival.[46]

This evidence of abnormal neurophysiology and dysmyelination is consistent with the limited available observations reported in children with ARG1-D. In one patient with toe walking and spastic paraplegia, among other signs of pyramidal tract dysfunction affecting his lower limbs, neurophysiologic assessment revealed prolonged latency of motor evoked potentials, indicating

involvement of the corticospinal tract.[47] In another case, a patient exhibited the characteristic ARG1-D clinical profile and trajectory, with an uneventful infancy before insidious onset of progressive neurologic deterioration.[48] At 2.5 years of age, spastic diplegia and permanent loss of speech were evident, followed by loss of locomotion over the course of several months, and ultimately spastic tetraplegia and reliance on a wheelchair at only 3 years and 10 months of age. Plasma ammonia was only slightly elevated above normal levels, whereas arginine levels were nine-fold higher than normal in the plasma and 2.5-fold higher than normal in the CSF. Electroencephalography (EEG) showed multifocal discharges with abnormal background activity and absence of short latency responses in brainstem evoked potentials. Magnetic resonance imaging revealed dysmyelination as well as an undersized cerebellum, enlarged cerebral ventricles, and thinning of the corpus callosum. At 9 months after diagnosis of ARG1-D and initiation of dietary restriction, background activity on EEG was normalized and short latency responses were improved in parallel with lowering of arginine levels. Increased severity of protein restriction produced further reductions in arginine that were accompanied by additional improvement or normalization of brainstem evoked potentials. Importantly, objective improvement of neurologic function was reflected through improvements in alertness and motor activity.[48] Lastly, a patient evaluated in a study conducted with the Urea Cycle Disorders Consortium (UCDC) was also found to have corticospinal tract abnormalities consistent with his neuromotor deficits.[49] This patient exhibited characteristics not uncommon in ARG1-D in the early postnatal period, including poor feeding, vomiting, and poor growth; however, developmental milestones were normal. Before diagnosis at 4 years of age, he demonstrated increasing fall frequency and decreasing motor skills followed by development of significant lower-limb spasticity and seizures. At diagnosis, plasma arginine was predictably elevated and treatment with dietary restriction and ammonia diversion was initiated. At 16 years of age, his cognitive performance with regard to visual memory and language was normal and he was succeeding scholastically, but impairments in complex problem-solving and organization were evident in addition to impaired motor strength. At 17 years, he was ambulatory without orthotics or assistive devices but had increased tone, hyperreflexia, and clonus in the lower extremities consistent with the spasticity that manifested in his early childhood. Diffusion tensor magnetic resonance imaging revealed altered integrity and microstructural damage in the white matter of regions involved in motor function—specifically, the central pons extending into the cerebellum at the level of corticospinal tract crossing as well as adjacent to the corpus callosum. There was also a significant reduction in corticospinal tract fiber count compared with matched control subjects, further indicating neuronal damage to motor circuitry in ARG1-D.[49] Abnormalities in neuromotor circuitry and corticospinal tract damage in particular have not been reported in patients with more proximal UCDs and were not observed in patients with ornithine transcarbamylase deficiency ($n = 23$) in the UCDC diffusion tensor imaging study, which further implicates arginine in the pathology of ARG1-D.[49]

We believe that these neurologic abnormalities reflect the neurotoxic effects of arginine and/or the guanidino compounds that accumulate in conjunction with, and as a result of, arginine elevation.[8,11,12,17] Guanidino compounds, both as a class and individually, have neurotoxic effects on the brain and on brain cells in culture.[16,18] For example, guanidino compounds that are increased in ARG1-D, such as guanidinoacetic acid and guanidinovaleric acid, have been empirically shown to induce epileptiform and convulsive activity in rodents.[18] Likewise, argininic acid and guanidinovaleric acid, at levels comparable to those observed in ARG1-D, alter evoked depolarizing responses in cultured spinal cord neurons.[50] Although this neurotoxicity has been demonstrated independent of the effects of arginine, guanidino compounds (and their effects) in ARG1-D are inextricably linked with elevation of arginine, the proximal substrate.[42] It has also been suggested that ornithine deficiency, which is observed in pyrroline-5-carboxylate synthetase deficiency (P5CSD), or distorted arginine/ornithine imbalance, which occurs in hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, may play a role in the spasticity sometimes observed in these two disorders.[34,51–53] However, ornithine deficiency is not an established feature of ARG1-D, and both P5CSD and HHH syndrome differ from ARG1-D in that spasticity occurs with variable prevalence and late onset, in contrast with the regular and relentless occurrence of spasticity in ARG1-D. As such, they would not support ornithine deficiency as an important pathogenic contributor in ARG1-D. Lastly, downstream effects of excessive arginine on nitric oxide and promotion of oxidative stress and excitotoxicity have also been hypothesized.[28,49]

1.3 | Clinical evidence implicates arginine in development and progression of ARG1-D manifestations

With an estimated global prevalence of only 1:726000,[54] the rarity of ARG1-D poses a challenge to characterizing the pathophysiology and mechanisms driving progression

in humans. Most clinical evidence to date is largely anecdotal and based on individual cases, familial series, or retrospective case analyses. Nonetheless, the clinical evidence is consistent with empirical evidence from mechanistic studies in mouse models.

The first ARG1-D patients described in the literature were three female siblings, the older two of whom developed seizures, psychomotor delays, and spasticity within the first years of life.[55–57] At presentation and biochemical evaluation for the two older sisters (ages 5 years and 1.5 years), significantly diminished/near-undetectable arginase one enzymatic activity and markedly increased arginine levels in serum and CSF were evident; only mild hyperammonemia was observed. Because of this family history, a third sister was assessed at birth and was found to also have ARG1-D.[57] Despite early initiation of treatment with a low-protein diet at 8 weeks of age, her plasma arginine remained significantly elevated at ~800 μmol/L and onset of motor abnormalities was evident by age 5 months. She experienced a progressive clinical course similar to her siblings, with psychomotor delays and lower-limb spasticity evident by 3 years of age.[57]

Over the ensuing five decades since these first patients were described, a clear clinical and pathophysiologic profile of ARG1-D been borne out with striking consistency through numerous reports: deleterious effects of high arginine and/or dysregulation of arginine metabolites become evident typically in the first years of life and increase in severity and extent throughout the patient journey.[2–4,7,9,28,30,32,34,47,58–65] Elevated plasma arginine, whether as the primary driver or proximal causal component of downstream toxicity, is associated with progressive intellectual disability, global developmental delay, seizures, and uniquely, with progressive spasticity. Of note, seizures in ARG1-D patients are not attributed exclusively to hyperammonemic events.[8,12] The neurotoxic effects of guanidino compounds, which increase in the plasma and CSF as a result of elevated plasma arginine, contribute to seizure susceptibility.[16–18] The morbidity associated with ARG1-D puts these patients at risk for early mortality.[30] The specific factors driving early mortality in ARG1-D are not yet clear; precipitating events reported in the literature are diverse and the end stages of disease remain to be more fully characterized.

A detailed clinical characterization of the relationship between biochemistry and functional outcomes in multiple UCDs, performed by the UCDC, more directly implicates chronic high arginine as the driver of development and progression of ARG1-D manifestations.[36] Patients with ARG1-D were at greater risk than those with other UCDs for low IQ and poor performance in all neuropsychologic domains assessed. Consistent with the known biochemical profiles of ARG1-D and other UCDs, mean lifetime plasma ammonia was lower in the ARG1-D cohort compared with other UCDs (mean, 78.87 μmol/L vs. 127.22–139.59 μmol/L) and hyperammonemic episodes were less common. Elevated arginine (several fold normal in the ARG1-D cohort) was more tightly associated with poorer functioning in global and memory domains than any other biochemical marker evaluated, and higher plasma arginine levels were significantly correlated with poorer motor composite scores. Lastly, increasing cumulative arginine exposure (in terms of longer duration of disease) was an indicator of worse neuropsychiatric outcome among patients with ARG1-D. Individual case reports of patients with long-term follow-up have also documented phenomena strongly suggestive of arginine toxicity in ARG1-D. Periods of worsening hyperargininemia, whether because of poor treatment adherence or other factors such as biologic stressors, were accompanied by worsening of cognitive and mobility impairments that returned to patients' functional baseline upon re-establishment of their typical plasma arginine levels.[59,65–67]

In the first reports of ARG1-D treatment, dietary protein restriction was able to control hyperammonemia but not plasma arginine (which was lowered from pretreatment levels but remained elevated), and achieved only limited clinical improvement.[10,55–57] An important outcome of this early work was the exclusion of ammonia and the implication of arginine as a direct driver of disease pathophysiology; additionally, these reports established the challenge of lowering arginine levels in patients with ARG1-D. In subsequent reports, rigorous management with chemically defined amino acid diets was more effective, lowering plasma arginine and achieving clinical stability or improvement even in patients with advanced/severe disease **(**Table 1**)**.[9,48,59,61] In adolescent/teenage siblings with established neurocognitive and neuromotor manifestations of ARG1-D, lowering of plasma arginine with a chemically defined diet resulted in clinical improvement.[9,61] Specifically, spasticity was lessened and mobility improved, independent feeding and toilet training were regained, and language improved.[61] Initiation of treatment in younger patients has been described to yield more meaningful clinical benefits.[58,63] In a patient with overt cognitive impairment, lower-limb spasticity, and toe walking, treatment was initiated upon diagnosis at age 7 years.[63] Limitation of natural protein lowered her plasma arginine by approximately 50%, from 8-fold to 4-fold normal levels. Further restriction with a second dietary formulation was able to reduce plasma arginine to near the upper limit of

TABLE 1 Clinical Evidence Supporting the Effectiveness of Arginine Reduction* for Improving Outcomes in ARG1-D

	Pre-treatment History of Manifestations	Plasma Arginine[a]	Clinical Outcomes
Case report			
Cederbaum[9] Cederbaum[61]	• 6 years: severe spasticity, hyperreflexia • 15 years: progressive physical and intellectual deterioration (severe psychomotor impairment with no speech or language comprehension, no interaction with environment, severe spasticity with difficulty moving, decreased gag reflex, poorly coordinated swallowing)	• Pretreatment: 7-fold ULN • Initial restricted diet: 5- to 6-fold ULN • Stricter diet: 2-fold ULN	• Regained ability to dress, feed self, brush teeth, use toilet independently • Improved language and regained capacity to respond to simple commands • Diminished spasticity and improved mobility
Cederbaum[9] Cederbaum[61]	• 2.5 years: clumsiness, hyperreflexia, ankle clonus, spasticity (predominantly affecting lower limbs) • 8 years: wheelchair-dependent, severe psychomotor impairment with no speech and minimal language comprehension, no bladder/bowel control, tiptoe gait, reduced gag reflex, poorly coordinated swallowing	• Pretreatment: 5-fold ULN • Initial restricted diet: 4-fold ULN • Stricter diet: near-normal	• Regained ability to speak and construct phrases/sentences • Regained bowel/bladder control • Regained ability to feed self, brush teeth independently • Improved concentration • Improved spasticity and mobility
Brockstedt[48]	• 2.5 years: spastic diplegia, loss of speech, worsening of mobility impairment • 3 years 10 months (diagnosis): intellectual disability, no intelligible speech, spastic tetraplegia (predominantly affecting lower limbs), wheelchair-bound, no reproducible short latency response in brainstem acoustic evoked potentials	• Pretreatment: 907 μmol/L (9-fold ULN) • Initial restricted diet: 4-fold ULN • Stricter diet: 2- to 3-fold ULN	• Improved alertness and motor activity • Improved/normalized brainstem evoked potentials
Lambert[63]	• 5 years: motor and cognitive impairment • 6 years 1 month: lower-limb spasticity, hyperreflexia, tiptoe gait, • 6 years 11 months (diagnosis): spasticity, tiptoe gait, hyperactivity • 7 years 7 months: progressive worsening of motor deficits	• Pretreatment: 895 μmol/L (10.5-fold ULN) • Initial restricted diet: 6-fold ULN • Stricter diet: 1.7-fold ULN	• Progressive improvement of muscle strength, mental skills, and mobility • Patient a community ambulator; able to run, ride bike, climb stairs
Snyderman[58]	• 3 months: vomiting, lethargy, tremor • 5 months: seizures, hyperreflexia, bilateral ankle clonus • 20 months: seizure recurrence, ataxia • 4 years (diagnosis): intellectual disability, tiptoe gait, ataxia, hyperactivity	• Pretreatment: 9.4 mg/dL (6-fold ULN) • Initial restricted diet ineffective • Stricter diet: 2- to 3-fold ULN	• Reduced hyperactivity • Improved ataxia and coordination • Improved mental capacity

(Continues)

TABLE 1 (Continued)

	Pre-treatment History of Manifestations	Plasma Arginine[a]	Clinical Outcomes
Snyderman[5]	• 2.5 years: vomiting, lethargy, hyperreflexia • 3 years 7 months (diagnosis): intellectual disability, developmental delay, hyperactivity, tiptoe gait, lower-limb spasticity	• Pretreatment: 9.95 mg/dL (7-fold ULN) • Initial restricted diet: 4-fold ULN • Stricter diet: 2- to 3-fold ULN	• Reduced hyperactivity • Improved ataxia and coordination • Improved mental capacity
Snyderman[59]	• Patient identified at and treated from birth (pre-symptomatic)	• Until 4 months of age: normal • Beyond 4 months: 2- to 3-fold ULN	• Physiologically, neurologically, and mentally normal • Average developmental assessments, through 2.5 years
Observational study			
Huemer[28]	• Three patients identified at and treated from birth (pre-symptomatic)	• Pretreatment: not applicable • Last follow-up at age 1–3 years: 256–574 μmol/L (ULN not available)	• Last follow-up at age 1–3 years: asymptomatic course in all three patients

Abbreviation: ULN, upper limit of normal.

[a]ULN reflects normal range or control range as defined in each case report.

*Arginine-lowering intervention comprised dietary protein restriction with essential amino acid supplementation for all patients.

normal, which was accompanied by substantial lowering of guanidino compounds. Over 2.5 years of treatment, the patient's cognitive function improved, spasticity was markedly decreased, and muscle strength improved; the patient was ultimately able to run, climb stairs without support, and ride a bicycle, and was a community ambulator.[63] Treatment from birth has actually been shown to delay or reduce progression, with some patients showing no overt manifestations of ARG1-D through 5 years of age (Table 1).[28,59] For example, in a 2016 case series, three patients ascertained through newborn screening and treated from infancy remained clinically asymptomatic through toddlerhood, the age of most recent follow-up.[28]

Additional clinical evidence supporting the relationship between plasma arginine levels and clinical outcomes comes from a 1984 case report of a boy with ARG1-D who lost his ability to stand, sit, or crawl by himself at the age of 3 years and was also experiencing rigidness in his legs and spastic quadriplegia. At the age of 5 years, an experimental therapeutic approach involving transfusion of healthy red blood cells (i.e., with functional arginase) was used to lower plasma arginine.[23,68] This approach, though not without limitations precluding clinical adoption, markedly decreased arginine levels in the serum and, as a result, in the CSF and resulted in clear clinical improvements, such that the boy became able to sit and roll by himself and manifested reduced spasticity.[68]

1.4 | Current management is insufficient to maintain adequately low arginine and does not prevent ARG1-D progression in the long term

Dietary protein restriction to lower plasma arginine levels is the mainstay of management for all UCDs, with particularly extreme protein restriction required in ARG1-D.[20] The flux of arginine into plasma depends on three key sources (dietary arginine intake, de novo arginine synthesis via the intestinal-renal axis, and whole-body intracellular protein turnover), of which the endogenous flux from protein turnover is the major contributor in humans.[15] Dietary restriction in ARG1-D is focused on limiting exogenous supply of arginine, but cannot address the endogenous production[15]; even during periods of good adherence to a restrictive diet, elevated arginine levels can persist.[3] As in all UCDs, ammonia is a product of the catabolism of every amino acid and the flux through the cycle is far greater than the flux for the catabolism of other individual carbon skeletons. Patients with ARG1-D may receive nitrogen scavengers as part of their management[20] to address ammonia levels but also to lower arginine levels based on a potential downstream effect of offloading nitrogen from the urea cycle. The combination of dietary protein restriction and ammonia diversion therapy can stabilize the ammonia levels in all UCDs in non-catabolic situations but is insufficient to lower plasma arginine levels to anywhere near the

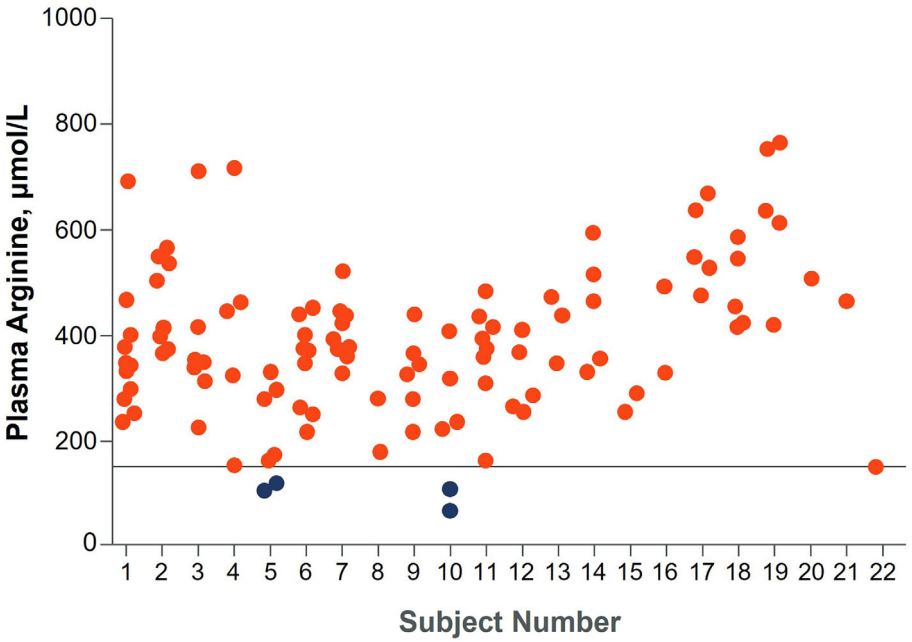

FIGURE 2 Plasma Arginine Levels With Current Standard of Care. Analysis of data from patients ($n = 22$) with Arginase 1 Deficiency in the Urea Cycle Disorder Consortium database. Dashed line indicates upper limit of normal applied to the study's laboratory assessments; current guidelines recommend maintaining plasma arginine <200 µmol/L. Blue dots represent arginine levels below the applied upper limit of normal of 150 µmol/L. Adapted with permission from Burrage LC, Sun Q, Elsea SH, et al. *Hum Mol Genet*. 2015;24 (22):6417–6427. doi:10.1093/hmg/ddv352

normal range in ARG1-D.[60] Nonetheless, as is evident throughout the literature and based on our clinical experience, even suboptimal reduction of plasma arginine can halt or delay progression and even improve patient outcomes, demonstrating the importance of effective arginine-lowering management approaches.

With currently available approaches, achieving and maintaining adequate reduction of plasma arginine in the long term is extremely difficult; thus, the guideline-recommended level of <200 µmol/L[20] is rarely achieved. As a result, most patients deteriorate over time and poor long-term outcomes are the norm.[2,6,28,65] In an analysis of published case reports of patients with ARG1-D, the median plasma arginine level (reported at any time in the patient journey, $n = 112$ patients) was 572 µmol/L; levels under treatment with dietary protein restriction ($n = 33$ patients) were also markedly elevated at a median of 400 µmol/L.[30] Even with a relatively young median age of 11 years in these patients, significant disease progression was evident, with lower-limb spasticity and intellectual disability reported in 84% and 82%, respectively.[30] Similarly, analysis of UCDC plasma arginine data from patients receiving standard of care management (22 patients; 1–13 measurements per patient) revealed that nearly all samples evaluated (97%) were above 150 µmol/L (value used as the upper limit of normal) and very few were <200 µmol/L; no patient had levels in the normal range in all samples/timepoints assessed **(**Figure 2**)**.[60] Median age at the most recent visit was 14.75 years; diagnosis was made at a median age of 3.25 years. Despite standard of care management in this cohort and the relatively young age at diagnosis/treatment initiation and follow-up, 89% of patients had developmental delay or intellectual disability; abnormal reflexes and abnormal tone were evident in 53% and 63% of patients, respectively, and 60% were nonambulatory.[60]

2 | SUMMARY

Collectively, the scientific literature demonstrates a key mechanistic role of elevated arginine as the proximal or direct driver of disease in ARG1-D. The ARG1-D biochemical profile and clinical manifestations are distinct from most other UCDs in which hyperammonemia is the primary concern. Persistent high plasma arginine in ARG1-D is accompanied by consistently and progressively manifesting debilitating neurologic and functional impairments, whereas reducing plasma arginine improves manifestations even in patients with established disease. Since tissue and CSF levels of arginine are in equilibrium with those of plasma, lowering plasma arginine to guideline-recommended levels is an important therapeutic approach, and is supported by improvements in neurologic and functional manifestations occurring with modulation of plasma arginine levels in ARG1-D demonstrated both in animal models and clinically. Furthermore, worsening severity of disease manifestations during acute decompensation events indicate toxic effects of spikes in arginine levels. Even when lowering of arginine is suboptimal, intervention with current management approaches has been shown to delay development of manifestations and to reverse many aspects of established cognitive and mobility impairment at both

the neurophysiologic and functional levels. However, the aggregate data from the UCDC highlight the difficulty in maintaining adequately low arginine levels with the current standard of care, even at highly specialized centers and with rigorous individualized disease management strategies; long-term outcomes remain poor with many patients developing significant disability over time. There is an urgent need for effective treatments that maintain long-term reduction, or even normalization, of plasma arginine levels in patients with ARG1-D to address the underlying mechanism of disease, thereby preventing progression and improving outcomes.

3 | PERSPECTIVE

As we seek better outcomes in ARG1-D, improvements in newborn screening algorithms for ARG1-D will allow diagnosis to be made with high sensitivity and specificity.[35,69] Whereas standard of care can maintain arginine levels in an acceptable therapeutic range for the first months or years of life, we have seen how difficult this can be in the longer term. Enzyme therapy has been shown to lower plasma arginine levels to the therapeutic range and to substantially reduce guanidino compounds; these biochemical changes are accompanied by meaningful improvements in mobility.[70–72] This potential therapy currently awaits FDA approval and represents the first step in advancing treatment of ARG1-D, which has been awaiting a therapeutic breakthrough for 40 years. Both gene and mRNA therapies have been validated in animal models[39,73] and must be demonstrated to be effective and safe in humans before they can be considered part of this more hopeful future of ARG1-D treatment. One of the authors (SDC) has been investigating ARG1-D for nearly 50 years and has been hoping for these promising therapeutic breakthroughs.

AUTHOR CONTRIBUTIONS

George A. Diaz: planning and design, drafting the article, revising the article critically for important intellectual content, and approval of the final version of this work.
Mark Bechter: planning and design, drafting the article, revising the article critically for important intellectual content, and approval of the final version of this work.
Stephen D. Cederbaum: planning and design, drafting the article, revising the article critically for important intellectual content, and approval of the final version of this work.

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ETHICS STATEMENT

All authors were compliant and followed the ethical guidelines, according to the requirements of JIMD.

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CONFLICT OF INTEREST

Dr Diaz has served as an advisor and clinical trial investigator for Aeglea. Dr Cederbaum has served as a consultant and/or advisor for several biopharmaceutical companies, including Aeglea. Dr Bechter is an Aeglea employee (Medical Affairs). No author received compensation for their role in writing this article.

DATA AVAILABILITY STATEMENT

There is no data associated with this manuscript.

INFORMED CONSENT/ANIMAL RIGHTS

This article does not contain any studies with human or animal subjects performed by any of the authors.

REFERENCES

1. Carvalho DR, Brand GD, Brum JM, Takata RI, Speck-Martins CE, Pratesi R. Analysis of novel ARG1 mutations causing hyperargininemia and correlation with arginase I activity in erythrocytes. *Gene*. 2012;509(1):124-130.
2. Carvalho DR, Brum JM, Speck-Martins CE, et al. Clinical features and neurologic progression of hyperargininemia. *Pediatr Neurol*. 2012;46(6):369-374.
3. Keshavan N, Wood M, Alderson LM, et al. Clinical status, biochemical profile and management of a single cohort of patients with arginase deficiency. *JIMD Rep*. 2022;63(2):123-130.
4. Diez-Fernandez C, Rufenacht V, Gemperle C, Fingerhut R, Haberle J. Mutations and common variants in the human arginase 1 (ARG1) gene: impact on patients, diagnostics, and protein structure considerations. *Hum Mutat*. 2018;39(8):1029-1050.
5. Sin YY, Baron G, Schulze A, Funk CD. Arginase-1 deficiency. *J Mol Med (Berl)*. 2015;93(12):1287-1296.
6. Schlune A, Vom Dahl S, Haussinger D, Ensenauer R, Mayatepek E. Hyperargininemia due to arginase I deficiency: the original patients and their natural history, and a review of the literature. *Amino Acids*. 2015;47(9):1751-1762.
7. Crombez EA, Cederbaum SD. Hyperargininemia due to liver arginase deficiency. *Mol Genet Metab*. 2005;84(3):243-251.
8. Deignan JL, De Deyn PP, Cederbaum SD, et al. Guanidino compound levels in blood, cerebrospinal fluid, and post-

mortem brain material of patients with argininemia. *Mol Genet Metab*. 2010;100(Suppl 1):S31-S36.
9. Cederbaum SD, Shaw KN, Spector EB, Verity MA, Snodgrass PJ, Sugarman GI. Hyperargininemia with arginase deficiency. *Pediatr Res*. 1979;13(7):827-833.
10. Cederbaum SD, Shaw KN, Valente M. Hyperargininemia. *J Pediatr*. 1977;90(4):569-573.
11. Marescau B, De Deyn PP, Qureshi IA, et al. The pathobiochemistry of uremia and hyperargininemia further demonstrates a metabolic relationship between urea and guanidinosuccinic acid. *Metabolism*. 1992;41(9):1021-1024.
12. Marescau B, De Deyn PP, Lowenthal A, et al. Guanidino compound analysis as a complementary diagnostic parameter for hyperargininemia: follow-up of guanidino compound levels during therapy. *Pediatr Res*. 1990;27(3):297-303.
13. Closs EI, Simon A, Vekony N, Rotmann A. Plasma membrane transporters for arginine. *J Nutr*. 2004;134(10 Suppl):2752S-2759S. discussion 2765S-2767S.
14. Wu G, Davis PK, Flynn NE, Knabe DA, Davidson JT. Endogenous synthesis of arginine plays an important role in maintaining arginine homeostasis in postweaning growing pigs. *J Nutr*. 1997;127(12):2342-2349.
15. Wu G, Morris SM Jr. Arginine metabolism: nitric oxide and beyond. *Biochem J*. 1998;336(Pt 1):1-17.
16. De Deyn PP, D'Hooge R, Van Bogaert PP, Marescau B. Endogenous guanidino compounds as uremic neurotoxins. *Kidney Int Suppl*. 2001;78:S77-S83.
17. Amayreh W, Meyer U, Das AM. Treatment of arginase deficiency revisited: guanidinoacetate as a therapeutic target and biomarker for therapeutic monitoring. *Dev Med Child Neurol*. 2014;56(10):1021-1024.
18. Mori A. Biochemistry and neurotoxicology of guanidino compounds. History and recent advances. Pavlov. *Aust J Biol Sci*. 1987;22(3):85-94.
19. Luneburg N, Xanthakis V, Schwedhelm E, et al. Reference intervals for plasma L-arginine and the L-arginine:asymmetric dimethylarginine ratio in the Framingham offspring cohort. *J Nutr*. 2011;141(12):2186-2190.
20. Haberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. *J Inherit Metab Dis*. 2019;42(6):1192-1230.
21. Sun A, Crombez EA, Wong D. Arginase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews (R)*. University of Washington, Seattle; 2000 [updated 2021].
22. Jorda A, Rubio V, Portoles M, Vilas J, Garcia-Pino J. A new case of arginase deficiency in a Spanish male. *J Inherit Metab Dis*. 1986;9(4):393-397.
23. Jain-Ghai S, Nagamani SCS, Blaser S, Siriwardena K, Feigenbaum A. Arginase I deficiency: severe infantile presentation with hyperammonemia: more common than reported? *Mol Genet Metab*. 2011;104(1–2):107-111.
24. Braga AC, Vilarinho L, Ferreira E, Rocha H. Hyperargininemia presenting as persistent neonatal jaundice and hepatic cirrhosis. *J Pediatr Gastroenterol Nutr*. 1997;24(2):218-221.
25. Schiff M, Benoist JF, Cardoso ML, et al. Early-onset hyperargininaemia: a severe disorder? *J Inherit Metab Dis*. 2009;32(Suppl 1):S175-S178.
26. Scholl-Bürgi S, Sigl SB, Häberle J, et al. Amino acids in CSF and plasma in hyperammonaemic coma due to arginase1 deficiency. *J Inherit Metab Dis*. 2008;31(Suppl 2):S323-S328.
27. Bakhiet M, AlAwadi AMI, AlHammadi MM, Ali MF, Butti N. A case report of neurological complications owing to lately diagnosed hyperargininemia emphasizing the role of national neonatal screening policies in the Kingdom of Bahrain. *Medicine (Baltimore)*. 2018;97(20):e10780.
28. Huemer M, Carvalho DR, Brum JM, et al. Clinical phenotype, biochemical profile, and treatment in 19 patients with arginase 1 deficiency. *J Inherit Metab Dis*. 2016;39(3):331-340.
29. Uchino T, Snyderman SE, Lambert M, et al. Molecular basis of phenotypic variation in patients with argininemia. *Hum Genet*. 1995;96(3):255-260.
30. Diaz GA, Longo N, Bubb G, et al. Delays in diagnosis are associated with poor clinical outcomes in patients with arginase 1 deficiency. *Ann Neurol*. 2019;86:S137.
31. Pearson TS, Pons R, Ghaoui R, Sue CM. Genetic mimics of cerebral palsy. *Mov Disord*. 2019;34(5):625-636.
32. Prasad AN, Breen JC, Ampola MG, Rosman NP. Argininemia: a treatable genetic cause of progressive spastic diplegia simulating cerebral palsy: case reports and literature review. *J Child Neurol*. 1997;12(5):301-309.
33. Ebrahimi-Fakhari D, Saffari A, Pearl PL. Childhood-onset hereditary spastic paraplegia and its treatable mimics. *Mol Genet Metab*. 2021;S1096-7192(21)00735-6.
34. Panza E, Martinelli D, Magini P, Dionisi Vici C, Seri M. Hereditary spastic paraplegia is a common phenotypic finding in ARG1 deficiency, P5CS deficiency and HHH syndrome: three inborn errors of metabolism caused by alteration of an interconnected pathway of glutamate and urea cycle metabolism. *Front Neurol*. 2019;10:131.
35. Therrell BL, Currier R, Lapidus D, Grimm M, Cederbaum SD. Newborn screening for hyperargininemia due to arginase 1 deficiency. *Mol Genet Metab*. 2017;121(4):308-313.
36. Waisbren SE, Cuthbertson D, Burgard P, et al. Biochemical markers and neuropsychological functioning in distal urea cycle disorders. *J Inherit Metab Dis*. 2018;41(4):657-667.
37. Iyer RK, Yoo PK, Kern RM, et al. Mouse model for human arginase deficiency. *Mol Cell Biol*. 2002;22(13):4491-4498.
38. Lee EK, Hu C, Bhargava R, et al. Long-term survival of the juvenile lethal arginase-deficient mouse with AAV gene therapy. *Mol Ther*. 2012;20(10):1844-1851.
39. Lee EK, Hu C, Bhargava R, et al. AAV-based gene therapy prevents neuropathology and results in normal cognitive development in the hyperargininemic mouse. *Gene Ther*. 2013;20(8):785-796.
40. Kasten J, Hu C, Bhargava R, et al. Lethal phenotype in conditional late-onset arginase 1 deficiency in the mouse. *Mol Genet Metab*. 2013;110(3):222-230.
41. Liu XB, Haney JR, Cantero G, et al. Hepatic arginase deficiency fosters dysmyelination during postnatal CNS development. *JCI Insight*. 2019;4(17):e130260.
42. Deignan JL, Marescau B, Livesay JC, et al. Increased plasma and tissue guanidino compounds in a mouse model of hyperargininemia. *Mol Genet Metab*. 2008;93(2):172-178.
43. Sin YY, Ballantyne LL, Mukherjee K, et al. Inducible arginase 1 deficiency in mice leads to hyperargininemia and altered amino acid metabolism. *PLoS One*. 2013;8(11):e80001.
44. Richmond CR, Ballantyne LL, de Guzman AE, Nieman BJ, Funk CD, Ghasemlou N. Arginase-1 deficiency in neural cells does not contribute to neurodevelopment or functional outcomes after sciatic nerve injury. *Neurochem Int*. 2021;145:104984.

45. Cantero G, Liu XB, Mervis RF, et al. Rescue of the Functional Alterations of motor cortical circuits in arginase deficiency by neonatal gene therapy. *J Neurosci*. 2016;36(25):6680-6690.
46. Khoja S, Liu XB, Truong B, et al. Intermittent lipid nanoparticle mRNA administration prevents cortical dysmyelination associated with arginase deficiency. *Mol Ther Nucleic Acids*. 2022;28:859-874.
47. Cui B, Wei L, Zhu ZJ, Sun LY. Neurophysiological characteristics in argininemia: a case report. *Transl Pediatr*. 2021;10(7): 1947-1951.
48. Brockstedt M, Smit LM, de Grauw AJ, van der Klei-van Moorsel JM, Jakobs C. A new case of hyperargininaemia: neurological and biochemical findings prior to and during dietary treatment. *Eur J Pediatr*. 1990;149(5):341-343.
49. Oldham MS, VanMeter JW, Shattuck KF, Cederbaum SD, Gropman AL. Diffusion tensor imaging in arginase deficiency reveals damage to corticospinal tracts. *Pediatr Neurol*. 2010; 42(1):49-52.
50. De Deyn PP, Marescau B, Macdonald RL. Guanidino compounds that are increased in hyperargininemia inhibit GABA and glycine responses on mouse neurons in cell culture. *Epilepsy Res*. 1991;8(2):134-141.
51. Coutelier M, Goizet C, Durr A, et al. Alteration of ornithine metabolism leads to dominant and recessive hereditary spastic paraplegia. *Brain*. 2015;138(Pt 8):2191-2205.
52. Marco-Marin C, Escamilla-Honrubia JM, Llacer JL, Seri M, Panza E, Rubio V. Delta(1) -Pyrroline-5-carboxylate synthetase deficiency: an emergent multifaceted urea cycle-related disorder. *J Inherit Metab Dis*. 2020;43(4):657-670.
53. Olivieri G, Pro S, Diodato D, et al. Corticospinal tract damage in HHH syndrome: a metabolic cause of hereditary spastic paraplegia. *Orphanet J Rare Dis*. 2019;14(1):208.
54. Catsburg C, Anderson S, Upadhyaya N, Bechter M. Arginase 1 deficiency: using genetic databases as a tool to establish global prevalence. *Orphanet J Rare Dis*. 2022;17(1):94.
55. Terheggen HG, Schwenk A, Lowenthal A, van Sande M, Colombo JP. Hyperargininemia with arginase deficiency. A new familial metabolic disease. II. Biochemical studies. *Z Kinderheilkd*. 1970;107(4):313-323.
56. Terheggen HG, Schwenk A, Lowenthal A, van Sande M, Colombo JP. Hyperargininemia with arginase deficiency. A new familial metabolic disease. I. Clinical studies. *Z Kinderheilkd*. 1970;107(4):298-312.
57. Terheggen HG, Lowenthal A, Lavinha F, Colombo JP. Familial hyperargininaemia. *Arch Dis Child*. 1975;50(1):57-62.
58. Snyderman SE, Sansaricq C, Chen WJ, Norton PM, Phansalkar SV. Argininemia. *J Pediatr*. 1977;90(4):563-568.
59. Snyderman SE, Sansaricq C, Norton PM, Goldstein F. Argininemia treated from birth. *J Pediatr*. 1979;95(1):61-63.
60. Burrage LC, Sun Q, Elsea SH, et al. Human recombinant arginase enzyme reduces plasma arginine in mouse models of arginase deficiency. *Hum Mol Genet*. 2015;24(22):6417-6427.
61. Cederbaum SD, Moedjono SJ, Shaw KN, Carter M, Naylor E, Walzer M. Treatment of hyperargininaemia due to arginase deficiency with a chemically defined diet. *J Inherit Metab Dis*. 1982;5(2):95-99.
62. Garg D, Bijarnia-Mahay S, Elwadhi A, Ray S, Haberle J, Sharma S. Neurological deterioration in three siblings: exploring the Spectrum of Argininemia. *Indian J Pediatr*. 2021;88(3):266-268.
63. Lambert MA, Marescau B, Desjardins M, et al. Hyperargininemia: intellectual and motor improvement related to changes in biochemical data. *J Pediatr*. 1991;118(3):420-424.
64. Lee BH, Jin HY, Kim GH, Choi JH, Yoo HW. Argininemia presenting with progressive spastic diplegia. *Pediatr Neurol*. 2011; 44(3):218-220.
65. Schlune A, vom Dahl S, Häussinger D, Ensenauer R, Mayatepek E. Arginase 1 deficiency: long-term follow-up of the original patients. *Z Gastroenterol*. 2015;53(12):A3_8.
66. Burton B. Diagnosis and long-term treatment of arginase 1 deficiency (poster 62). *14th International Congress of Inborn Errors of Metabolism; 2021 November 21–23; Sydney, Australia*; 2021.
67. Marsden D, Eaton A. Management and progression of arginase 1 deficiency over 2 decades of follow-up (poster 118). *14th International Congress of Inborn Errors of Metabolism; 2021 November 21–23; Sydney, Australia*; 2021.
68. Sakiyama T, Nakabayashi H, Shimizu H, Kondo W, Kodama S, Kitagawa T. A successful trial of enzyme replacement therapy in a case of argininemia. *Tohoku J Exp Med*. 1984;142(3):239-248.
69. Huang Y, Sharma R, Feigenbaum A, et al. Arginine to ornithine ratio as a diagnostic marker in patients with positive newborn screening for hyperargininemia. *Mol Genet Metab Rep*. 2021;27:100735.
70. Diaz GA, Bechter MW, Sloan LS, Rao RM, Zori RT. 1 year data from first in human study of Pegzilarginase for the treatment of arginase 1 deficiency (ARG1-D). *Eur J Neurol*. 2020;27:1271.
71. Diaz GA, Schulze A, McNutt MC, et al. Clinical effect and safety profile of pegzilarginase in patients with arginase 1 deficiency. *J Inherit Metab Dis*. 2021;44(4):847-856.
72. Enns GM, Sanchez Russo R, Bradford E, et al. Pegzilarginase in arginase 1 deficiency: results of the PEACE pivotal phase 3 clinical trial (poster #30). *Mol Genet Metab*. 2022;135:269.
73. Truong B, Allegri G, Liu XB, et al. Lipid nanoparticle-targeted mRNA therapy as a treatment for the inherited metabolic liver disorder arginase deficiency. *Proc Natl Acad Sci USA*. 2019; 116(42):21150-21159.

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Arginine to ornithine ratio as a diagnostic marker in patients with positive newborn screening for hyperargininemia

Yue Huang [a,*], Rajesh Sharma [b], Annette Feigenbaum [c], Chung Lee [d], Inderneel Sahai [e], Rossana Sanchez Russo [f], Juanita Neira [f], Susan Sklower Brooks [g], Kelly E. Jackson [h], Derek Wong [a], Stephen Cederbaum [a,i], Felicitas L. Lacbawan [b], Charles M. Rowland [b], Pranoot Tanpaiboon [b,**], Denise Salazar [b]

[a] Division of Medical Genetics, Department of Pediatrics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA 90095, United States of America
[b] Biochemical Genetics, Advanced Diagnostics-Genetics, Genomics and R&D, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA 92675, United States of America
[c] Department of Pediatrics, University of California San Diego and Rady Children's Hospital, San Diego, CA 92161, United States of America
[d] Division of Medical Genetics, Lucile Packard Children's Hospital, Stanford School of Medicine, Stanford, CA 94305, United States of America
[e] New England Newborn Screening Program, University of Massachusetts, Worcester, MA 01605, United States of America
[f] Department of Human Genetics, Emory University, Atlanta, GA 30322, United States of America
[g] Division of Medical Genetics, Department of Pediatrics, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ 08901, United States of America
[h] Norton Children's Hospital and University of Louisville School of Medicine, Louisville, KY 40202, United States of America
[i] Departments of Psychiatry and Human Genetics and the Intellectual and Developmental Disabilities Research Center, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA 90095, United States of America

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ABSTRACT

Arginase deficiency is a rare inborn error of metabolism that interrupts the final step of the urea cycle. Untreated individuals often present with episodic hyperammonemia, developmental delay, cognitive impairment, and spasticity in early childhood. The newborn screening (NBS) algorithms for arginase deficiency vary between individual states in the US but often include hyperargininemia and elevated arginine to ornithine (Arg/Orn) ratio. Here, we report 14 arginase deficiency cases, including two patients with positive NBS for hyperargininemia in whom the diagnosis of arginase deficiency was delayed owing to normal or near normal plasma arginine levels on follow-up testing. To improve the detection capability for arginase deficiency, we evaluated plasma Arg/Orn ratio as a secondary diagnostic marker in positive NBS cases for hyperargininemia. We found that plasma Arg/Orn ratio combined with plasma arginine was a better marker than plasma arginine alone to differentiate patients with arginase deficiency from unaffected newborns. In fact, elevated plasma arginine in combination with an Arg/Orn ratio of $\geq$1.4 identified all 14 arginase deficiency cases. In addition, we examined the impact of age on plasma arginine and ornithine levels. Plasma arginine increased 0.94 μmol/L/day while ornithine was essentially unchanged in the first 31 days of life, which resulted in a similar increasing trend for the Arg/Orn ratio (0.01/day). This study demonstrated that plasma Arg/Orn ratio as a secondary diagnostic marker improved the detection capability for arginase deficiency in newborns with hyperargininemia, which will allow timely detection of arginase deficiency and hence initiation of treatment before developing symptoms.

Abbreviations: NBS, newborn screening; Arg, arginine; Orn, ornithine; Arg/Orn, arginine to ornithine ratio; DOL, day of life; DBS, dry bloodspot; ROC, receiver operating characteristic.

* Correspondence to: Y. Huang, Division of Medical Genetics, Department of Pediatrics, David Geffen School of Medicine, University of California, Los Angeles, 10833 Le Conte Ave, MDCC 12-334, Los Angeles, CA 90095, United States of America.

** Correspondence to: P. Tanpaiboon, Biochemical Genetics, Advanced Diagnostics-Genetics, Genomics and R&D, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA 92675, United States of America.

E-mail addresses: yuehuang@mednet.ucla.edu (Y. Huang), Pranoot.x.tanpaiboon@questdiagnostics.com (P. Tanpaiboon).

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1. Introduction

Arginase, sometimes referred to as arginase-1 (E.C·C 207800), is the final enzyme in the urea cycle, a six-enzyme, two-transporter pathway responsible for the detoxification of ammonia in the body and its conversion to urea [1]. The inherited deficiency of arginase has been shown to cause a unique syndrome, the hallmarks of which are high plasma arginine (Arg) levels, low to absent (<1% of normal) arginase activity in red blood cells, progressive spasticity, and slowing and eventual loss of cognitive milestones [2]. Current standard treatment for arginase deficiency includes lowering plasma arginine levels by dietary protein limitation, essential amino acid supplementation, and nitrogen scavengers which may have a favorable outcome both in preventing the progression of symptoms and partial reversal of some symptoms [2,3]. Moreover, enzyme replacement therapy and various DNA and RNA therapies are in clinical or preclinical development [4]. Thus, it is essential to identify patients presymptomatically and treat cases as early as possible. Most importantly, cases should not be missed. The advent of expanded newborn screening (NBS) has enabled the early diagnosis of arginase deficiency in many patients with the condition in countries with this program. Screening has allowed patients to be identified prior to the development of symptoms [5]. In the US, the U.S. Recommended Uniform Screening Panel included hyperargininemia as a secondary target for newborn screening. The primary marker for screening is the arginine level.

Arginine is a conditionally essential amino acid that plays an important quantitative and qualitative role in a number of biological pathways. It is a precursor for nitric oxide, polyamines, creatine and possibly glutamate and proline, especially in the postnatal period. The plasma arginine (Arg) level is influenced by dietary intake, endogenous synthesis both within and independent of the urea cycle, and protein turnover [6]. Given that plasma Arg level could be normal in newborns with arginase deficiency, it is necessary to utilize a secondary marker to improve test sensitivity for arginase deficiency. We have demonstrated that newborn screening can effectively and efficiently identify newborns with arginase deficiency. The use of the ratio of arginine to ornithine (Arg/Orn) or to the product of phenylalanine×leucine as secondary markers will ascertain virtually all affected individuals, with an acceptable false positive rate [5]. The challenge now is to be equally effective with clinical confirmation and treatment.

Here, we report two patients who were positive for arginase deficiency on newborn screening but who received delayed diagnoses because follow-up testing indicated normal or near normal plasma arginine levels. By incorporating the plasma Arg/Orn ratio as a secondary diagnostic marker, these two patients would have received diagnoses earlier, and the symptoms of arginase deficiency in one patient could have been prevented or lessened. An algorithm was developed using the data from 12 other patients who received a diagnosis of arginase deficiency during the newborn period and the unselected newborn population. We also showed that plasma arginine (Arg) and ornithine (Orn) levels, and the Arg/Orn ratio were relatively stable over the first month of life, obviating the need to stratify the control data.

2. Methods

2.1. Study design

In this study, we aimed to evaluate the plasma Arg/Orn ratio as a secondary diagnostic marker in newborns with positive NBS for hyperargininemia. A study request email was sent to Metab-1, an electronic mailing list for professionals in the field of inborn errors of metabolism. Cases with a confirmed diagnosis of arginase deficiency by molecular analysis, arginase activity assay in red blood cells or both were collected from respondents. The plasma Arg, Orn, and Arg/Orn ratio from these cases were analyzed and compared to those in newborns without arginase deficiency in the Quest Diagnostics database. In addition, we evaluated the correlation between age in days and plasma amino acid levels for Arg, Orn, and the Arg/Orn ratio in the unselected newborn population. The institutional review board at UCLA reviewed the study protocol and granted permission for this study.

2.2. Data collection

Patient data and demographics were collected from care providers with all protected health information removed. The results of NBS and plasma Arg, Orn, and Arg/Orn ratio levels from 14 individuals with arginase deficiency were collected for this study. The plasma Arg and Orn levels from individuals without a confirmed diagnosis of arginase deficiency between 0 and 31 days of life were acquired from the Quest Diagnostics (San Juan Capistrano, CA USA) Biochemical Genetics Laboratory database, which included 6587 samples over 6 years spanning January 2013 to December 2019.

2.3. Data analysis

The plasma Arg, Orn, and Arg/Orn levels from the 14 cases with arginase deficiency were compared to the distributions from newborns without arginase deficiency. The 97.5th percentile of this population was determined and McNemar's test was used to compare the number of cases below the 97.5th percentile between plasma arginine and Arg/Orn ratio [7]. The area under the receiver operating characteristic curves (AUC) formed using Arg and Arg/Orn ratio to discriminate between those with and without arginase deficiency were also compared by Delong's test to compare two correlated ROC curves [8]. The relationships between age and plasma Arg, Orn, and Arg/orn ratio were analyzed by linear regression. The p value <0.05 was considered statistically significant. Analysis was performed using R software version 3.4.3 [9].

3. Results

3.1. Delayed diagnosis of arginase deficiency owing to normal plasma arginine level

Patient 1 was a 4-year-old male who was born at full term following an uncomplicated pregnancy. An NBS sample collected at 17 h of age was positive for hyperargininemia (101 μmol/L, cutoff <50 μmol/L) and elevated Arg/Orn ratio (10.1, cutoff <1.4). Confirmatory tests including plasma amino acids, ammonia, and comprehensive metabolic panel were sent on day of life (DOL) 5. The plasma Arg level was within the normal range (134 μmol/L, normal range 14–135 μmol/L). He had a normal history and examination at the follow-up clinic visit. The patient was discharged with a false-positive newborn screening result for hyperargininemia. After a period of normal development, the patient developed bilateral lower extremity spasticity at 18 months of age. Plasma Arg was markedly elevated at 587 μmol/L (normal range 30–147 μmol/L). Results of an RBC arginase enzyme activity assay confirmed arginase deficiency with undetectable enzyme activity. Since the diagnosis, the patient has been on protein restriction with nonessential amino acid-free formula and has shown improvement in development and spasticity.

Patient 2 was a 4-year-old male who was born at 38 weeks following an uncomplicated pregnancy. NBS performed at 25 h of life showed elevated arginine (68 μmol/L, cut-off <50 μmol/L) and Arg/Orn ratio 4.4 (cut-off <1.4). Plasma amino acid performed on DOL5 showed mildly elevated arginine (150 μmol/L, normal range 14–135 μmol/L) with normal ammonia level. Repeated plasma amino acid levels were mildly elevated for arginine. The child continued to have normal growth and development. Subsequently, RBC arginase enzyme activity assay and plasma amino acid were performed simultaneously when the patient was 7-month-old. Plasma arginine level was normal (113 μmol/L, normal range 12–133 μmol/L) while RBC arginase enzyme activity was

undetectable, confirming arginase deficiency. The patient was followed in a clinic monthly. Plasma amino acids were also monitored monthly, and treatment was initiated following an arginine level of 402 μmol/L (normal range 30–147 μmol/L) at 9 months of age. With protein restriction and glycerol phenylbutyrate (Ravicti®) treatment, he continues to have a normal neurologic exam, though is noted for speech delay.

3.2. Arginine to ornithine ratio as a secondary marker for arginase deficiency

Given that plasma Arg levels can be normal in patients with arginase deficiency during the neonatal period, it is clearly necessary to add a secondary marker to improve the diagnostic sensitivity in NBS cases positive for hyperargininemia and arginase deficiency. The Arg/Orn ratio and other ratios have been popular second-tier discriminators used in NBS to reduce the number of false positive cases. Therefore, we collected the plasma Arg, Orn, and Arg/Orn ratio data on their initial NBS follow-up from 14 arginase deficiency patients identified by screening in the newborn period (Table 1). We found that all cases of arginase deficiency had an Arg/Orn ratio equal to or greater than 1.7 (range 1.7–16.0). Interestingly, the two cases with delayed diagnoses have the lowest plasma arginine levels as well as the lowest Arg/Orn ratios of the group. To compare the validity of using the plasma Arg level and the Arg/Orn ratio to discriminate true positives from false positive cases, we evaluated the distribution of Arg and Arg/Orn ratio in neonates with and without arginase deficiency. Data from the unselected newborn population revealed plasma Arg levels ranging from 10 to 191 μmol/L (2.5–97.5%tile), Orn levels from 27 to 312 μmol/L (2.5–97.5% tile), and Arg/Orn ratios from 0.1–1.6 (2.5–97.5%tile). Four of 14 (29%) of patients with arginase deficiency had an initial plasma Arg level (range 134–192 μmol/L) below or slightly above the 97.5th percentile (191 μmol/L) in unselected newborn population, while all 4 patients had an Arg/Orn ratio below the 97.5th percentile (ratio 1.6), which was a statistically significant difference ($p = 0.046$, Fig. 1). In addition, discrimination of newborns with arginase deficiency and unselected newborn population by ROC curve analysis was better with Arg/Orn ratio than with arginine alone (AUC = 0.998 vs. 0.980, respectively; p-value = 0.005).

3.3. Trend of plasma arginine and ornithine levels in neonatal period

A previous study suggests that plasma Arg levels change with age in children [10], which could have an impact on the diagnosis of arginase deficiency. To examine the age-related change in plasma Arg levels, we analyzed plasma Arg levels of 6587 unselected newborn population (0–31 days) obtained from Quest Diagnostics database (Fig. 2). We found that plasma Arg levels increased with age, averaging 0.94 μmol/L per day in the first 31 days of life. Plasma Orn levels, in contrast, were essentially unchanged during the neonatal period (−0.02 μmol/L per day). As a result, the Arg/Orn ratio showed a similar trend of increasing with age (0.01 per day) as the Arg alone.

4. Discussion

Arginase deficiency is a rare urea cycle disorder with an estimated minimal incidence of 1 in 1.1 million newborns in the United States [5]. It is a treatable disorder for which newborn screening and early diagnosis are now recognized as a high priority. In our previous study published in 2017 [5], we demonstrated a NBS algorithm for arginase deficiency, in which Arg in combination with Arg/Orn ratio can identify all affected individuals with a relatively low false-positive rate. To date, hyperargininemia in combination with a secondary discriminator such as Arg/Orn ratio is the most commonly used algorithm that has identified virtually all arginase deficiency newborns in screened patients [5]. However, our data showed the plasma arginine levels in newborns with arginase deficiency have significant overlap with that from the newborns without arginase deficiency. This is an important challenge in the diagnosis of arginase deficiency following a positive NBS and has led to the delayed diagnosis in the two patients reported in this study. The delayed diagnosis resulted in developmental delay, cognitive impairment, and spasticity in one patient, which could have been prevented or lessened by dietary modification if the NBS findings had been confirmed in the neonatal period.

The Arg/Orn ratio has been widely used as a second-tier discriminator in NBS for hyperargininemia and has been very successful in discriminating the affected from the unaffected in NBS. The NBS cutoff for Arg/Orn ratio ranges from 0.45 to 1.5 between the states in the US [5]. Interestingly, the two cases with delayed diagnosis of arginase deficiency in our study have the lowest plasma arginine levels (134 and 150 μmol/L) as well as the lowest plasma Arg/Orn ratios (2.2 and 1.7) on the initial NBS follow-up when compared to other arginase deficiency cases (2.9 to 16.0). At least for the small set of case study, the findings demonstrated that the Arg/Orn ratio could provide additional discriminating power to distinguish mild Arginase deficiency cases from normal newborns.

All 14 cases of arginase deficiency would be identified if an Arg/Orn ratio ≥ 1.7 was used as a secondary diagnostic marker. Since the number of newborns with arginase deficiency included in this study is limited, it is possible to have a case with an Arg/Orn ratio lower than 1.7, although it is unlikely to be much lower based on our experience in NBS. We suggest continued use of the NBS algorithm for arginase deficiency outlined in the paper by Therrell et al. [5]. With this approach, screen-positive patients will have a high probability of being true positive for arginase deficiency. In the follow-up confirmatory test, we recommend

Table 1
Plasma and NBS Arg, Orn, and Arg/Orn ratio in patients with arginase deficiency.

	Plasma					NBS		
Patient	Arginine (μmol/L)	Ornithine (μmol/L)	Arg/Orn (μmol/L)	Range (μmol/L)	DOL	Arginine (μmol/L)	Ornithine (μmol/L)	Arg/Orn (μmol/L)
1[a]	134	60	2.2	14-135	5	101	10	10.1
2[a]	150	86	1.7	14-135	5	68	16	4.3
3	263	91	2.9	14–135	15	188	46	4.1
4	192	60	3.2	14–135	16	138	26	5.3
5	268	67	4	14–135	12	351	N/A	N/A
6	179	43	4.2	6–140	2	100	29	3.4
7	233	51	4.6	N/A	N/A	261	N/A	N/A
8	299	63	4.7	6–140	5	177	22	8
9	204	42	4.9	15–160	6	248	17	15
10	282	51	5.5	N/A	N/A	233	N/A	N/A
11	881	110	8	N/A	3	377	16	22.9
12	259	32	8	N/A	6	137	9	16.1
13	528	56	9.4	20–148	7	242	N/A	N/A
14	930	58	16	14–135	7	218	N/A	N/A

[a] Cases with delayed diagnosis of arginase deficiency.

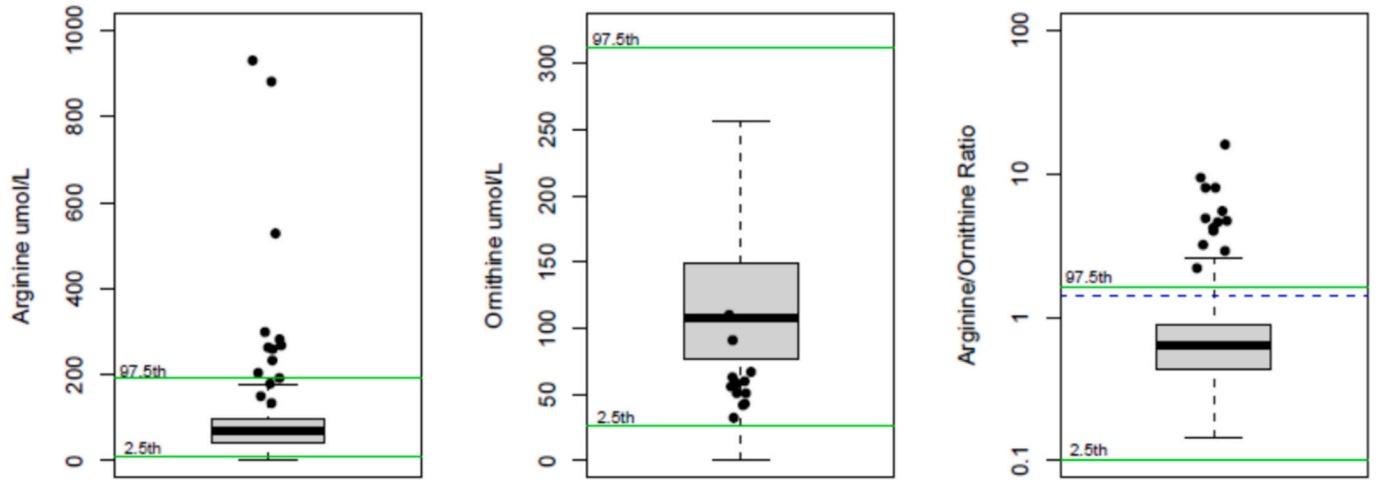

Fig. 1. The distribution of Arg, Orn, and Arg/Orn ratio in newborns.
The blue dotted line represents an Arg/Orn ratio of 1.4. The distribution of unselected newborns is represented by the box and whiskers while the points represent the cases with arginine deficiency.

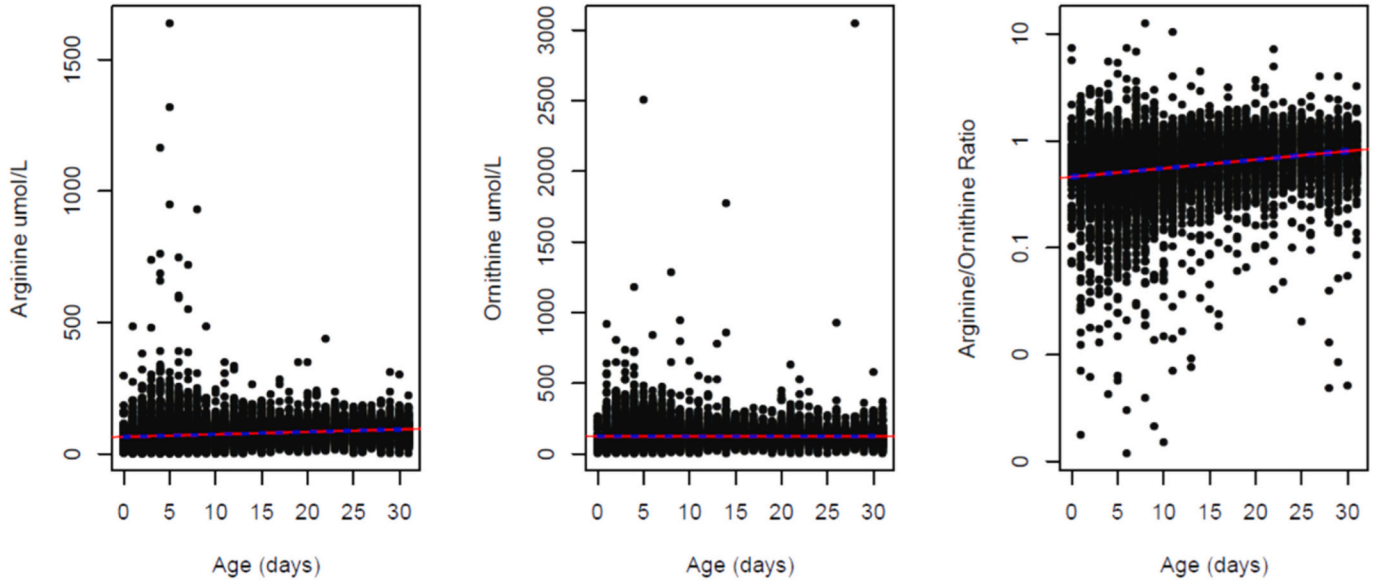

Fig. 2. The distribution of Arg, Orn, and Arg/Orn ratio during the neonatal period.
The colored line represents the trend of respective amino acids over time.

using the plasma Arg/Orn ratio $\geq$ 1.4 as the cutoff to confirm the diagnosis of arginase deficiency, which is approximately the 96th percentile among unselected population (Fig. 3). A ratio of $\geq$1.4 is also the cutoff for the DBS Arg/Orn ratio used in the California NBS program [5]. However, no referred patient should be discharged from care without a normal RBC arginase activity level or absence of *ARG1* gene mutation, because of the potential overlap with normal values and the high prior probability from the NBS algorithm. Conversely, an Arg/Orn ratio above 1.4 alone is not a valid criterion for suspecting arginase deficiency in patients who had a negative NBS or a normal plasma arginine level.

In our efforts to determine the appropriate approach to ensure accurate confirmation of arginase deficiency following a positive screening, we also established the normal values of Arg and Orn in the newborn period in a large dataset of more than 6000 newborns. The analysis demonstrated that the arginine and Arg/Orn values change slightly during the first 31 days of life whereas no significant change of ornithine values occurs, suggesting an age-related adjustment of reference range is not necessary for the neonatal period.

Author contributions

Y.H., R.S., A.F., D.W., S.C., F.L.L., P.T., D·S. were involved in conception, study design, data collection, interpretation, and manuscript preparation. C.L., I.S., R.S., J.N., S.S.B., K.J. were involved in data collection and manuscript review. C.M.R. provided statistical analysis. Y.H. and P.T. take responsibility for the collection of data, the analyses, interpretation, and publication. All authors have given approval for publication of this manuscript.

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None.

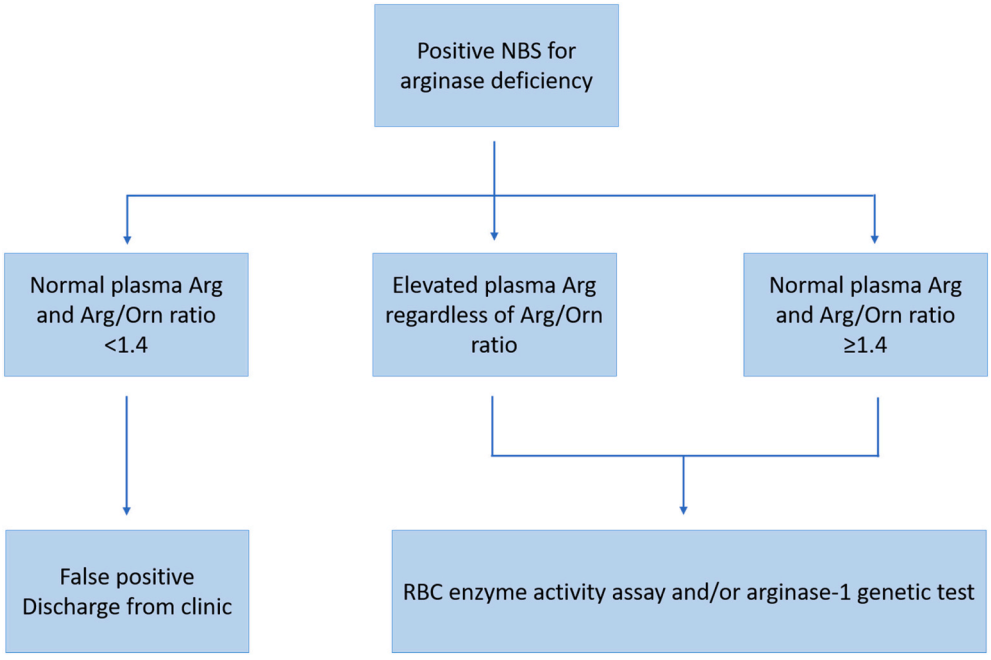

Fig. 3. Proposed algorithm for arginase deficiency workup following a positive NBS.

Ethics statement

This study involved retrospective analysis of existing patient data that were collected without patient identifiers. This study was reviewed by the institutional review board at UCLA with permission to proceed granted.

Declaration of Competing Interest

P.T, F.L.L, D.S, R.S, and C.M.R are employee of Quest Diagnostics. Other authors declare no potential conflicts of interests. None of the authors have financial gain or loss from the results of this study.

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References

[1] A. Schlune, S. Vom Dahl, D. Häussinger, R. Ensenauer, E. Mayatepek, Hyperargininemia due to arginase I deficiency: the original patients and their natural history, and a review of the literature, Amino Acids 47 (9) (2015) 1751–1762.

[2] A. Sun, E.A. Crombez, D. Wong, Arginase deficiency, in: M.P. Adam, H.H. Ardinger, R.A. Pagon (Eds.), GeneReviews(®), University of Washington, Seattle, 1993. Copyright © 1993–2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

[3] S.D. Cederbaum, S.J. Moedjono, K.N. Shaw, M. Carter, E. Naylor, M. Walzer, Treatment of hyperargininaemia due to arginase deficiency with a chemically defined diet, J. Inherit. Metab. Dis. 5 (2) (1982) 95–99.

[4] B. Truong, G. Allegri, X.B. Liu, et al., Lipid nanoparticle-targeted mRNA therapy as a treatment for the inherited metabolic liver disorder arginase deficiency, Proc. Natl. Acad. Sci. U. S. A. 116 (42) (2019) 21150–21159.

[5] B.L. Therrell, R. Currier, D. Lapidus, M. Grimm, S.D. Cederbaum, Newborn screening for hyperargininemia due to arginase 1 deficiency, Mol. Genet. Metab. 121 (4) (2017) 308–313.

[6] S.M. Morris Jr., Arginine metabolism: boundaries of our knowledge, J. Nutr. 137 (6) (2007) 1602S–1609S.

[7] A. Agresti, Categorical Data Analysis, Wiley, 1990.

[8] E.R. DeLong, D.M. DeLong, D.L. Clarke-Pearson, Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach, Biometrics. 44 (3) (1988) 837–845.

[9] R.C. Team, R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, 2017.

[10] F. Hammarqvist, G. Angsten, S. Meurling, K. Andersson, J. Wernerman, Age-related changes of muscle and plasma amino acids in healthy children, Amino Acids 39 (2) (2010) 359–366.

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Newborn screening for hyperargininemia due to arginase 1 deficiency

Bradford L. Therrell [a,*], Robert Currier [b], David Lapidus [c], Meredith Grimm [d], Stephen D. Cederbaum [e]

[a] National Newborn Screening and Global Resource Center, Austin, TX, Department of Pediatrics, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States
[b] Genetic Disease Screening Program, California Department of Public Heath, Richmond, CA, United States
[c] LapidusData Inc., Oklahoma City, OK, United States
[d] Aeglea Biotherapeutics, Austin, TX, United States
[e] Departments of Psychiatry, Pediatrics and Human Genetics, The Intellectual Development and Disabilities Research Center, University of California, Los Angeles, CA, United States

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ABSTRACT

Hyperargininemia caused by Arginase 1 deficiency is a rare disorder of the urea cycle that can be diagnosed by elevation of arginine in newborn screening blood spots when analyzed by tandem mass spectrometry. Hyperargininemia is currently included as a secondary target on the U.S. Recommended Uniform Screening Panel, which directly influences state-based newborn screening. Because of the apparent low disease frequency and lack of case detection and treatment data, detailed attention has not been given to a model newborn screening algorithm including appropriate analytical cutoff values for disease indicators. In this paper we assess the frequency of hyperargininemia in the U.S. identified by newborn screening to date and document the current status and variability of hyperargininemia newborn screening across U.S. newborn screening programs. We also review other data that support improved screening efficacy by utilizing the arginine/ornithine ratio and other amino acid ratios as discriminators in the screening algorithm. Analysis of archived California screening data showed that an arginine cutoff of 50 μM combined with an arginine/ornithine ratio of 1.4 would have resulted in a recall rate of 0.01%. Using an arginine cutoff of 60 μM and an arginine/(phenylalanine x leucine) ratio of 1.4, reportedly used in one screening program, or the R4S Tool Runner, would have resulted in a recall rate of <0.005%. All 9 diagnosed patients would have been found for either protocol. Thus, use of appropriate ratios as part of the screening algorithm has the potential to increase both screening sensitivity and specificity. Improved newborn screening effectiveness should lead to better case detection and more rapid treatment to lower plasma arginine levels hence improving long term outcome of individuals with hyperargininemia.

1. Introduction

Arginase 1 is the 6th and final enzyme and one of 8 proteins that are commonly thought of as comprising the urea cycle (see Fig. 1). Its products are urea and ornithine, the latter recycled into the nitrogen elimination pathway and the former excreted in the urine Deficiency of arginase 1 resulting in hyperargininemia is one of the least frequent disorders of the urea cycle and its more indolent, late-onset presentation usually leads to its diagnosis only after irreversible neurological symptoms have occurred. These symptoms initially include loss of intellectual milestones, spasticity and mild liver dysfunction. Later, more severe liver abnormalities such as liver fibrosis, cirrhosis and even hepatocellular carcinoma may occur [1,2]. A strict dietary and pharmacologic regimen has been shown to reduce the plasma arginine level to normal or near normal levels [3]. Even in the presence of irreversible neurological damage, improvement in neurological function can occur. The few older patients treated from birth were much less severely affected than their symptomatically diagnosed family members despite sub-optimal adherence to the treatment regimen [4].

There is limited information regarding hyperargininemia incidence or prevalence. Reports of incidence vary by an order of magnitude: 0.5 to 5.0 per million [5,6]. A relatively large U.S. study estimated 1.1 cases per million births [7], but it used an indirect methodology that introduces uncertainty about the precision of the result.

The advent of expanded newborn bloodspot screening (NBS) for amino acid disorders using tandem mass spectrometry (MS/MS) includes the possibility to determine arginine levels, thus allowing for the detection of increased risk for hyperargininemia at or near birth. The overlap between normal arginine levels in affected and unaffected newborns is sufficiently great so that determining optimal arginine cutoff levels in NBS is problematic. The goal of laboratory algorithms used in NBS is to minimize or eliminate late diagnosed (missed) cases (false

Abbreviations: ACHDNC, Advisory Committee on Heritable Disorders in Newborns and Children; MS/MS, tandem mass spectrometry; NBS, newborn bloodspot screening; NCHS, National Center for Health Statistics; R4S, Region 4 Stork; SACHDNC, Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children; RUSP, Recommended Uniform [Newborn] Screening Panel.

* Corresponding author at: National Newborn Screening and Global Resource Center (NNSGRC), 3907 Galacia Dr, Austin, TX 78759, United States.
E-mail address: threrrell@uthscsa.edu (B.L. Therrell).

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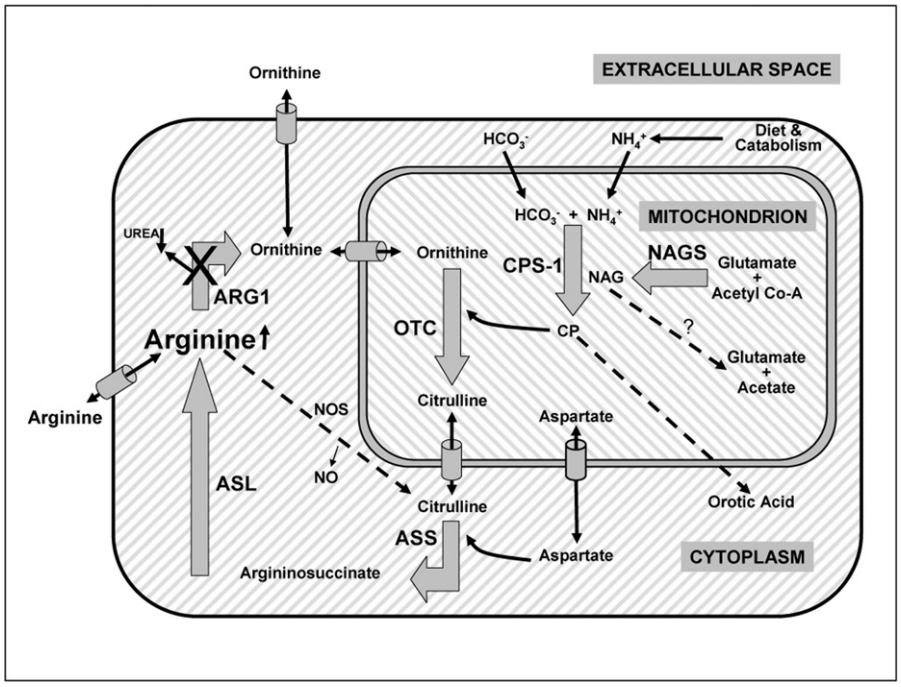

Fig. 1. The Complete Urea Cycle: Focusing on the left side of the figure, the consequences of Arg1 deficiency are illustrated. Arginine accumulates both intra- and extracellularly and urea production is diminished. Ornithine production should be diminished, but neither this nor lowered ornithine in man has been formally demonstrated.

negatives) while reducing unnecessary follow-up (false positives). Because MS/MS simultaneously detects many amino acids, the possibility for assessing various amino acid ratios as a second-tier screening strategy exists. Such ratios have been found useful in improving screening algorithm efficiency for some screened conditions [8,9], including use of the arginine to ornithine ratio (Arg/Orn) for hyperargininemia [10]. The utilization of other individual amino acid ratios [e.g. Arginine to Alanine (Arg/Ala), Arginine to Phenylalanine (Arg/Phe), Citrulline to Arginine (Cit/Arg), etc.] are also possible and provide additional variables for consideration in establishing the most effective screening algorithm.

While NBS is widely acknowledged as a critical public health prevention strategy [11], currently capable of identifying in excess of 50 different congenital inherited disorders including hyperargininemia, a national newborn screening requirement does not exist in the U.S. Instead NBS is state-based with national recommendations provided by the Secretary of Health and Human Services in consultation with an Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC; previously called the SACHDNC) tasked with providing real time analysis of the national screening situation. In 2005, the SACHDNC accepted a report from the American College of Medical Genetics and Genomics (ACMGG), which included a Recommended Uniform Screening Panel (RUSP) to be considered for implementation by each state screening program [12,13], and recommended its implementation by the Secretary. The RUSP was originally developed using an empirical scoring system and included both 'core' and 'secondary' conditions depending on treatability, screening test availability, family benefits, and other relevant information available at the time [12]. The Secretary accepted the SACHDNC recommendation and the RUSP now strongly influences the conditions included in state screening mandates, particularly the core conditions. A formal nomination and evidence review process has since evolved for nominating and adding conditions to the RUSP [14,15]. Part of this process involves assessment of public health impact and readiness to include the proposed condition.

We report here a basic assessment of public health readiness useful in assessing whether hyperargininemia should be adopted as a core condition on the RUSP. Since hyperargininemia is already included as a RUSP secondary condition, our primary goal was to determine the degree of screening homogeneity across state NBS programs, to approximate a national incidence of the disease from NBS findings, and to consider screening algorithm alternatives for program improvement. Specifically, we surveyed state NBS programs to determine whether they screened for hyperargininemia and if so, whether it was included in their mandated screening panel, what laboratory screening results triggered follow-up actions, whether (and which) second-tier ratio calculations were part of screening algorithm, and the number of cases of hyperargininemia confirmed since their screening program began. Further, we reviewed possible alternative screening laboratory algorithms for possible impact in improving overall NBS effectiveness using archived laboratory data and diagnosed case information from the California NBS program.

2. Methods

In mid-November 2015, a short questionnaire was emailed to state newborn screening laboratory and/or follow-up personnel identified as primary program contact persons (see Acknowledgments). The questions sought to assess the extent to which U.S. newborn screening programs include arginase 1 deficiency in their newborn screening panel and related screening information. Included were questions regarding whether arginase 1 deficiency screening was formally a part of the screening mandate, what and how laboratory data were assessed, follow-up processes, and case detection information. After an initial 2-week response period, a follow-up email was sent to programs that had not responded. Additional email and telephone follow-up resulted in completed surveys for all 51 state programs (50 states and the District of Columbia). All data were reviewed and summarized, and in mid-2016 a table containing the summarized data was circulated to all respondents for approval. Corrections and updates were made as necessary and the case data were updated through the end of 2015.

In addition to reviewing the relevant literature, we assessed the available data from U.S. NBS programs on confirmed cases and screened newborns as part of an ongoing effort to better define U.S. incidence. Since many U.S. NBS programs do not link NBS data with birth records, reliable national data giving unduplicated counts of births screened are not available. Instead, we used national data on births by place of occurrence available from the Centers for Disease Control and Prevention's

National Center for Health Statistics (NCHS). We assumed complete birth coverage by a screening program in order to provide consistency in evaluating the populations for which NBS was available within specific jurisdictions. In cases where hyperargininemia screening began on a date other than the first day of the year, we approximated the number of babies screened by assuming an even distribution of births daily throughout the year and calculated the number of births from the first day a state's hyperargininemia screening effort began.

To evaluate the validity of the various hyperargininemia screening algorithms reported by state NBS programs (i.e. Arg cutoffs and second-tier amino acid ratios), we analyzed newborn screening data from California on newborns screened from July 2005 through December 2015 ($n = 5.4$ M). Preliminary to a broader data analysis we first evaluated archived laboratory data for the 9 confirmed cases of hyperargininemia diagnosed from newborn screening during this time period in order to determine the detection capability of the screening algorithms. Specifically, we used ratio data for six different amino acids (Arg, Cit, Orn, Ala, Phe, Leu) in combination with various Arg cutoff levels. For an additional comparison, we used the analysis tool (Tool Runner) available as part of the international MS/MS database, Region 4 Stork (R4S). Further, we approximated the impact on follow-up that might result if various combinations of Arg cutoffs, Arg cutoffs in combination with various amino acid ratio cutoffs, and the R4S Tool Runner were used by applying each combination to the 2015 California newborn screening data ($n = 486{,}591$).

3. Results

Of the 51 U.S. jurisdictions surveyed (Table 1), 33 reported that hyperargininemia is one of the conditions for which all newborns are required to be screened, with the earliest screening reported in Massachusetts in 1999. Of the 18 other jurisdictions, an additional 5 reported that hyperargininemia would likely be detected by the screening algorithm currently in use for other metabolic conditions, and screen positive cases would be followed up accordingly, even though screening is not required. Thirteen state screening programs reported no screening for hyperargininemia (Alabama, Arizona, Arkansas, Florida, Kansas, Maryland, Montana, Nebraska, South Carolina, Virginia, Washington, West Virginia and Wisconsin). One jurisdiction indicated that arginine levels were not officially reported as part of the program, even though they were observable, since hyperargininemia was not included in the program's current screening mandate.

Between 1999, when screening for hyperargininemia first began, and the end of 2015, slightly over 29 million newborns were born in U.S. jurisdictions that included NBS for hyperargininemia with 26 confirmed cases identified. Assuming that all of eligible newborns (29,107,011) were screened, the prevalence of hyperargininemia across U.S. jurisdictions screening during this period was approximately 1:1,119,500 (95% confidence interval 1:640,392 to 1:1,763,942). Since we know that not all eligible newborns were screened or screened appropriately, the estimate represents the minimum prevalence.

While most survey respondents noted that an elevation of Arg was the trigger leading to further investigation of the possibility of hyperargininemia, the analytical cutoffs requiring additional follow-up (screen positive) varied widely. Multiple cutoffs related to age at time of screening and to birth weights were reported by some programs. Most reported using two Arg cutoff levels leading to two different follow-up pathways, repeat filter paper screening or referral for clinical evaluation. A few programs reported that elevated Arg values above a single cutoff simply resulted in clinical referral (i.e. a repeat filter paper was not part of the general follow-up protocol, although a repeat specimen after clinical referral might occur). The range of Arg values considered actionable (requiring additional follow-up of any type) varied from 20 μmol/L to 130 μmol/L. Some programs chose lower cutoffs for Arg initially and used a second-tier ratio or combination of ratios of other amino acids to ultimately reduce the number of patients recalled. Arg/Orn was the most popular second-tier discriminator with cutoffs for actionable levels varying from 0.45 to 1.5. Other ratios in use included Arg/Ala, Arg/Phe, Cit/Arg and Arg/[Phe × Leu].

Using archived analytical MS/MS data from confirmed cases in California, we constructed a table (Table 2) to illustrate the results that would be obtained using the various reported screening protocols. As a point of reference, 5.4 million specimens were screened during this time period and 138 were originally found to have both Arg ≥ 50 μmol/L and Arg/Orn ≥ 1.40, the criteria for screening positivity during this time period. Clinical evaluation resulted in the 9 cases referenced.

In order to assess the potential impact of some of these protocols on screening follow-up, we developed a table (Table 3) to show the percentage of newborns that would require additional follow-up based a proposed protocol using 2015 California NBS data. We chose consider Arg alone, Arg in combination with Arg/Orn, and Arg in combination with Arg/[Phe × Leu]. We also included the R4S Tool Runner multivariate/metabolic profile analysis [8,9]. While the California hyperargininemia protocol resulted in 0.01% follow-up, two other protocols (utilization Arg and Arg/[Phe × Leu] and R4S Tool Runner appeared to be at least as good.

4. Discussion

Ideally, newborn screening for a particular disorder would be uniform between jurisdictions and have a very low false negative rate and a low recall (false positive) rate. Screening algorithms would be based on sufficient case detection evidence to validate the algorithm with modification as new data accumulates. It is clear from the information presented here that NBS for hyperargininemia in the U.S. is far from ideal with significant variability between state screening programs. Variations appear to be based on anecdotal findings without a solid scientific basis (Table 1). Reliable national NBS incidence data beyond that reported here do not exist.

There are essentially two screening strategies to minimize the number of newborns recalled for additional testing without missing cases for most screening disorders. For hyperargininemia, one strategy uses Arg alone as the indicator of possible disease and the other uses Arg in combination with a ratio (or ratios) of related amino acids. In the first method (Arg alone), in order to eliminate missing cases, relatively large numbers of patients must be recalled to further assess other laboratory and clinical information before confirming the presence of disease (Table 3). Reduced recall can be accomplished by raising the cutoff value thus increasing the possibility for missing cases. The second strategy reduces the numbers recalled through a filtering process. A lower Arg cutoff can be used to initially create a larger pool of potentially abnormal patients (thus lowering the chances of missing a case) whose numbers are then reduced by examining laboratory values for other analytes, assessed as various amino acid ratios. The difficulty comes in determining which ratios are reliable discriminators of disease.

For either of these screening strategies, large numbers of screens are required in order to estimate the sensitivity and specificity of the screening algorithm. Screening algorithms for NBS can be developed using multivariate pattern recognition software and metabolic profile scoring along with large datasets such as the international R4S [16]. Additionally, tools such as the R4S Tool Runner have been created to provide further assistance in assessing various ratios as their value as secondary discriminators for various diseases [8,9].

While most U.S. NBS programs are aware of and participate in contributing to the R4S database, our state survey data indicated that its use in developing state NBS algorithms was minimal and only one state program reported routinely using Tool Runner as a NBS aid. In order to consider the possible effectiveness of the various hyperargininemia NBS protocols reported, we retrospectively compared various algorithms using California NBS data. In addition to the routine Arg/Orn ratio used in California and many other programs, the ratio of Arg/(Leu × Phe) is used in the New England Regional Program.

Table 1
Data from US newborn screening programs screening for hyperargininemia (arginase 1 deficiency).

State	Start Date	Cases	Screenable births	Screening result requiring follow-up screen	Screening result leading to clinical referral
Alaska[a]	10/01/03	0	135,112	110 μmol/L ≤ Arg < 180 μmol/L	Arg ≥ 180 μmol/L
California	07/07/05	9	5,499,189	All abnormal findings referred for clinical evaluation	Arg ≥ 50 μmol/L; Arg/Orn ≥ 1.4
Colorado[a]	07/01/06	0	642,633	Arg ≥ 100 μmol/L	Two successive findings of Arg ≥ 100 μmol/L
Connecticut	01/01/05	1	432,966	Arg ≥ 55 μmol/L (age < 10 days); ratios assessed: Arg/Ala; Arg/Orn; Arg/Phe; Cit/Arg [see footnote [b]]	See footnote [b].
District of Columbia	07/01/00[c]	0	224,217	125 μmol/L ≤ Arg < 270 μmol/L	Arg ≥ 270 μmol/L
Delaware[a]	01/01/03	0	154,811	Arg ≥ 33 μmol/L (age < 7 days)	Arg ≥ 43 μmol/L (Age < 7 days); Arg ≥ 58 μmol/L (age ≥ 7 days)
Georgia	01/01/07[d]	0	1,238,019	Arg ≥ 120 μmol/L (wt < 2500 g); Arg ≥ 105 μmol/L (wt ≥ 2500 g)	Clinical referral decided by follow-up contractor on basis of results
Hawaii	09/01/03	0	231,769	110 μmol/L ≤ Arg < 180 μmol/L	Arg ≥ 180 μmol/L
Idaho[a]	10/01/02	1(Prenatal)	301,083	110 μmol/L ≤ Arg < 180 μmol/L	Arg ≥ 180 μmol/L
Illinois	07/01/02	1	2,255,001	30 μmol/L ≤ Arg < 50 μmol/L (Arg/Orn ≥ 0.45) 40 μmol/L ≤ Arg < 50 μmol/L (Arg/Orn not elevated)	Arg ≥ 50 μmol/L
Indiana	05/01/04	0	1,010,397	100 μmol/L ≤ Arg < 180 μmol/L; Assessing Arg/Orn, Arg/Phe	Arg ≥ 180 μmol/L
Iowa	08/01/03	0	488,156	Any abnormal findings referred for clinical evaluation	Arg > 35 μmol/L; Arg/Orn > 0.6 (previously 1.0)
Kentucky	12/05/05	0	551,556	Any abnormal findings referred for clinical evaluation	Arg > 55 μmol/L (not on TPN)
Louisiana	11/01/04	0	710,746	Any abnormal findings referred for clinical evaluation	Arg > 120 μmol/L and Arg/Orn >1
Maine	07/01/01	0	191,996	60 μmol/L < Arg <132 μmol/L and Arg/[Leu × Phe] > 0.006	See footnote [e].
Massachusetts	02/01/99	1	1,232,171	60 μmol/L < Arg <132 μmol/L and Arg/[Leu × Phe] > 0.006	See footnote [e].
Michigan	04/01/05	1	1,259,984	Arg ≥ 50 μmol/L; Arg/Orn ≥ 0.8 (age < 180 h) Arg ≥ 90 μmol/L; Arg/Orn ≥1 (180 h ≤ age < 1 yr) If on TPN, inconclusive, request repeat	Arg ≥ 90 μmol/L; Arg/Orn ≥ 1.5(age < 180 h) Arg ≥ 110 μmol/L; Arg/Orn ≥ 1 (180 h ≤ age < 1 yr) If on TPN, inconclusive, request repeat
Minnesota	05/21/01	0	1,021,894	125 μmol/L ≤ Arg < 270 μmol/L	Arg ≥ 270 μmol/L
Mississippi	06/01/03	0	512,771	125 μmol/L ≤ Arg < 270 μmol/L	Arg ≥ 270 μmol/L
Missouri	07/01/05	0	827,604	100 μmol/L ≤ Arg < 150 μmol/L	Arg > 150 μmol/L
Nevada[a] (post 7/2015)	07/01/15	0	456,419	100 μmol/L ≤ Arg < 200 μmol/L (age ≤ 7 days) 130 μmol/L ≤ Arg < 200 μmol/L (age > 7 days)	Arg ≥ 200 μmol/L or 2 successive findings requiring a repeat (see preceding column)
Nevada[a] (pre 7/2015)	07/01/03	1		110 μmol/L ≤ Arg < 180 μmol/L	Arg ≥ 180 μmol/L
New Hampshire	03/01/10	0	73,715	60 μmol/L < Arg <132 μmol/L and Arg/[Leu × Phe] > 0.006	See footnote [e].
New Jersey	03/01/09	2	700,946	100 μmol/L ≤ Arg < 200 μmol/L	Arg ≥ 200 μmol/L or 2 successive findings of 100 μmol/L ≤ Arg < 200 μmol/L
New Mexico[a]	01/01/07	0	242,641	110 μmol/L ≤ Arg < 180 μmol/L	Arg ≥ 180 μmol/L
New York	05/02/05	5	2,622,604	52 μmol/L ≤ Arg < 115 μmol/L	Arg ≥ 115 μmol/L or 2 successive findings of 52 μmol/L ≤ Arg < 115 μmol/L
North Carolina	08/31/15	1	41,177	100 μmol/L ≤ Arg < 150 μmol/L	Arg ≥ 150 μmol/L
North Dakota	08/05/04[d,f]	0	124,460	All abnormal findings referred for clinical evaluation	Arg > 35 μmol/L; Arg/Orn > 0.6 (previously 1.0)
Ohio	06/28/02	0	1,959,931	Arg ≥ 110 μmol/L (Follow-up action decided by specialist)	Arg ≥ 110 μmol/L (Follow-up action decided by specialist)
Oklahoma	05/27/08	0	397,331	100 ≤ Arg < 200 μmol/L (low risk)	Arg ≥ 200 μmol/L (high risk) or 2 successive findings of 100 ≤ Arg < 200 μmol/L
Oregon[a]	10/28/02	1	619,068	110 μmol/L ≤ Arg < 180 μmol/L	Arg ≥ 180 μmol/L
Pennsylvania	07/01/09[d]	0	923,002	125 μmol/L ≤ Arg < 270 μmol/L	Arg ≥ 270 μmol/L (URGENT Repeat Request)
Rhode Island	07/01/06	0	114,270	60 μmol/L < Arg <132 μmol/L and Arg/[Leu × Phe] > 0.006	See footnote [e].
South Dakota	06/01/07[d]	0	108,987	All abnormal findings referred for clinical evaluation	Arg > 35 μmol/L; Arg/Orn > 0.6 (previously 1.0)
Tennessee	01/01/06	2	873,371	95 μmol/L ≤ Arg < 125 μmol/L	Arg ≥ 125 μmol/L.
Texas[a]	05/25/15	0	245,806	100 μmol/L ≤ Arg < 140 μmol/L (age ≤ 7 days) 115 μmol/L ≤ Arg < 150 μmol/L (age > 7 days)	Arg ≥ 140 (age ≤ 7 days); Arg ≥ 150 (age > 7 days); 2 successive findings requiring a repeat specimen (see preceding column)
Utah[a]	01/01/06	0	537,200	All abnormal findings referred for clinical evaluation	Arg > 20 μmol/L for first screens (<7 days) Arg > 35 μmol/L for second screens (≥7 days))
Vermont	01/01/03[d]	0	77,051	60 μmol/L < Arg <132 μmol/L and Arg/[Leu × Phe] > 0.006	See footnote [e].
Wyoming[a]	07/01/06	0	66,962	Arg ≥ 100 μmol/L	Two successive findings of Arg ≥ 100 μmol/L
Total		22	29,107,011		

[a] Routinely requires or recommends two screens on all newborns with high compliance – usually > 90%.
[b] Abnormal Arg on initial screen in newborn < 10 days old is repeated in duplicate and assessed using R4S ARG Tool Runner: Arg/Ala > 0.19; Arg/Orn > 0.70; Arg/Phe > 1.00; Cit/Arg < 0.32. If two out of the three analyses are outside of normal limits and the R4S ARG Tool indicates a possible abnormal result, the result is reported as abnormal. Any borderline or questionable results are reported as abnormal.
[c] Exact start date is not known, only the year. We have used 07/01/00 as the start date in order to approximate the number or screenable births.
[d] Not required, but likely to be detected by laboratory methodology currently in use.
[e] Arginine result is assessed versus ratios for Arg/[Leu × Phe] and Arg/Orn; Risks are assessed as follows: Moderate Risk: 60 μmol/L < Arg < 132 μmol/L with Arg/[Leu × Phe] > 0.006 and Arg/Orn > 1.5 or 132 μmol/L < Arg < 200 μmol/L with no ratios elevated; High Risk: 132 μmol/L < Arg < 200 μmol/L with either ratio elevated (high risk); Arg > 200 μmol/L (high risk) regardless of ratios.
[f] Pilot screening MS/MS screening began on 11/15/02 with official implementation on 08/05/04.

Using these two ratios and an initial cutoff value for arginine of 50 μM, all 9 known cases of arginase 1 deficiency detected in California over the 2005–2015 period (Table 1) would have been ascertained with no false screen positive cases reported. While the low frequency of arginase 1 deficiency in the population precludes absolute statements, we can state with certainty that the sensitivity of this screening protocol is

Table 2
Distribution of markers relevant for hyperargininemia screening among California newborns diagnosed with arginase 1 deficiency.

Case	Arg (μmol/L)	Cit (μmol/L)	Orn (μmol/L)	Ala (μmol/L)	Phe (μmol/L)	Leu (μmol/L)	Arg/Orn	Cit/Arg	Arg/Ala	Arg/Phe	Arg/Leu	Arg/[Phe × Leu]	R4S Score[a]
1	68	12	16	227	51.5	75.3	4.25	0.18	0.30	1.32	0.90	0.0175	112
2	101	22	25	318	62.3	80.8	4.04	0.22	0.32	1.62	1.25	0.0201	130
3	138	17	26	431	61.5	99.1	5.31	0.12	0.32	2.24	1.39	0.0226	210
4	142	15	26	237	70.7	97.1	5.46	0.11	0.60	2.01	1.46	0.0207	257
5	182	23	30	365	88.2	103.7	6.07	0.13	0.50	2.06	1.76	0.0199	248
6	209	16	23	366	54.8	142.9	9.09	0.08	0.57	3.81	1.46	0.0267	419
7	209	16	29	200	43.6	61.6	7.21	0.08	1.05	4.79	3.39	0.0778	423
8	233	19	52	314	60.6	151.6	4.48	0.08	0.74	3.84	1.54	0.0254	371
9	422	29	19	377	65.3	160.6	22.21	0.07	1.12	6.46	2.63	0.0402	468

Abbreviations: Arg = arginine; Cit = citrulline; Orn = ornithine; Ala = alanine; Phe = phenylalanine; Leu = leucine.
[a] R4S Results: Hyperargininemia highly likely if R4S Score ≥ 125; Hyperargininemia likely if 40 ≤ R4S Score < 125.

very high and the specificity approaches 100%. Because cases of metabolic disorders missed by newborn screening are reportable in California, it is relatively certain that no unknown cases of the disorder are present in California newborns, although early misdiagnosis is always a possibility. Thus, despite its rarity, screening for arginase 1 deficiency is practical when these ratios are used. Moreover, when each case was examined using the R4S Tool Runner, all were ascertained with a calculated false positive rate of <0.005%.

Determining status and value of newborn screening for hyperargininemia is complicated by a scarcity of published case detection and treatment data. Available case detection data do not support specific ethnic or geographic predilections, although hyperargininemia appears to be higher in Japan, Portugal and among French-Canadians of pioneer origin. While NBS in the U.S. is still not universal, 38 U.S. state programs currently report arginine results, and are therefore likely to observe hyperargininemia cases. While the apparent 1:1.2 M minimum incidence observed through NBS to date is similar in magnitude to that of some of the other metabolic conditions currently included in NBS, continued data collection is needed to establish a more reliable incidence.

The ACMGG ACT sheet for the follow-up of presumptive positive newborn screening results (i.e. elevated arginine) suggests obtaining a repeat arginine level along with a quantitative urinary orotic acid level [17]. While elevated orotic acid in the urine of hyperargininemia patients was reported by one of us, S.C., in 1981 [18] and subsequently found to be elevated in a number of infants with the disorder, we believe that this test has been insufficiently validated to be reliable for diagnosis. On the other hand, red blood cell arginase enzyme levels and mutation analysis of the exons of the arginase gene have been demonstrated to be reliable and together are the follow-up methods of choice [4]. Although the enzyme assay has been validated only in symptomatic patients, extrapolation to those who may be less severely affected seems appropriate. The normal levels in infants appear to be the same as in older children and adults, although this has not been studied extensively.

There is little question that as we become more proficient in the diagnosis of arginase 1 deficiency individuals with intermediary elevations in arginine on newborn screening and partial defects in enzymatic activity will be found. There are no reliable data to determine a safe level of arginine and indeed this may differ from patient to patient and vary with age. With any disorder, time and experience help with these decisions and they may be slow in coming with a disorder so relatively rare. In the meantime, NBS offers a means of early detection and treatment, and programs should consider using available resources such as R4S as a means to harmonizing screening algorithms. Because all relevant metabolites are already captured in routine MS/MS screening, adjustment of the interpretive algorithm is all that is needed to immediately implement one of the suggested approaches. As with any new and rare newborn screening condition, it will be critical to maintain a national (or international) database of relevant screening data (screening algorithm, time of screening, demographics of detected patients, etc.) that can be periodically analyzed in order to refine the screening algorithms being used [16,19].

Table 3
Estimated screen positive rate for arginase 1 deficiency based on alternative screening strategies.
(Data from California, 2015, $N = 486{,}591$).

Method	Arg	Arg/Orn	Arg/[Phe × Leu]	Newborns requiring follow-up
Using specified cutoff concentration for Arg	33			2.18%
	40			1.39%
	50			0.84%
	100			0.11%
	110			0.07%
	125			0.05%
Using specified cutoff for Arg and indicated ratio cutoff(s)	30	0.45		0.26%
	35	0.6		0.07%
	50	0.8		0.02%
	50	1.4		0.01%
	60	1.5	>0.0006	<0.005%
Using R4S Tool Runner	Not applicable			<0.005%

Abbreviations: Arg = arginine; Orn = ornithine; Phe = phenylalanine; Leu = leucine; R4S = Region 4 Stork international MS/MS database.

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References

[1] A. Schlune, S. vom Dahl, D. Haussinger, et al., Hyperargininemia due to arginase I deficiency: the original patients and their natural history and a review of the literature, Amino Acids 47 (9) (2015) 1751–1762.
[2] J.P. Tsang, W.L. Poon, H.M. Luk, et al., Arginase deficiency with a new phenotype and a novel mutation: contemporary summary, Pediatr. Neurol. 47 (4) (2012) 263–269.
[3] S.D. Cederbaum, S.J. Moedjono, K.N.F. Shaw, et al., Treatment of hyperargininemia due to arginase deficiency with a chemically defined diet, J. Inherit. Metab. Dis. 5 (2) (1982) 95–99.
[4] E.A. Crombez, S.D. Cederbaum, Hyperargininemia due to liver arginase deficiency, Mol. Genet. Metab. 84 (2005) 243–251.
[5] N. Nagata, I. Matsuda, K. Oyanagi, Estimated frequency of urea cycle enzymopathies in Japan, Am. J. Med. Genet. 39 (2) (1991) 228–229.
[6] D. Marsden, Expanded newborn screening by tandem mass spectrometry: the Massachusetts and New England experience, Southeast Asian J. Trop. Med. Public Health 34 (Suppl. 3) (2003) 111–114.
[7] M.L. Summar, S. Koelker, D. Freedenberg, et al., The incidence of urea cycle disorders, Mol. Genet. Metab. 110 (1–2) (2013) 179–180.
[8] G. Marquardt, R. Currier, D.M. McHugh, et al., Enhanced interpretation of newborn screening results without analyte cutoff values, Genet. Med. 14 (7) (2012 Jul) 648–655.
[9] P.L. Hall, G. Marquardt, D.M. McHugh, et al., Postanalytical tools improve performance of newborn screening by tandem mass spectrometry, Genet. Med. 16 (12) (2014) 889–895.
[10] A. Jay, M. Seeterlin, E. Stanley, R. Grier, Case report of argininemia: the utility of the arginine/ornithine ratio for newborn screening (NBS), JIMD Rep, 9, 2013, pp. 121–124.
[11] R. Koppaka, Ten great public health achievements—United States 2001–2010, MMWR 60 (2011) 619–623.
[12] American College of Medical Genetics, Newborn Screening Expert Group, Newborn screening: toward a uniform screening panel and system, Genet. Med. 8 (Suppl. 1) (2006) 1S–252S.
[13] N.S. Green, P. Rinaldo, A. Brower, et al., Advisory committee on heritable disorders and genetic diseases in newborns and children. Committee report: advancing the current recommended panel of conditions for newborn screening, Genet. Med. 9 (11) (2007) 792–796.
[14] N. Calonge, N.S. Green, P. Rinaldo, et al., Advisory committee on heritable disorders in newborns and children. Committee report: method for evaluating conditions nominated for population-based screening of newborns and children, Genet. Med. 12 (3) (2010) 153–159.
[15] A.R. Kemper, N.S. Green, N. Calonge, et al., Decision-making process for conditions nominated to the recommended uniform screening panel: statement of the US department of health and human services secretary's advisory committee on heritable disorders in newborns and children, Genet. Med. 16 (2) (2014) 183–187.
[16] D. McHugh, C.A. Cameron, J.E. Abdenur, et al., Clinical validation of cutoff target ranges in newborn screening of metabolic disorders by tandem mass spectrometry: a worldwide collaborative project, Genet. Med. 13 (3) (2011) 230–254.
[17] American College of Medical Genetics and Genomics, Act sheets and confirmatory algorithmsAvailable at: http://www.acmg.net/StaticContent/ACT/Arginine.pdf Accessed January 31, 2017.
[18] E.W. Naylor, S.D. Cederbaum, Urinary pyrimidine excretion in arginase deficiency, J. Inherit. Metab. Dis. 4 (1981) 207–210.
[19] B.L. Therrell, W.H. Hannon, National evaluation of US newborn screening system components, Ment. Retard. Dev. Disabil. Res. Rev. 12 (4) (2006) 236–245.

My daughter, Willow, was diagnosed with Arginase 1 Deficiency a month before her 5th birthday. Because of the delayed diagnosis, she suffers from many irreversible symptoms of the disease resulting in physical, behavioral, and learning disabilities. I will touch on a few of her symptoms here but keep in mind, this is a sampling of what she lives with, not the entirety.

Willow suffers from spasticity in all of her limbs but predominantly in her legs. This diagnosis is probably her most debilitating physical symptom. The spasticity requires her to wear AFOs (braces that wrap around her foot, ankle, and go to her knees) to walk with proper alignment. Even with these, she often trips over her feet and stumbles on uneven ground. Just a crack in the pavement can cause her to fall. She can't walk for long distances either. A trip to the grocery store will wipe her out. She can't take part in a lot of kid focused activities because they usually require too much physical exertion. She gets fatigued very quickly and has to sit out and watch the other kids play.

Willow has foot and toe malformations where her big toes curl under her other toes and her whole foot rolls inward, collapsing over her arch. Because of this, her nail beds are often infected and painful due to ingrown toenails. She is also missing some toenails due to her dragging her feet. She hyperextends her knees causing knee pain, has lordosis which causes back and hip pain and suffers from overall core weakness. With issues such as these comes many specialists and many appointments that require her to miss a lot of school.

Speaking of school, she is about 4 grade levels behind in math. She only just got caught up to grade level with reading and is still multiple grade levels behind in spelling. Her handwriting is often illegible, even after 6 years of physical therapy focusing on this. Willow has a hard time learning and staying focused but she is socially on point. This means that she is able to now recognize her differences and struggles with being so different from her classmates. She never gets to take part in class activities because she gets pulled out for one-on-one help. She frequently will hear of a fun and exciting assignment or activity but usually doesn't get to participate because of this pull-out. I often hear of how she winds up sitting on the bench at recess alone because she isn't able to play on the swings or play tag. Honestly, this part might be the hardest for me. Knowing that my kid is aware of her differences and is sad and alone.

If Willow had been diagnosed with Newborn Screening, many of these symptoms would have been prevented. I believe this to be true because of the individuals we have met who were diagnosed at birth. Their symptoms are much less pronounced, if present at all. We were just at a meet-up for people living with Arginase 1 Deficiency and the children that were diagnosed with Newborn Screening were up running around playing silly games of tag, catch, and just running and jumping around like a typical kid does. The children that were not diagnosed until later in life were stuck at tables due to their lack of physical capabilities or were completely reliant on their wheelchairs or walkers. Some were not able to feed themselves and were often not verbal. Even the children like Willow, who are able to be independent in some ways, were still not able to keep up with their peers diagnosed at birth. It is heartbreaking to see such a stark difference that could have been completely eliminated if only we all had equal access to newborn screening for Arginase 1 Deficiency.

Meet Jackson, age 30, with parents Jean and Leafy
Southern California
Living with ARG1-D

Jackson, age 30, is a self-described cooking fanatic. It is a joyful family experience, involving his mom Jean and stepmom Leafy, bringing this already close-knit family even closer together. “I love to make Thanksgiving dinner, with all the fixings,” Jackson explains. “But on my plate, there won’t be any turkey of course and I select my side dishes very carefully.”

If Jackson doesn’t choose what he eats carefully, the medical consequences are severe. Jackson lives with Arginase 1 Deficiency (ARG1-D) a debilitating and progressive inherited metabolic disorder affecting children, teens, and adults that can significantly impact a patient’s health over time.

Jackson was born with ARG1-D, but it took the family nearly five years to get a diagnosis. “When Jackson was a baby, he slept a lot and we were delighted to have such a ‘good’ baby,” recalled mom Jean. “But we started having some concerns.” Jackson did not nurse, and he was prone to vomiting when exercising or laughing at cartoons on television. At first, Jackson’s pediatrician was not concerned. But when other physical symptoms emerged – toe walking, falling easily, and more vomiting when he exerted himself - Jackson was finally sent for metabolic testing.

Late on a Friday, Jean and Leafy anxiously waited to learn officially what was happening with Jackson. “I knew something was not right,” said Leafy. “They kept testing his blood and he had an extraordinarily high amount of ammonia in his urine.” Finally, the physician had the diagnosis of ARG1-D.

ARG1-D is characterized by complete or partial lack of the enzyme arginase in the liver and red blood cells. Arginase helps to break down and remove nitrogen from the body. The lack of the arginase enzyme results in excessive accumulation of nitrogen, in the form of ammonia, in the blood and arginine in the blood and cerebrospinal fluid. Children may exhibit seizures, spasticity, short stature and intellectual disability. The reason why Jackson had slept so much as a baby was likely that excessive protein was causing him to go into long stretches of comatose state. “He was not simply a good baby sleeping peacefully,” said Jean.

Jean and Leafy had vastly different reactions to hearing Jackson’s diagnosis. For Leafy, “It was a surreal experience. It was like I was hovering from above and listening to a conversation someone else was having. And then I started to panic.” Jean’s reaction was calm. “I thought, okay protein is making him sick, we have to figure out a way to cope. We can fix this.”

While much still is being learned about ARG1-D, back in the late 1990s when Jackson was diagnosed there was even less guidance for patients and caregivers. “We were told ‘don’t give him protein’ and then sent on our way,” said Leafy.

Jean and Leafy struggled for many months to care for Jackson appropriately, given the limited information available about ARG1-D. While trying to manage the diet, Jackson’s weight dropped precipitously, he continued to vomit regularly, and he suffered from spasticity. In addition, while Jean and Leafy tried to manage the care of their son, they also endured judgement from others. One doctor suggested their own anxieties were possibly making Jackson sick, not ARG1-D. And at a rest stop during

a family vacation, an onlooker became upset when the women were limiting Jackson's food despite his pleas for more and threatened to call police. "It was a long and lonely journey not knowing what to do," said Leafy.

Eventually, Jean and Leafy met another family also caring for a child with ARG1-D. The family became a source of support and strength and introduced them to a physician who would change their lives, Dr. Stephen Cederbaum, a geneticist from UCLA that they are still in touch with 26 years after meeting him. Dr. Cederbaum established a treatment plan for Jackson consisting of nutritional drinks, a limited diet, leg injections to help with spasticity and much more. Until he was in grade 7, Jackson needed to eat his lunch alone in the principal's office so he would not come into contact with peanuts (an allergy diagnosed as an infant) or potentially eat high protein foods. He could not go on school field trips without Jean or Leafy, and playdates and sleepovers were arduous to plan. Jackson also had to go for physical therapy to learn simple tasks like how to tie his shoes and button his shirts.

Today, Jackson still follows a similar diet and routine as he had as a child, though therapies to potentially treat ARG1-D are now in development. When he is not cooking with his family, Jackson works at Amazon and enjoys music, art and playing his guitar. He follows a strict diet and the instructions for managing ARG1-D very carefully. In his 30 years he has learned many lessons. "Do your own research, but don't pretend that you alone are the expert," Jackson advises. "Listen to what you're told to do, and don't give up or become complacent." Jackson hopes to see a treatment approved to treat ARG1-D in his lifetime, as he lives with the many restrictions and side effects of this rare disease. He appreciates the researchers and healthcare providers who have devoted many decades of study into ARG1-D. "We have learned so much over the past 26 years." Jean and Leafy are very proud of Jackson's accomplishments. In 2014, he graduated from California Baptist University with a Bachelor of Art in graphic designs.

For Jean, she offers advice for families who are new to ARG1-D. "We went to so many doctors until we found the ones that worked best for us," she said. "Don't' give up or settle, find the right doctor and create a team of specialists that will work together. And yes, you will need a lot of specialists." She also offers practical advice for parents and other caregivers:

- ✓ Get your child used to the taste of the formula early. They need it and they will become accustomed over time like Jackson did.
- ✓ Always make and keep all doctor appointments.
- ✓ Meet regularly with several specialists: metabolic specialist, orthopedic surgeon, ophthalmologist (not optometrist), dentist, and physical therapist. Also, see a neurologist if your child has seizures.

The family remains eternally grateful for finding and connecting with others living with ARG1-D, as the community has grown over the last two and a half decades. They recommend reaching out to community groups like the Arginase 1 Deficiency Foundation for support, an organization Jean, Leafy and Jackson all give back to today. "We have been through it ourselves and we know what it's like," said Leafy. "We are there for each other 24-7. That's what you do when you are part of a family. It does not end with a conversation. We continue to think about them."

Jackson added, "We want to give hope to those who need it. You were given a bad hand, but you can play your cards right. Listen and make the right decisions, and let people help you along the way."

On the value of newborn screening:
"Our diagnosis came many years late because newborn screening was not an option. And I know there are more families just like ours out there." Leafy, stepmom of son with ARG1-D

Lessons learned:

"We went to so many doctors until we found the ones that worked best for us. Don't give up or settle, find the right doctor and create a team of specialists that will work together. And yes, you will need a lot of specialists." Jean, mom of son with ARG1-D

"We worried tremendously in the beginning about everything for our son. But he is smart and strong, and I know he can do anything." Jean, mom of son with ARG1-D

"You were given a bad hand, but you can play your cards right. Listen and make the right decisions, and let people help you along the way." Jackson, living with ARG1-D

On community:

"We have been through it ourselves and we know what it's like. We are there for each other 24-7. That's what you do when you are part of a family. It doesn't end with a conversation." Leafy, stepmom to son with ARG1-D

Jackson was born in January 1991. The day he was born, according to his physician, he was a perfect baby in every way with no known birth defects or disease. That all changed 4 ½ years later on September 28, 1995. The following story could have been avoided had California had Newborn Screening at the time of his birth. They could have started treatment / medications for Argininemia / Arginase 1 Deficiency.

The day of Jackson's diagnosis they told us Jackson would always be small, would stop walking on his own, would develop "tics" with symptomatic Tourette's syndrome, and would probably die from the flu and not Arginase 1 Deficiency. They also told us to stop giving him food with protein. There was no support or recommendation on how to move forward from the worst day of our lives.

Within days of changing his diet, Jackson started throwing up and falling more often throughout the day. If we walked out the front door, we always had the pan and towels to catch his vomit and clean up the floors or furniture. He vomited 6 to 12 times a day, throwing up what little he could eat and all his formula. Because he was unable to walk, run, or laugh without vomiting, his world was limited to riding in a stroller and no cartoons which he would laugh at. This went on for 110 days before an Orthopedic Surgeon gave him Botox shots in his calves. It helped after three days of treatment.

Our doctor asked for a wheelchair for Jackson and our insurance denied it. It took over a year to get the insurance to pay for a wheelchair. Our nights were spent trying to find information on Arginase 1 Deficiency and writing letters to the insurance companies in order for them to pay for or assist in the payment of care. Battling the health insurance companies was a constant, daily struggle. They did not want to pay for any of the drugs / formulas that were recommended to maintain his current health. The insurance company considered his formulas to be "protein drinks / bodybuilding drink" and refused to pay for them. To this day, every year we spend countless hours jumping through all the hoops we have jumped through for the past 25 years.

Because of his unusual diet, allergies, and propensity for injury, we could never hire or trust anyone to help with his daily care. This caused us to eventually lose our business forcing us into bankruptcy because of the amount of time we had to devote to his care.

We are absolutely confident that had Jackson been diagnosed at birth, we could have avoided many of the symptoms of his disabling disease. Most children now diagnosed at birth avoid spasticity, hospital visits, vomiting, seizures, broken bones, horrible mood swings, glaucoma, awful skin outbreaks, and outburst of mood swings from high ammonia.

Jackson continues to have occasional hyperammonemia, he toe walks, is spastic, has osteoporosis, glaucoma, and has suffered through two broken hand due to falls. Whenever he does get a cold or flu, he spends weeks in bed unable to do anything.

Jackson does not make friends and shies away from social events unless attended by family or the ARG1D community / family. He does not like to go out with groups of people because of his walking characteristics and unusual diet. He spends most of his free time in his room, reading or playing games.

We do our best to have a normal life.

I would like to thank you for allowing us to share our lives with you and hope that you will not only consider but pass the newborn screening request to add Arginase 1 Deficiency to the blood test panel. It

has been an absolute honor working on this project with our Arginase 1 family and have 100% confidence in any way that they represent us.

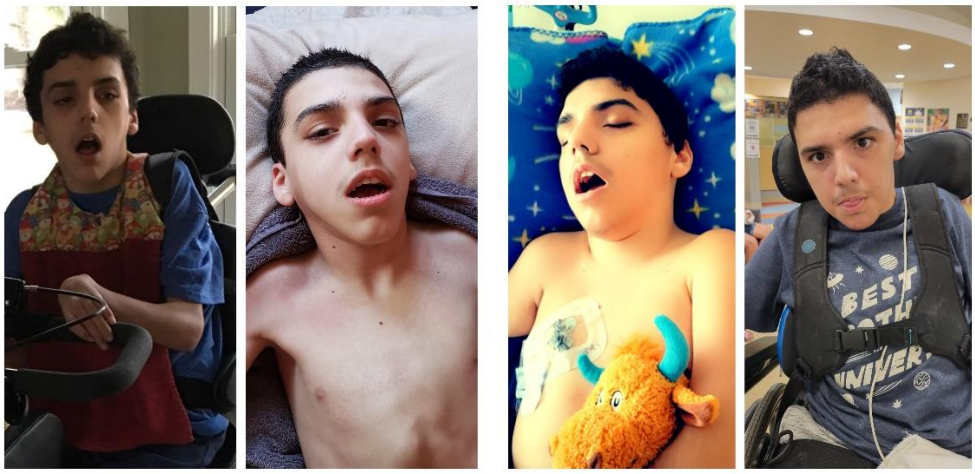
Hi I'm Brandy, Landon's mom and this is Landon's story.

I had a perfectly normal pregnancy. Landon was born via c-section September 3, 2004. Right around 6 months old Landon started having seizures. Immediately, I called my pediatrician, and we began an extremely long journey. He was sent to a neurologist, genetics, and a whole bunch of other specialists. Neurology confirmed the seizures and he started medications to control them. Genetics did testing and found nothing. Mind you this was in 2005 and maybe there wasn't even testing for Arginase 1 Deficiency (ARG1D) at the time. He was diagnosed with Cerebral Palsy and Epilepsy. He had many abilities throughout his life. Crawling, walking, propelling his chair, use of his hands, feeding himself, eating orally and the list goes on of his abilities. Slowly over time, these things stopped one by one with no apparent reason why.

Fast forward to April 2021. Landon and I received our first dose of the COVID vaccine on a Monday. I felt fine and by Friday Landon was eating less, more sleepy, irritable (he was always very irritable but even more so now), low urine output, vomiting and just not himself. Now, also, in this time I was in the process of switching all of our doctors from the past 16 years to new doctors at University of Michigan Motts Children's Hospital. It's one of the top hospitals in the country and I wanted all new eyes on him. I took him in on a Saturday, 6 days after the vaccine and thinking it was just side effects from it. He was lethargic when we got there, just in rough shape. They immediately got to work. Labs, labs and even more labs.

Landon's ammonia came back 1,672 (normal is around 45 and anything over 100 can lead to brain damage). He was immediately placed in PICU, put on a vent and had dialysis to clean his blood to get him to the normal ammonia level range. The doctors were concerned about hyperammonemia. What was he going to be like? Has this caused brain damage? Well 10 days on a vent, blood draws every 2 hours for days, and a feeding tube placed to keep him on a strict formula recipe. He was 62 pounds at 16 years old when I got to the hospital. How did I not notice?

Well, 6,073 days of life and he was FINALLY diagnosed with Arginase 1 Deficiency. It's been a ride. But he needed me as much as I needed him. Almost 2 years later and he's doing AMAZING. He will never get back all the abilities he lost but we are in a good spot right now. There will obviously be bumps in the road but we can handle those. The doctors at Motts not only saved his life that day but saved mine as well, our whole family's actually. Landon is so so loved by everyone. We have a small village. He is his brother's best buddy and his aunts love him to death. Doctors and nurses have become friends and confidantes. Landon is the only person at the genetics clinic at our hospital that has ARG1D, but yet they have taught me everything about it. I'm so happy to have found this group. I wish his diagnosis was found years sooner through newborn screening. I wish he was on the proper formula plan sooner. I wish he was on nitrogen scavenger medications earlier. Maybe he would still be able to do some of the things or all of the things he used to do. But most of all regardless of everything he is STILL HERE and that's truly what matters the most. He is my heart, my existence, my sun, moon, and stars.



Left two photos are prior to diagnosis, right two photos are post diagnosis. 40 pound weight gain due to proper nutrition and medications.

From a Mother's perspective...

What if?

Just what if my son was diagnosed correctly from newborn screening?

Could the outcome have been better?

Arginase 1 Deficiency was not on newborn screening when my son Josh was born in 1997. There was a red flag though. Josh's newborn screening came back positive for PKU (phenylketonuria) but repeated testing came back negative! We were so scared but relieved my son was healthy. Then things changed and Josh wasn't meeting his milestones and many of us including his doctor, thought he was a late bloomer. His legs were tight and he was showing signs of developmental delay. Then right before Josh's 3rd birthday, he had an onset of seizures and his liver enzymes were elevated. Josh went through numerous tests including MRI's and a spinal tap. Days later, a blood lab showed elevated Arginine. Josh was diagnosed with Arginase 1 Deficiency!

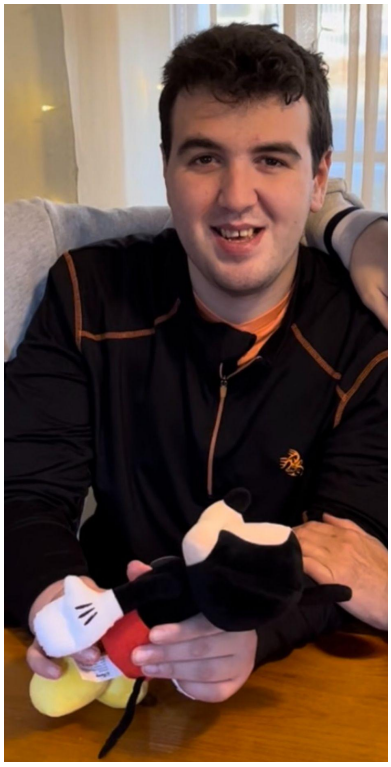
If newborn screening was available for Arginase 1 Deficiency, Josh would've been diagnosed immediately as an infant. Newborn screening and early treatment would've given him the possibility of meeting all his milestones in the first few years of life. Because he didn't have early treatment, his legs became very stiff from spasticity and can only walk for short periods. He needs speech therapy, occupational therapy, physical therapy, leg braces and behavioral therapy. Josh has developmental delay, a seizure disorder and physical disabilities. Early diagnoses and early treatment could've stopped or reduced the effects of this condition and might have made a big difference in Josh's development. It's unfortunate that Josh was left untreated and became severely brain damaged.

As a mother it's heartbreaking to realize that if newborn screening were available Josh could've had early treatment and had the chance of being higher functioning or even mentally capable of living a normal independent life! Early diagnosis of Arginase 1 Deficiency and early treatment could've prevented countless days of seizures, vomiting, hospitalizations, behavioral issues and Josh becoming medically complex needing 24 hour care. The lack of newborn screening robbed Josh the chance to have a typical life and the effects of late diagnosis continues to plague him today at age 25.

What if….this was your child?

Sincerely,

Alexandra Eaton



Hello, my name is Angela Garcia and I'm the mother of Isaiah Lopez.

My son was diagnosed in 2016 with argininemia (Arginase 1 Deficiency) through a newborn screening panel. When Isaiah was first diagnosed, I was very scared of the unknown. I have now accepted that everyday is a learning process. I am thankful that my son was diagnosed before having to go through any kind of crisis. His condition has been controlled since day one. We know he has a special diet. We know what he has to avoid and we know what he can and cannot have on a day-to-day basis. I feel that my son was a miracle and was blessed with being able to be tested through a newborn screening panel. If it weren't for the newborn screening, my son would not be diagnosed on time and would have gone through a medical crisis before we could figure out what was wrong with him. So, therefore, a newborn screening was a lifesaver for my son and gave him a brighter future. I am thankful everyday that I was able to prepare beforehand and able to save my son from a whole lot of unknown crises. I hope that the newborn screening will be approved for everyone's new born baby everywhere.

In March of 2017, my daughter, Briana, was 2.5 years old when she was diagnosed with Arginase Deficiency. Briana had met all her milestones before being diagnosed. The Genetics doctor informed us Briana could have Cerebral palsy symptoms later down the road since Arginase Deficiency was a progressive diagnosis. We were clueless how quickly her mobility would change. After two months of being diagnosed, Briana started to show spasticity in both legs. A few weeks later, she began toe walking and started to lose mobility. She could no longer walk without assistance. Briana began physical therapy 3 months after being diagnosed.

Briana has been taking physical, occupational, and speech therapy for over 5 years. Briana still suffers from spasticity and is extremely flat footed. We have been told by her physical therapist Briana could have hip problems by the time she's in her 20's if footing and posture do not align properly. Briana's enzyme levels have to be constantly monitored when her Arginase levels are high. This is a constant concern we have and monthly labs have to be drawn.

We live in the State of Arkansas and unfortunately Newborn Screening for Arginase Deficiency is not offered. I truly believe if Briana would have been diagnosed at birth, several of her symptoms would not exist or would be minimal. We've had the opportunity to meet other families with Arginase deficiency who had Newborn Screening. These families were able to get their child started on the right diet and medicine and their child has benefited from it. We would love this opportunity for all.

It all started with an ominous, dark grey sky and two of the most vibrant, beautiful double rainbows over a hospital in Temple, Texas. Almost seven years ago this July our lives were changed and not in any way we could have ever imagined. My husband and I watched our siblings have birth after birth that were normal and healthy. So, when we found out we were pregnant, we were anxious like many new parents, but ultimately, we were confident and thrilled for a new adventure.

On July 26, 2016, Lincoln James Istre (pronounced East) was born. During the night while he was being monitored, Lincoln stopped breathing twice and had to be resuscitated, so they moved him into the Neonatal Intensive Care Unit. On July 27th they ran the mandatory Newborn screen 24 hours after birth, via a heel stick, while Lincoln was in the NICU. In addition to low oxygen levels, his bilirubin and white blood cell levels were high, his platelets were low, his red blood cells were all over the place in their levels and size. All we knew at the time was that our newborn son had wires all over his tiny body, required oxygen around the clock or he would stop breathing on his own and that he had to stay in the hospital under the blue light to fix his jaundice. After a week in the hospital, we finally got to go home. We were never told what any of his test results were. The doctors just said, he can breathe on his own, he's not jaundiced any more, and his platelets are normal so we could leave. Three days later, while still adjusting to life with a newborn, we got an urgent phone call while at Lincoln's audiology appointment from a nurse at the state level telling us to go to the ER immediately for testing. We didn't know why. Lincoln was acting fine, we just got out of the hospital after being there for a week and we did not want to go back because the "State of Texas said so." The Newborn Nurse explained what tests were being requested because the Newborn Screen Test "Amino Acidemia" levels were coming back elevated consistently and Lincoln needed to have his Plasma Amino Acids checked. So, at 8 days old, they ran Lincoln's second required Newborn Screen, and we got an official diagnosis of Argininemia.

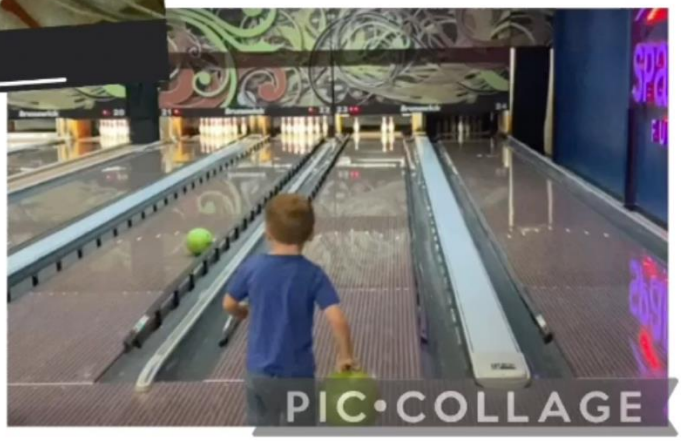
The Texas Newborn Screen tests for 55 rare genetic disorders. On each of Lincoln's test results the "Amino Acidemias" was coded as HIGH. Further testing of his specific amino acids showed that he had elevated Arginine in his blood with a level of 427 at birth. The normal range is anywhere from 40-120. The Newborn Screen changed the course of our life and our son's life. When we met with his specialist we asked for the bottom line. What does this diagnosis mean? "Your son, if not treated, will not be able to walk, talk, could have physical delays, cognitive delays. He could develop seizures, go into a coma, and die." Thanks to the newborn screen, we put Lincoln on the medical/dietary restrictions immediately at **two weeks old!** I am a firm believer that having knowledge is power and with that power, we were able to take measures to set Lincoln up for success which has allowed him to be doing as well as he is. He's better off than most kids his age with the same diagnosis. We were told there could be physical issues-we put him in physical therapy at a month old. We had him in speech therapy at a year to keep his brain sharp. We were told his muscles could get spastic, he could have issues walking- we put him in baseball and encourage all physical exercise. The mandatory newborn screen gave our family important and critical information that has allowed our son to be able to be healthy, happy, and relatively unaffected by his diagnosis of Agininemia. No one in either of our families has this diagnosis, so had we lived anywhere else in the US, we wouldn't have known to check for it, and Lincoln's life could be very different. Instead, in his 7 years, he's only had 2 hospitals stays with hyperammonemic episodes and minimal lingering effects that we can tell. Of the 250 people in the US that have Argininemia, Lincoln is 1 of 5 that are healthy all because of the Newborn Screen.

It takes a lot of work and commitment on our parts as parents and caregivers to love these children, but God gives special children to special people. At least that's what my dad says. Lincoln would not be here or doing as well as he is without the Newborn Screen test. It's literally life altering. He's as healthy as he is because of hard work and dedication to his care by his medical care team and our loved ones. This road has not been easy, and it is not well traveled; but for us, it all began with a heel stick, an ominous grey day, and two of the most beautiful, vibrant double rainbows you've ever seen; promising us a life of challenges, but with double the hope, double the hard work, and double the love we can overcome it all.





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Washington State Board of Health

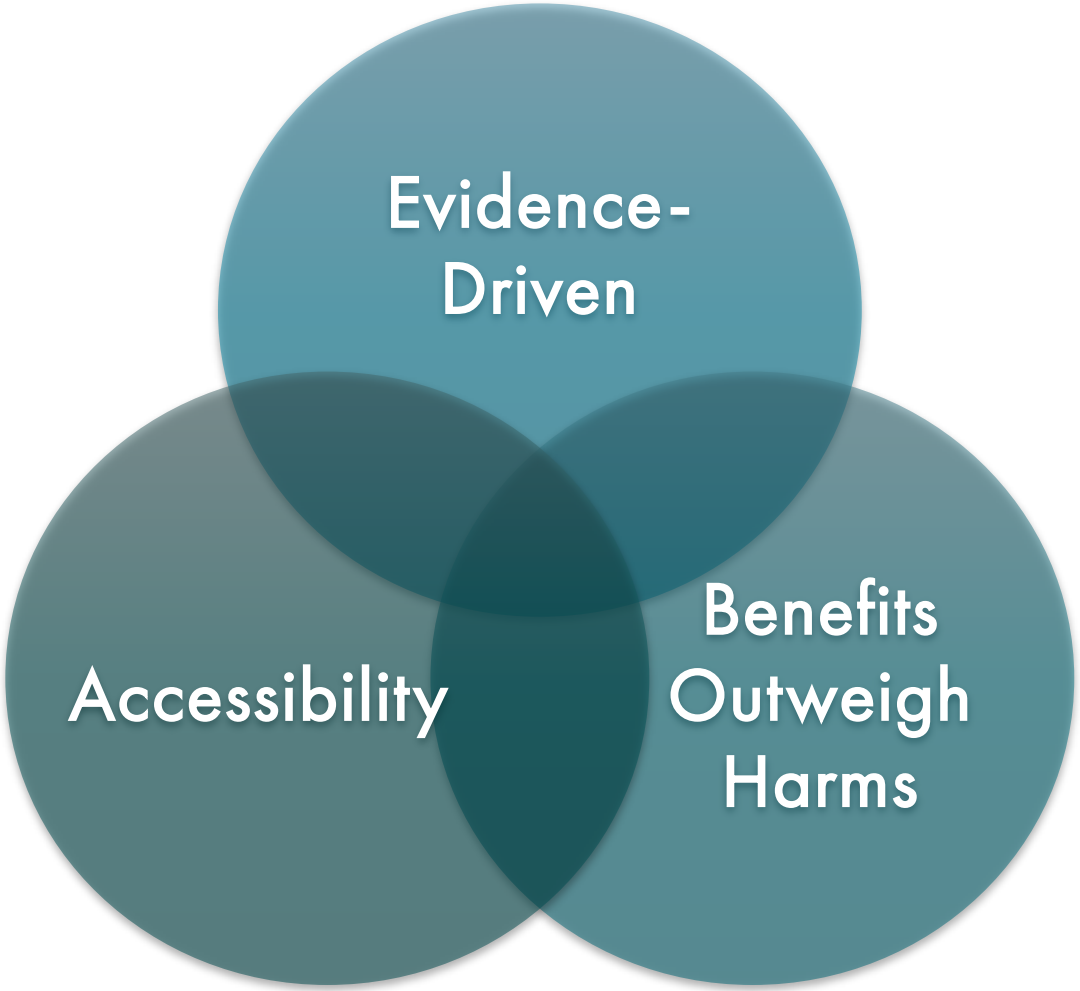
Petition for Rulemaking – Chapter 246-650 WAC, Newborn Screening, Arginase 1 Deficiency (ARG1-D)

April 12, 2023

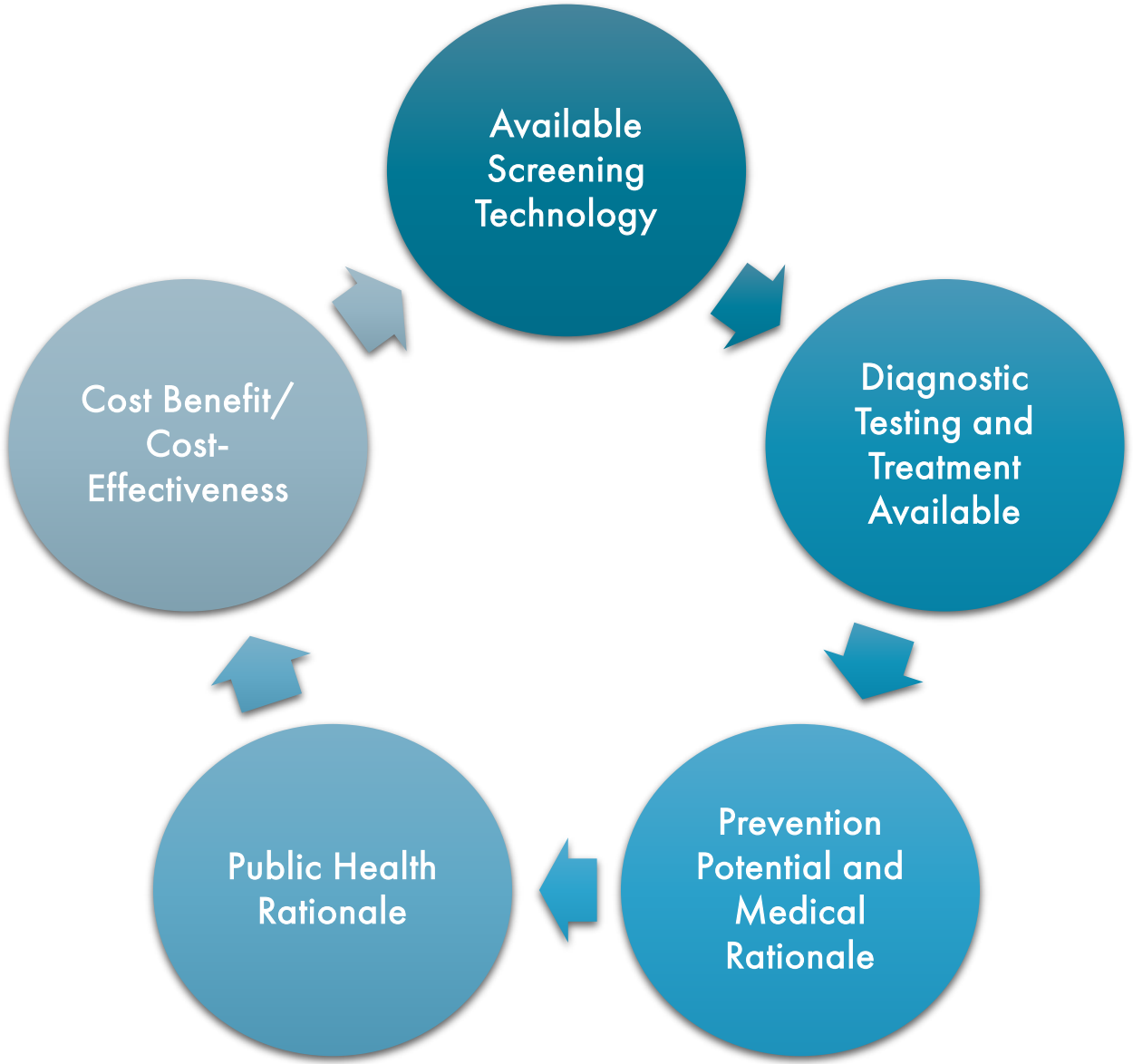
Molly Dinardo, MPH
Policy Advisor, State Board of Health (SBOH)
John Thompson, PhD, MPH, MPA
Director, Department of Health (DOH) Newborn Screening Program

Board Policy for Newborn Screening

Three guiding principles govern all aspects of the evaluation of a candidate condition for possible inclusion in Washington's Newborn Screening panel:



Five Newborn Screening Criteria

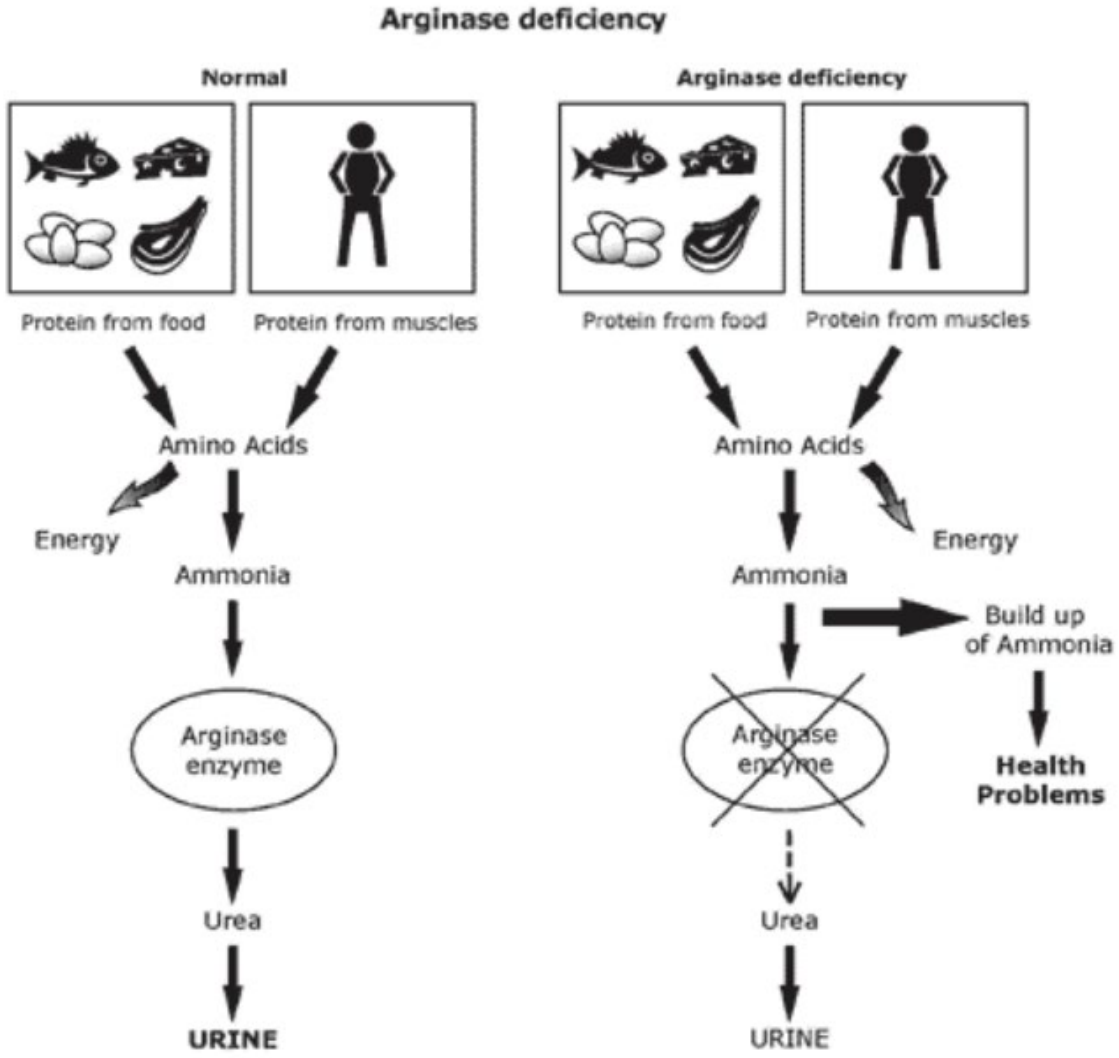


Petition for Rulemaking

- On March 29, 2023 the Board received a petition request to amend chapter 246-650 WAC to add ARG1-D as a mandatory condition on the state's newborn screening panel

- The petition states that a diagnosis of ARG1-D at birth allows for immediate treatment to slow down/prevent severe symptoms from occurring rather than waiting until symptoms appear at a later age

What is ARG1-D?

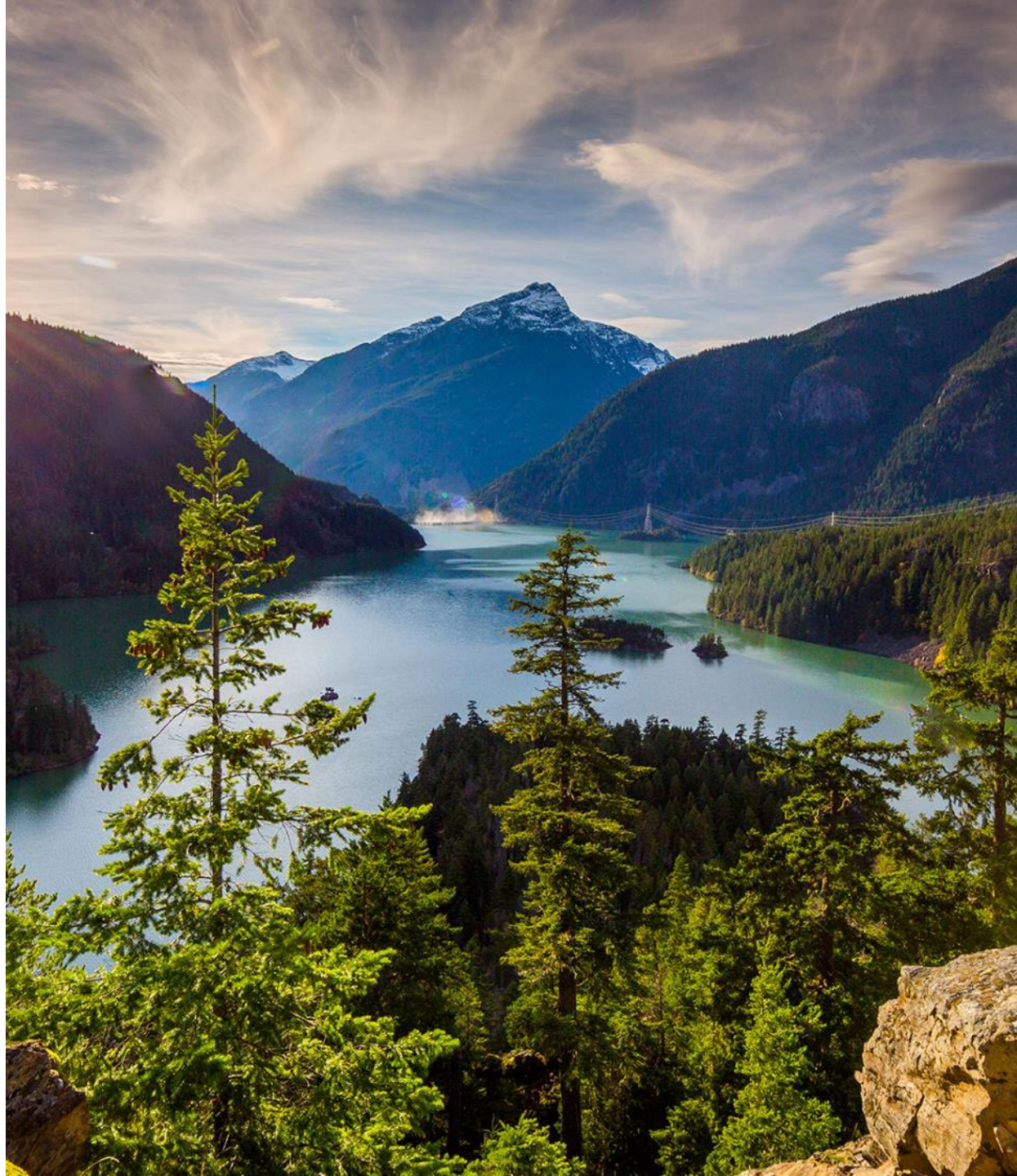


Source: Newbornscreening.info

Considerations

Supplemental information from petition materials:

- ARG1-D is listed as a secondary condition on the Federal Recommended Uniform Screening Panel (RUSP)
- Washington is 1 of 17 states that does not require testing for ARG1-D
- The Washington newborn screening lab currently runs ARG1-D blood testing for Idaho



For Board Member Discussion

- Would the Board consider accepting or denying this petition? Why or why not?
- Do Board Members want to direct staff to conduct a preliminary review of the condition and return to the Board at an upcoming meeting? Or proceed to a TAC?
- Discussion and justification for the Board's decision will be included in the Board's determination letter to the petitioner.

THANK YOU

WASHINGTON STATE BOARD OF HEALTH

To request this document in an alternate format or a different language, please contact the Washington State Board of Health at 360 236 4110 or by email at wsboh@sboh.wa.gov.
TTY users can dial 711

RCW 70.83.020

Screening tests of newborn infants.

(1) It shall be the duty of the department of health to require screening tests of all newborn infants born in any setting. Each hospital or health care provider attending a birth outside of a hospital shall collect and submit a sample blood specimen for all newborns no more than forty-eight hours following birth. The department of health shall conduct screening tests of samples for the detection of phenylketonuria and other heritable or metabolic disorders leading to intellectual disabilities or physical defects as defined by the state board of health: PROVIDED, That no such tests shall be given to any newborn infant whose parents or guardian object thereto on the grounds that such tests conflict with their religious tenets and practices.

(2) The sample required in subsection (1) of this section must be received by the department [of health] within seventy-two hours of the collection of the sample, excluding any day that the Washington state public health laboratory is closed.

[**2014 c 18 § 1**; **2010 c 94 § 18**; **1991 c 3 § 348**; 1975-'76 2nd ex.s. c 27 § 1; **1967 c 82 § 2**.]

RCW 70.83.030

Report of positive test to department of health.

Laboratories, attending physicians, hospital administrators, or other persons performing or requesting the performance of tests for phenylketonuria shall report to the department of health all positive tests. The state board of health by rule shall, when it deems appropriate, require that positive tests for other heritable and metabolic disorders covered by this chapter be reported to the state department of health by such persons or agencies requesting or performing such tests.

[**1991 c 3 § 349; 1979 c 141 § 113; 1967 c 82 § 3.**]

RCW 70.83.050

Rules and regulations to be adopted by state board of health.

The state board of health shall adopt rules and regulations necessary to carry out the intent of this chapter.

[**1967 c 82 § 5.**]

Washington State Board of Health
Policy & Procedure

Policy Number:	**2005-001**
Subject:	**Responding to Petitions for Rule-Making**
Approved Date:	**November 9, 2005 (revised August 13, 2014)**

Policy Statement

RCW 34.05.330 allows any person to petition a state agency to adopt, repeal, or amend any rule within its authority. Agencies have 60 days to respond. The agency can deny the request—explaining its reasons and, if appropriate, describing alternative steps it is prepared to take—or it must initiative rule-making. If a petition to repeal or amend a rule is denied, a petitioner can appeal the agency's decision to the Governor.

This policy defines who must be notified and consulted when the Board is petitioned, who may respond on behalf of the Board, and whether Board action is required.

- **Board Response**: When the Board receives a written petition for rule-making within its authority that clearly expresses the change or changes requested, the Board will respond within 60 days of receipt of the petition. The response will be made at the direction of the Board. The response will be in the form of a letter from the Chair denying the petition or informing the petitioner the Executive Director has been directed to initiate rule-making.

- **Consideration of the Petition:** The Chair may place a petition for rule-making on the agenda for a Board meeting scheduled to be held within 60 days of receipt of the petition. Alternatively, if the Board does not have a regular meeting scheduled within 60 days of receipt of the petition, or if hearing the petition at the next regular meeting would defer more pressing matters, the Chair shall call a special meeting of the Board to consider the petition for rulemaking.

Procedure

- **Notifications:** Board staff, in consultation with the Executive Director, will respond to the petitioner within three business days acknowledging receipt of the petition and informing the petitioner whether the request is clear. The Executive Director or staff will notify Board members that a petition for rule-making has been received and will be brought to the Board for consideration at the next regularly scheduled board meeting or will be considered at a special meeting. If

no regular meeting is scheduled before the 60-day response deadline, or if the agenda for the regular meeting cannot accommodate the petition, the Executive Director will notify the Chair of the need to schedule a special board meeting for the purposes of considering the petition. Upon Board action on the petition, the Executive Director shall assure Board members receive electronic copies of the final petition response.

- **Appeals:** If a petitioner appeals the Board's decision to deny a petition to the Governor, the Executive Director will inform the Board of the Governor's action on the appeal at the next scheduled Board meeting.

- **Consultation:** The Executive Director and Board staff will gather background information for the Board's use when it considers the petition. In this regard, the Executive Director will consult with the Board member who sponsored the most recent revisions to the rule being challenged or the appropriate policy committee. The Executive Director may also consult with appropriate representatives of the implementing agency or agencies, and may consult with stakeholders as appropriate.