Health Evidence Review Commission's Evidence-based Guideline Subcommittee

December 2, 2021

2:00 PM - 5:00 PM

Online meeting

Join online meeting here

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Section 1.0

Call to Order

AGENDA

EVIDENCE-BASED GUIDELINES SUBCOMMITTEE (EbGS)
December 2, 2021
2:00pm - 5:00pm
Online meeting

Public comment will be taken on each topic per HERC policy at the time at which that topic is discussed.

#	Time	Item	Presenter
1	2:00 PM	Call to Order	Devan Kansagara
2	2:05 PM	Review of 9/9/2021 minutes	Devan Kansagara
3	2:10 PM	Staff update	Jason Gingerich
4	2:15 PM	Review public comments: High Frequency Chest Wall Oscillation Devices	Ariel Smits Bethany Godlewski
5	3:15 PM	Draft coverage guidance: PANDAS/PANS	Ariel Smits Bethany Godlewski
6	4:45 PM	Confirmation of the next meeting, February 3, 2022	Devan Kansagara
7	4:50 PM	Next Topics	
8	5:00 PM	Adjournment	Devan Kansagara

Note: All agenda items are subject to change and times listed are approximate

MINUTES

Evidence-based Guidelines Subcommittee

Virtual meeting
September 9, 2021
2:00-5:00pm

Members Present: Devan Kansagara, MD, Chair; Vice-Chair; Alison Little, MD, MPH; Lynnea Lindsey, PhD (joined 2:15pm); Leslie Sutton; Max Kaiser, DO; Vern Saboe, DC.

Members Absent: Michael Adler, MD; Eric Stecker, MD, MPH; Leda Garside, RN, MBA.

Staff Present: Ariel Smits, MD, MPH; Jason Gingerich; Liz Walker, PhD, MPH; Daphne Peck.

Also Attending: Bethany Godlewski, Ph.D., Shauna Durbin & Val King, MD, MPH (OHSU Center for Evidence-based Policy); Aaron Trimble, MD; Alison Christy, MD; Paria Zarrinnegar, MD; Carrie Woodman; Cathy Daraee; Christy Jagdfeld; Claire Prihoda & Senator Kate Lieber (Office of Senator Kate Lieber); Deborah Miller; Dritan Agalliu, Ph.D.; Emily Kaine; Sara L Fletcher; Gary Hansen, Ph.D.; Herbert Lachman; Inga Deckert; Ivan Vejar; Jeff Scroggin (OHA); Jennifer Matson, MPH; Jennifer Rowan; Jessica Johnson; Joey Razzano; Kelley Utterback; Kym McCornack; Madison Walters; Maryland Black, MBA; Meggan Bennett, MPH; Melanie Ewald; Mike Daines; Molly Ryan Ochoa; Morgan; Diana Pohlman (PANDAS Network); Paul Ryan (PACE Foundation); Recan; René Akre; Representative. Rachel Prusak; Rob Le; Rob Millis; Sarah Lemley, MPA, HA (Northwest PANDAS/PANS Network); Senator Deb Patterson; Shani Noel, MBA (Hillrom); Soren S Bennett; Suzanne Millis; Wendy Nawara.

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1. Call to Order

Devan Kansagara called the meeting of the Evidence-based Guidelines Subcommittee (EbGS) to order at 2:03 pm. A quorum of members was present at the meeting.

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2. Minutes Review

Minutes from the June 3, 2021 meeting were reviewed and approved 6-0.

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3. Staff Report

Jason Gingerich read the orientation statement. Gingerich then gave a brief update of the Oregon Medicaid waiver renewal process. He also updated members about the recent rules advisory committee which met in August and gave feedback on a new rule incorporating the recently approved bylaws. Once that rule is in effect, members will be asked to fill out a new conflict of interest survey that reflects those changes.

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4. Review public comment disposition: High-Frequency Chest Wall Oscillation Devices

Gingerich began the public comment disposition review by introducing the appointed ad-hoc expert:

Dr. Aaron Trimble is Assistant Professor in Pulmonary and Critical Care Medicine at Oregon Health and Science University. He has expertise in pulmonology and conducts research in cystic fibrosis and mucociliary clearance. He prescribes high-frequency chest wall oscillation devices for patients with cystic fibrosis and bronchiectasis and is also part of the adult CF clinic at OHSU. He has received grant funding from the Cystic Fibrosis Foundation to study high-frequency chest wall oscillation devices. He has also received research funding and food/travel/beverages for his work on CF medications.

Gingerich reviewed the public comments submitted during the formal comment period as well as the discussion table that was in the meeting document. He summarized the main issues raised by the commenters. Kansagara asked if members had any questions about the disposition document. Staff presented the proposed recommendation for the draft coverage guidance.

Public testimony

Joey Razzano, parent: Razzano introduced herself as the Oregon representative for the International Rett Sydrome Foundation and said she is speaking on behalf of the Northwest Rett Syndrome Association. She disclosed that she is employed by the Oregon Health Authority but is speaking on behalf of her developmentally disabled daughter. She said that studies for conditions such as Rett Syndrome will always be too small to be considered for these kinds of policy decisions. She described her personal experience of intensive hospital care every winter and how "vest therapy" can be a cost-effective alternative to emergency room use. Manual chest physiotherapy is not effective or safe for someone who is as medically complex as her daughter. She asked the subcommittee to expand the coverage recommendation to include conditions such as her daughter's.

Gary Hansen, Director of Scientific Affairs for RespirTech (manufacturer of devices): Hansen thanked the subcommittee for their thorough review of the evidence that was submitted by RespirTech. He is disappointed with the narrowness of the criteria and said he is hopeful that the subcommittee will be open to accepting future evidence that RespirTech is working to produce.

Sutton had a question for Joey Razzano, asking how many people in Oregon have Rett Syndrome. Razzano said she knows of between 80-100 families with an affected member. Kansagara asked Sutton to expand on her thinking behind her question. Sutton responded that small populations often do not have the science or evidence that demonstrate a benefit given their small and vulnerable size. This is a challenge that HERC often grapples with, and the need for HERC to be responsive to the needs of Oregonian families is needed. Trimble agreed with Sutton, stating that other limitations, such as lack of consensus around study endpoints, are barriers to getting the evidence developed. The well-defined diagnostic criteria for cystic fibrosis (CF) is what makes it easier to study. Bronchiectasis is less-defined, and the heterogenous group of patients with neuromuscular diseases that also have respiratory failure is complex to study.

Shani Noel, Director of Market Access for Hillrom (manufacturer of devices): Noel began her testimony by discussing her employer's recent publication of the budget impact of the vest for managing airway clearance in patients with complex neurological disorders. She presented the Hillrom study findings, disclosing that she is a co-author, and said that there were significant cost reductions associated with

high-frequency chest wall oscillation. The cost analysis also demonstrates that use of this device is cost effective for patients with complex neurological disease.

Kansagara asked to see the draft coverage guidance recommendation. Staff presented the GRADE tables for each of the four conditions. Kansagara pointed out that the exception process exists for exceptions to the rule and that is why the rationale is a weak recommendation. Little asked about the study referenced by Noel and if it was incorporated into the coverage guidance report. King responded that that study was not identified in their literature search and was not submitted during the formal comment period. Kansagara continued with the neuromuscular disease GRADE table, stating that it is not an individual disease but rather a collection of many types of heterogenous diseases. He asked Trimble if he had any thoughts as to the biological plausibility of the vest for these populations. Trimble responded that a cough assist device is often used for muscle weakness, but that it requires engagement by the patient whereas the vest is more passive, making the use of cough assist devices challenging when there is any cognitive impairment involved. Trimble also said that if there is presence of inflammation or an abscess, a cough assist device may not be enough and mechanical therapy may be needed, though that is based on plausibility and not based on the evidence in the report. For bronchiectasis, even though it represents a subset of heterogenous conditions, the same mechanism of benefit would exist for mechanical therapy as for CF, with the only differences being the molecular makeup of the sputum and the genetic origin of CF.

Sutton asked the expert why then the proposed recommendation excludes bronchiectasis and includes CF. Smits responded that the evidence did not show a benefit for bronchiectasis. Trimble added that when he cares for CF-bronchiectasis versus non-CF-bronchiectasis, the variability is much greater in the latter group, as it's drawing from a broader collection of underlying diseases. This makes it difficult to study primary outcomes with a more diverse set of patients. As a provider, patient selection becomes very important when deciding for whom to prescribe inhaled dornase alfa, inhaled hypertonic saline, or mechanical therapy.

Sutton said that given the heterogeneity of the different populations, she was uncomfortable with the weak recommendation against coverage when someone might benefit from this therapy. If the decision is switched to a weak recommendation for coverage, then that pathway can be considered for a patient. The exceptions process is difficult. Little asked Sutton which conditions she was referring to. Sutton responded that her comments are directed at neuromuscular disease. Smits asked Trimble if the currently proposed criteria for CF would be applicable to both bronchiectasis and neuromuscular diseases. Trimble said the criteria apply to bronchiectasis, but it's more complicated for neuromuscular diseases, as the hospitalizations requirement could be for a number of different complications. Chronic airway infection would be a possible addition for this group, defined as persistent culture positivity. Little said that as a medical director, the more defined the criteria for each of these conditions, the better it'll be in implementing this guidance. She asked staff to briefly refresh the subcommittee on the state of the evidence for each of these conditions. Godlewski gave the overview of the GRADE tables. Kansagara said that given the time limitations for this topic, he suggested that staff work wit the expert to revise the recommendation language and bring it back to the group. Smits asked for direction from the group and which indications to revise language for. Kaiser said that he was comfortable with the initial recommendation language given the dearth of evidence. Gingerich said that staff can prepare a few options and post it for public comment and then bring it back to the committee in December to finalize. Kansagara asked if there is a motion for staff to revise the recommendation for a weak recommendation for coverage for CF, bronchiectasis, and neuromuscular diseases, with specifics worked out by staff and the expert.

A motion was made to ask that revise the draft recommendation based on today's discussion and in consultation with Kansagara and Trimble, then post it for an additional public comment period. **Motion approved 6-0.**

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5. Review coverage guidance for PANDAS/PANS/Pediatric Autoimmune Encephalitis

Gingerich began the presentation by introducing the three appointed ad hoc experts.

Dr. Alison Christy is the Clinical Director for Providence Pediatric Neurology at Providence St. Vincent Medical Center. She is a pediatric neuroimmunologist and her areas of expertise include neuroimmunological disorders, pediatric neurology and movement disorders. She has given multiple talks on the topic of PANDAS/PANS at professional conferences in Portland. She is director of the Doernbecher Immune Brain Disorders Clinic. Christy has no relevant conflicts of interest to disclose.

Dr. Michael Daines is Associate Professor and Division Chief of Pediatric Allergy, Immunology and Rheumatology. He is also the Co-Director for the Children's Post Infectious Autoimmune Encephalitis Center of Excellence in Tucson, AZ. His specialties are pediatric allergy and immunology. Daines is the lead investigator of a FDA-approved phase 3 clinical trial for IVIG in the treatment of PANS. His Division also oversees several active research projects related to PANDAS/PANS and has a registry for patients and family members. Dr. Daines has received industry funding from Octapharma for the design of the Phase 3 IVIG trial (paid to the university). He has also received travel reimbursements from the PACE Foundation, a PANDAS/PANS advocacy organization.

Dr. Paria Zarrinnegar is Assistant Professor of Psychiatry at OHSU, joining in 2018. She is a board-certified psychiatrist who specializes in biopsychosocial assessment among children and adolescents. Zarrinnegar has no relevant conflicts of interest to disclose.

Godlewski gave an overview of the scope statement and walked through the evidence synthesis. Smits presented the values and preferences section of the presentation, as well as the resource allocation considerations and the staff's draft weak recommendations. Kansagara thanked the presenters for the evidence overview and to moved to hear public testimony.

Public testimony
Kym McCornack, outreach coordinator for Northwest PANDAS PANS Network: McCornack ceded her time to Dr. Dritan Agalliu.

Dritan Agalliu, Columbia University Associate Professor in the Department of Neurology: Dritan began his testimony by questioning the expertise and literature that was used to inform the report and presentation. He said he has worked in PANDAS and PANS for 10 years and many of his studies are not cited or discussed, and described two of his group's basic science papers. He has mice models that study the mechanisms of these diseases and that strep infections elicit an immune response that targets the brain, which can lead to neuropsychiatric symptoms. He described other studies that are under review that show that PANS patients have a cytokine profile in their blood indicative of inflammation. He said these children have abnormal immunity and that azithromycin reduces obsessive compulsiveness in these children, as does cognitive therapy.

Sutton asked Agalliu if he would recommend corticosteroids, antibiotics, or therapy for coverage for these conditions. Agalliu responded that with the current IVIG trials underway, he completely agrees that the published studies are inconclusive, and that this subcommittee should withhold their decision on IVIG until these trials are concluded. His data from the animal models demonstrates that antibodies target the central nervous system. He states that in his opinion, there is still a lot of evidence out there to suggest that this might be a form of post-infectious autoimmune encephalitis.

Daines said that he thinks all of the IVIG studies cited so far have been appropriate and hopes that his study that is currently being run by Octapharma is going to be conclusive. He described the current evidence on IVIG trials and reductions in OCD and said that despite the one-month follow up, the benefit was significant. He said the small size of the study is a limitation, but it still demonstrates the benefits and that was not the consensus of the earlier discussion. Kansagara responded that no consensus has been reached yet as the subcommittee is still discussing the content of the report. Kansagara asked the next testifier to speak.

Sarah Lemley, Director of the Northwest PANDAS PANS Network: Lemley began her testimony by describing her 12-year old daughter who has PANDAS and whose condition was reversed by azithromycin and steroids. Lemley stated that in 2019, a house bill was passed to promote awareness for PANDAS/PANS and the declaration stated that treatments may include antibiotics, steroids, IVIG, therapy, and other modalities as needed. Lemley said this report dismisses work done by NIMH and the legislative work in other states. She said adopting this guidance would be irresponsible for Oregon children and that expertise from national experts and bodies are needed.

Deborah Miller, parent: Miller described her 12-year old son who has not been able to get treatment for his PANDAS condition. She said he is a victim of the broken health care system because he does not have access to the treatments he requires. The IVIG treatment that has been recommended for him is every 4 to 6 weeks at a cost of $50,000. She urged the subcommittee to make treatments accessible for children like her son.

Meggan Bennett, parent: Bennett described her 11-year old son with PANDAS, saying he is receiving social security benefits because of his symptoms. He has not improved on antibiotics, steroids, or tonsillectomy and is unable to take psychiatric medication. His pediatrician has recommended IVIG but her family is unable to afford the treatment. She described her son before he got sick and how their family has been experiencing this since he was 6 years old. She pays out of pocket for many treatments that insurance doesn't cover, including hyperbaric infusions and supplements.

Jennifer Matson, parent: Matson described how her 14-year old son was diagnosed with PANDAS when was 12, developing psychiatric and compulsive symptoms. Physicians in the hospital would not consider a PANDAS diagnosis so she sought a Chicago pediatrician who treated many PANDAS and PANS children. Her son had his tonsils and adenoids removed and her employer paid for IVIG treatments. Today, her son is free of PANDAS symptoms. She said that her insurance company paid over $30,000 to acutely hospitalize her son but the IVIG only cost $12,000. His medical care has been about $1,200 per year since he received IVIG.

Paul Ryan, President of PACE Foundation: Ryan discussed the national standard of care for PANDAS and PANS, presenting a slide of a map that showed national locations of centers of excellence across the country, some of which were created with assistance from the NIMH. The standard of care includes the treatments that are under consideration in the draft coverage guidance report. Eight states have

authorized insurance coverage for such medical treatments. The subcommittee should join the recent legislative expansions by recommending these treatments, as any other decision would deny Oregon families the same treatment protocols that are available elsewhere.

Rachel Prusak, Oregon House Representative: Prusak introduced herself and stated she is the Chair of the House Healthcare Committee as well as a family nurse practitioner. She supports evidence-based decisions regarding PANDAS and PANS treatment. After working with advocates on this issue, and hopes that the subcommittee can consider this discussion more broadly than just the evidence. During legislative session, she was looking forward to HERC's deliberation of this topic. She said that while side effects exist for any of these treatments, that practitioners must weigh the risk and benefit of such interventions. She concluded by stating it is vital to increase access to care for Oregon families who experience these conditions.

Kansagara thanked the testifiers and stated that this is a challenging topic as many of those present here are parents and empathize with the testifiers' stories. He invited the experts to weigh in on the report and presentation. Daines commented that the weak recommendation for SSRIs and behavior therapy for those who exhibit OCD symptoms is misguided, as the major diagnostic criterion for PANDAS and PANS is OCD. A revised wording of that language could be that SSRIs and therapy are approved to treat OCD in PANDAS/PANS, rather than the current, potentially confusing, wording. Kansagara agreed. Daines also said that even though IVIG has a black box warning, that complications are typically seen in those patients who have significant comorbidities and that children who are relatively healthy do not commonly experience such symptoms. Peck said that one more testifier is present.

Diana Pohlman, Director of PANDAS Network: Pohlman founded the network in 2009 because of her two children who had PANDAS at the age of 7. Repeated strep infections led her to discover PANDAS and the IVIG protocol and within one year of treatment, her son was fine and is now a young adult and successful. Her daughter also recovered in a relatively short amount of time. She didn't understand a lot of the research presented today but hopes that the conversation can be broader than just the evidence. She has spoken to thousands of families over 14 years, and IVIG is important to families.

Christy summarized her background and emphasized that there isn't much data behind the different medications under consideration. There is a clear distincition between PANDAS/PANS and autoimmune encephalitis, as PANDAS/PANS have been around for 27 years and no clear biomarker has been found. For autoimmune encephalitis, which was discovered in 2005, an antibody was identified within two years as well as the pathophysiology. There are clear diagnostic criteria for this condition. Given the clear distinctions, she is not sure all of these conditions belong together in the report. There is no great treatment for PANDAS/PANS and is not clear how the diagnostic criteria will evolve. Given the current treatments, and the sick children who present for care, physicians should be able to prescribe medications and not leave parents in a desparate position to pay out of pocket. Kansagara thanked Christy and said one approach could be carving out the autoimmune encephalitis from the report given the clear distinctions. Christy agreed that with a clear biomarker for autoimmune encephalitis, it puts it in a different category. Daines said his trial will be doing pre- and post-psychiatric testing so that they can demonstrate an objective benefit. Kansagara said that the subcommittee members may wish to set aside pediatric autoimmune encephalitis for now and continue with the discussion for PANDAS/PANS. He asked for Zarrinnegar to provide her input. Zarrinnegar introduced herself and stated she thinks PANDAS is a rare illness that exhibits OCD in a unique way from the broader pediatric population. This poses uncertainty around which approach to take to treat these patients, as some worry that every child with treatment-resistant OCD will seek out these interventions. She and Christy share many of the same

patients, and it will be important to collaborate with clinicians from different disciplines to decrease the chance of children receiving unnecessary antibiotics and medications.

Little asked if the evidence specialists can respond to the concerns voiced by the testifiers. Kansagara said he wants to prioritize subcommittee member delieration first. Lindsey said that some wording revision could benefit the current proposed recommendations. Lindsey asked how removing the autoimmune encephalitis indiciation would impact testimony heard today. Kansagara responded that by setting that indiciation aside, given the different diagnostic criteria, that that would simplify the types of the decisions being made. Smits said that the initial inclusion of this condition was because advocates asked for a broad inclusion of conditions and treatments. Christy agreed with carving out this indication, as these patients will be seen in the hospital and generally not receiving IVIG in the outpatient setting. Little asked if that indication was included in the house bill earlier in the session. Gingerich said no, and that another issue is that PANDAS and PANS do not have an ICD-10-CM code, there is just an index entry for for PANDAS. Prusak clarified that the bill did not pass. Agalliu said that, clinically, autoimmune encephalitis is different from PANDAS/PANS. But from a mechanistic point of view, there are similarities. Kansagara said that there may be similarities but excluding the condition would be a practical consideration for the report. He also said that Zarrinnegar's point about OCD being common in the pediatric population, as is getting a strep infection, is worth discussing. The sudden onset of symptoms seems to be a distinction, but the concern remains regarding broad application since PANDAS/PANS is a diagnosis of exclusion. Daines said that setting up a multidisciplinary center and filtering patients through that would solve that issue. Zarrinnegar stated tha the Stanford clinic does outreach and education of local pediatricians on these conditions. Sutton said that given her own family experience, she appreciates the idea of a multidisciplinary team but that given the sudden nature of this disease, being on a waiting list to be seen at a specialty center can be impractical for families.

Kaiser asked about the practicalities of IVIG. Daines described his currently ongoing study and the use of pre and post psychometric testing and how their clinic determines who receives ongoing IVIG and who is not showing benefit. Daines said only about 10% of the children at his center get IVIG. Kaiser said that this speaks to the necessity of having a multidisciplinary center. Daines said in order to remain accessible, he provides phone consults to out-of-state physicians and holds open spots in his schedule for emergency cases. The existence of a registry also helps with decision making in this poorly understood condition. Sutton clarified her earlier comment that she is not against a multidisciplinary center but that she wants to make sure people have timely access to treatments. Kansagara asked Gingerich and Smits about next steps for revising the coverage guidance draft, including carving out the autoimmune encephalitis and incorporating the expert testimony, as well as responding to some testifiers' concerns about not including evidence. Gingerich asked if staff should lower their evidence threshold to include lower levels of evidence sources. Kansagara said that the evidence criteria for inclusion should not change but staff should respond to why some studies were not considered. Gingerich said that anyone can submit a study for consideration during the formal comment period, which is the step that follows the subcommittee's deliberation and initial vote. Staff will bring back a revised draft guidance in December and that can be discussed and voted on, and then put out for formal public comment. Smits reiterated that each step in this process will provide ample opportunity to rework language. Kansagara thanked everyone for their involvement and adjourned the meeting.

No motion was made. Staff will bring back a revised draft coverage guidance to the next meeting.

6. Adjournment

The meeting was adjourned at 5:00 pm. The next online meeting is scheduled for December 2, 2021 from 2:00-5:00 pm.

Section 2.0

Review Public Comment

Disposition

HERC Coverage Guidance: High-Frequency Chest Wall Oscillation Devices
Disposition of Public Comments

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Discussion Table

IDs/#s	Summary of Issue	Subcommittee Response
A2, C1–C2, C9	Chest physiotherapy and airway clearance devices are not effective for patients with intellectual or developmental disabilities who cannot actively engage with such therapies effectively.	The revised coverage guidance recommendation includes a recommendation for coverage of high-frequency chest wall oscillation (HFCWO) devices for patients for whom chest physiotherapy and positive expiratory pressure device therapy are not tolerated, contraindicated, or not available (e.g., inability of a caregiver to perform).
A3	Some bronchiectasis patients do not have a cough and thus the coverage guidance should remove the daily productive cough as a requirement for HFCWO device therapy	The inclusion of daily productive cough was added as a requirement for HFCWO therapy for patients with non-cystic fibrosis (non-CF) bronchiectasis based on information extrapolated from studies of the cystic fibrosis (CF) population, and as recommended by our appointed ad hoc expert. *For EbGS discussion.*
C3–C4	This coverage guidance should include a list of covered conditions and include Rett Syndrome in that list.	This subcommittee declined to produce a list of covered conditions given the heterogeneity of neuromuscular disorders for whom HFCWO therapy may be effective. Instead, detailed coverage indications ensure that a patient with a very rare disorder may still be eligible for HFCWO therapy provided they meet the criteria.

HERC Coverage Guidance: High-Frequency Chest Wall Oscillation Devices
Disposition of Public Comments

Commenters

Identification	Stakeholder
A	Jenna Kelly, parent/caregiver of a child with non-CF bronchiectasis *[Submitted September 24, 2021]*
B	Sharon Skidmore, PT, DPT Physical Therapy for Kids, LLC *[Submitted September 28, 2021]*
C	Joey Razzano, parent/advocate/caregiver of person experiencing Rett Syndrome, International Rett Syndrome Foundation, NW Rett Syndrome Association *[Submitted October 14, 2021]*

Public Comments

ID/#	Comment	Disposition
A1	Please make the vests affordable for families. My child has non-CF-bronchiectasis. It took me years to pay his off and it was a significant struggle for my family.	*Thank you for your comments. We have written specific responses to individual sections of your letter in the rows that follow.*
A2	He also is Autistic and blowing in the little devices was not feasible. He was too young and not able to use them effectively. Once he started using the vest he improved so incredibly much.	*The revised draft coverage guidance includes a pathway to coverage for HFCWO device therapy if other treatments are not tolerated, available or contraindicated.*
A3	Also, I don't like the cough requirement. My son never coughed. He just had a ton of mucus and couldn't/would not expel it on his own, so he would get infections constantly.	*Based on expert testimony, HFCWO device therapy is most effective among patients with non-CF bronchiectasis who have a daily productive cough.*
A4	By expanding the coverage of devices It will also make it easier to get them serviced and sized.	*Thank you for your comment.*
B1	I agree with coverage as the use of High Frequency Chest Wall Oscillation Devices has shown to be very effective and reduces hospitalization when used correctly and consistently which ultimately leads to better patient care and reduced overall cost.	*Thank you for your comment.*

HERC Coverage Guidance: High-Frequency Chest Wall Oscillation Devices
Disposition of Public Comments

ID/#	Comment	Disposition
C1	I am just a mom and Rett rep who has personally seen ICU's fill every winter with Rett patients in respiratory distress. When determining criteria for when a HFCWO device should be covered, there are a few observations I've made specific to Rett Syndrome - that is the presence of both scoliosis and hypotonia, often including the use of a wheelchair. Rett patients cannot speak and have no functional hand use to indicate difficulty breathing. Most are at risk of constant aspiration as well. The "cycle" is this: a Rett patient aspirates or is exposed to a virus, develops pneumonia, end up in the emergency room at their O2 sats drop and they will be hospitalized. Respiratory therapy is ordered and the HFCWO device is used, often in conjunction with a cough-assist device.	*Thank you for your comments. We have written specific responses to individual sections of your letter in the rows that follow.*
C2	If scoliosis is present, the kiddo will get well enough to recover at home but a dimness or small amount of infection tends to remain in the lower lobe of one or both lungs. Kiddos with low-tone, scoliosis and a wheelchair can never really expand their chest cavity so the HFCWO provides an effective home therapy that can be done safely and in the home to provide lung clearance. It is not typically prescribed before hospitalization but the pulmonologist will often send the device home as part of routine care following an emergency room visit or hospitalization.	*This level of clinical specificity is not included in the studies identified for this review.*
C3	I would suggest Rett Syndrome or similarly complex syndromes be added to the list defined on page 18 in the background section.	*The subcommittee elected to produce detailed coverage criteria instead of producing a list of covered conditions in order that persons with very rare disorders can obtain access to HFCWO therapy provided they meet the criteria.*
C4	I also suggest that this group look at other states' recommendations for coverage in neuromuscular conditions for more definitive criteria.	*Our policy is to report coverage for Medicare, Washington's Medicaid program, and selected payers active in Oregon (e.g., Aetna, BlueCross BlueShield of Oregon, Cigna, and Moda).*

HERC Coverage Guidance: High-Frequency Chest Wall Oscillation Devices
Disposition of Public Comments

ID/#	Comment	Disposition
C5	I also think there should be a return on investment study performed on the neuromuscular population that evaluates the cost of the device versus the expense of a single night in an ICU and I know you will find it is comparatively cheap insurance for this specific population.	*We searched for comparative cost effectiveness studies for this coverage guidance and did not identify any that met our inclusion criteria.* *The subcommittee relies on existing, peer-reviewed published research to make coverage recommendations. It is outside of this group's scope to independently conduct economic studies.*
C6	I also think th4ere's typo on page 24 where it should read CONGENITAL muscular dystrophy under pulmonary complications.	*Thank you for drawing our attention to this typographical error. We have corrected this in the current draft.*
C7	I also wonder if the lungs themselves are considered part of the airway since the wording of the recommendation specifically says "chronic airway infection" - and what defines chronic? My daughter was hospitalized 6 times in one year with pneumonia but we have been able to avoid hospitalization multiple times since then.	*The subcommittee decided against defining "chronic," leaving ability for the exercise of clinical judgment.*
C8	The word CONTRAINDICATED is included in the neuromuscular bronchiecstatis guidance but not the CF guidance. I wonder why they are different.	*We agree and we have updated the wording in both sections.*
C9	The inability of the caregiver to provide chest physiotherapy is an important factor and I am glad to see it included in the criteria for recommendation	*Thank you for your comments.*

HERC Coverage Guidance: High-Frequency Chest Wall Oscillation Devices
Disposition of Public Comments

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Discussion Table

IDs/#s	Summary of Issue	Subcommittee Response
A3, A4, A6, B2–B8, C3–C6, C8	Evidence not included in this review shows effectiveness of HFCWO for COPD, bronchiectasis, neuromuscular disease, and cystic fibrosis.	Most of the data submitted from commenters were not published in peer-reviewed journals (e.g., posters and conference abstracts) or used noncomparative before-after designs. Others did not appropriately include the relevant populations or appropriate outcomes to address the Key Questions. One study did meet inclusion criteria and has since been added to the coverage guidance, but it did not change conclusions.
B1, B2, B9, C3	The state of the evidence for HFCWO therapy is sparse given the rare diseases it treats, lack of consensus on study endpoints, and inability to use blinding. Lower-quality evidence obtained from real-world data (claims databases) shows this therapy is effective and cost-effective. This lower-quality evidence should be considered, and coverage should be recommended for other conditions.	Although observational before-and-after studies (like those submitted by commenters), do appear to show benefit, the study designs do not permit us to determine whether the effect was caused by HFCWO devices; these study designs cannot control for confounding factors. More robust study designs exist, such as the randomized trial, or if that is not feasible, a matched-cohort or interrupted-time-series study. Though a randomized trial would be very challenging for the heterogenous population with neuromuscular disease, it would be feasible for COPD and bronchiectasis, as they are relatively common conditions. Initially, evidence related to non-CF bronchiectasis and neuromuscular conditions supported non-coverage. However, we have revised our recommendation to allow limited coverage based on the potential benefit and expert recommendation to extrapolate evidence from CF to other non-CF bronchiectasis and on pathophysiological reasoning. For neuromuscular conditions, the variety of disease manifestations makes

IDs/#s	Summary of Issue	Subcommittee Response
		the development of a strong evidence base for each condition unlikely. Thus, we have based our recommendation on expert input and the potential to reduce costs associated with hospitalization and chronic airway infection.
A9, C2, D1, D4	Patients prefer the convenience and independence afforded by HFCWO. The availability of HFCWO devices respects patient preferences and offers several practical advantages. Some patients with varying conditions cannot use chest physiotherapy for practical reasons or because of contraindications related to their conditions.	We note patient preferences for convenience and independence in our GRADE tables and the Values and Preferences section in the report. Patient values and preferences are an important part of the rationale for coverage of HFCWO for patients with cystic fibrosis, for which evidence indicates HFCWO is comparably safe and effective to chest physiotherapy.
A5, C3, C7	Medicare, most state Medicaid programs, and most commercial payers provide coverage for cystic fibrosis, neuromuscular disease, and bronchiectasis. HERC should recommend coverage for patients with these conditions for whom other therapies are ineffective or contraindicated.	The report describes coverage for Medicare, Washington's Medicaid program, and selected payers active in Oregon (e.g., Aetna, Moda, Cigna, and BlueCross BlueShield of Oregon). These payers do cover HFCWO device therapy for cystic fibrosis and bronchiectasis, as well as for certain neuromuscular disorders. However, the subcommittee views other payer policies as contextual information rather than evidence of effectiveness. Step therapy is an appropriate utilization management tool for facilitating limited access to higher-cost services. However, even second-line covered services need to have sufficient evidence of effectiveness for improving critical or important outcomes.
D1–D5	Description of personal experience with a child with Rett's Syndrome and knowledge of other families whose children use the devices and are part of the Children's In-Home Intensive Waiver program.	Personal experiences, including reports of variation in provider and health plan decisions and processes, provide important context for the subcommittee's decisions. HERC's coverage decisions are made at the population level based on available evidence, informed by testimony and expert opinion. These decisions are intended primarily for health plans, including the Oregon Health Plan. The Children's In-Home Intensive Waiver program is not a health plan, and recommendations for that program are outside the scope of this report and outside the purview of the HERC.

HERC Coverage Guidance: High-Frequency Chest Wall Oscillation Devices
Disposition of Public Comments

Commenters

Identification	Stakeholder
A	David Chandler, Senior Director of Payer Relations at American Association for Homecare *[Submitted July 2, 2021]*
B	Gary Hansen, Director of Scientific Affairs at RespirTech *[Submitted June 29, 2021]*
C	Kari Roehrich, Executive Director Managed Care Market Access at Hillrom Respiratory Health *[Submitted July 1, 2021]*
D	Joey Razzano, Oregon Representative for the International Rett Syndrome Foundation, NW Rett Syndrome Association Board member, and mother to child with Rett Syndrome *[Submitted July 5, 2021]*

Public Comments

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A1	Dear Committee Members, The American Association for Homecare ("AAHomecare") includes a cross section of durable medical equipment ("DME") suppliers, manufacturers, and other stakeholders that furnish DME to acute patients and chronically ill individuals. AAHomecare's members are proud to be part of the continuum of care that assures that individuals receive cost-effective medical equipment and supplies, and related services, in their homes. AAHomecare supports high frequency chest wall oscillation (HFCWO) coverage for patients with airway clearance needs and appreciates the opportunity to comment on the Evidence-based Guidance Subcommittee coverage recommendations for HFCWO. HFCWO is an airway clearance therapy that healthcare professionals have long-used to treat patients with impaired mucociliary clearance and mucus hypersecretion – specifically for the clinical management of cystic fibrosis, neuromuscular disease (NMD), bronchiectasis, and chronic obstructive pulmonary disease (COPD). Due to the lack of coverage criteria and fee schedule for HFCWO in Oregon Medicaid's Durable Medical Equipment (DME), Prosthetics, Orthotics and Supplies	*Thank you for your comments. We have written specific responses to individual sections of your letter in the rows that follow.*

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	Administrative Rulebook and corresponding fee schedule, there may be access issues for patients with airway clearance concerns. AAHomecare strongly supports the subcommittee's guidance to recommend HFCWO coverage for patients with cystic fibrosis (CF) and urges the committee to consider HFCWO coverage for patients with NMD, bronchiectasis and COPD for the following reasons:	
A2	1) HFCWO therapy is an established technology that has served chronic respiratory patients for decades and is considered the standard of care for cystic fibrosis patients with an estimated 76% of the US CF population using the therapy for airway clearance, according to the 2019 CF Foundation Patient Registry Annual Data Report.	*Our background section acknowledges HFCWO device therapy is a commonly used treatment option for cystic fibrosis.*
A3	2) Respiratory complications are the leading cause of morbidity and mortality for patients with NMD, and HFCWO has been shown to reduce these complications. Some NMD patients are not able to tolerate manual CPT or be put in all of the required positions to receive the treatment.	*Our review found insufficient evidence that HFCWO device therapy reduces exacerbations and hospitalizations for conditions other than cystic fibrosis.*
A4	3) For patients with non-cystic fibrosis bronchiectasis, HFCWO therapy reduces the frequency of acute exacerbations, hospitalizations, antibiotic use and costs.	*For bronchiectasis, our review found very-low-confidence evidence that HFCWO device therapy improves key outcomes.*
A5	4) Medicare, most state Medicaid programs, and nearly all commercial payers, provide HFCWO coverage for CF, NMD and bronchiectasis patients.	*Our policy is to report coverage for Medicare, Washington's Medicaid program, and selected payers active in Oregon (e.g., Aetna, Moda, Cigna, and BlueCross BlueShield of Oregon). These payers do cover HFCWO device therapy for cystic fibrosis and bronchiectasis as well as for certain neuromuscular disorders.*
A6	5) For COPD, airway clearance devices reduce exacerbations and hospitalizations. According to a recent meta-analysis across 18 studies of airway clearance devices, future exacerbations were reduced by 50%. In addition, analysis of real-world data	*We identified the meta-analysis that you refer to (Daynes et al., 2021). The single included study of HFCWO devices that reported exacerbations for patients with COPD in this*

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	from the Optum claims database found that respiratory-related hospitalizations were reduced by 17% with the application of vest therapy. All-cause hospitalizations were reduced by 40%, ER visits by 27%, and office visits by 12% during the same time in a 2017 study using the Truven MarketScan database.	*meta-analysis was included and summarized in the coverage guidance. The other 17 studies included in this meta-analysis did not report exacerbations for patients with COPD in studies testing the effectiveness of HFCWO devices.* *The 2 other studies that you refer to (Berry et al., 2019; McEvoy et al., 2020) do not meet the study design requirement of the scope of this coverage guidance, as they were retrospective registry studies which additional devices and a broader set of disease entities than was included in this review. The analysis of claims from the Optum database was published as a poster (McEvoy et al., 2020), and is ineligible for inclusion.*
A7	6) Coverage criteria can ensure appropriate utilization by requiring patients to either try and fail other airway clearance therapies or have the therapy be contra-indicated by the patient's prescriber.	*Step therapy is an appropriate coverage tool for enabling access to higher-cost services. However, even second-line covered services need to have sufficient evidence of effectiveness for improving critical or important outcomes.*
A8	7) It is in the best interest of the patient to give physicians access to all therapies and devices to address specific patient needs.	*Thank you for your comment.*
A9	8) Coverage for HFCWO would respect patient preference, increase adherence to therapy, and provide assurance of reliable and consistent treatment, which would ultimately offset costs through reduced exacerbations and hospitalizations. 9) HFCWO offers practical advantages over other airway clearance approaches. For example, unlike chest physical therapy (e.g. chest physiotherapy, which is when a respiratory therapist claps on the chest to loosen mucus from the lungs), HFCWO	*Our review did not look at evidence regarding adherence to therapy and found insufficient evidence that HFCWO device therapy reduces exacerbations and hospitalizations for conditions other than cystic fibrosis. We have noted patient preference for convenience and efficiency in our GRADE table.*

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	devices make it easier and more efficient to perform chest physical therapy at home without the need for care delivery by a respiratory therapist or caregiver.	*The Values and Preferences section of the coverage guidance details how the lack of trained or willing caregivers can be a barrier to care, as well as how the use of HFCWO device therapy provides independence from caregivers.*
A10	HFCWO reduces respiratory complications for patients with CF, NMD, bronchiectasis and COPD. AAHomecare believes every effort should be made to facilitate access to effective therapies that can improve patient outcomes, reduce hospitalizations, and reduce further burdens to the healthcare system. For these reasons, AAHomecare encourages the committee to provide HFCWO coverage for CF, NMD, bronchiectasis and COPD patient populations. AAHomecare appreciates the opportunity to provide these comments.	*Thank you for your comments.*
B1	To Whom It May Concern: We reviewed the draft guidance for coverage of high-frequency chest wall oscillation (HFCWO) and are pleased with the recommendation for coverage of cystic fibrosis (CF). Thank you for this change and for hearing my testimony at the HERC meeting on June 3. We ask that you reconsider the recommendation for denial of coverage to patients with bronchiectasis (BE), neuromuscular conditions, and COPD in light of real-world evidence that was possibly not considered in the analysis presented. We would first like to comment on the state of evidence for HFCWO therapy. Despite being used for over 20 years, there is a paucity of comparative evidence for any airway clearance technique and a particular paucity of randomized control trials (RCT). There are good reasons for this.	*Thank you for your comments. We have written responses to specific individual sections of your letter in the rows that follow.*

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	1. HFCWO often treats rare diseases which makes it difficult to recruit cohorts of adequate size. There is little agreement on study endpoints. Prior studies did not identify or control for machine power settings or adherence. 2. Airway clearance studies cannot be blinded, making it impossible to do a double-blind study. HFCWO patients tend to be considerably sicker because of current prescribing habits, making post hoc comparisons between different types of devices difficult to interpret. 3. Lastly, there seems to be little interest among independent researchers on this topic, perhaps because the therapy has been around for so long. These difficulties should be considered when setting expectations for the evidence.	
B2	Here we provide additional evidence about the impact of HFCWO for bronchiectasis, neuromuscular disorders, and COPD that may have been overlooked in the systematic review. This evidence is derived from several objective sources (principally healthcare claims databases) and is complemented by patient-reported outcomes collected in a clinical registry of users of the Philips InCourage System. Collectively, real-world data supports the effectiveness of HFCWO for outcomes such as hospitalization, quality of life, and antibiotic use. We respectfully ask that this evidence be taken into account as you work to finalize the guidance. In 2016, your group expressed enthusiasm about our HFCWO outcomes in bronchiectasis patients and recommended that we publish the results - advice that we followed. We and others have made efforts to address evidence gaps by reporting patient outcomes as well as leveraging external databases of cleared healthcare claims. Collectively, these complementary sources have been published and/or presented at national and international conferences. Based on the data overview provided at the recent HERC meeting, much of this evidence was not considered or shared with the members of the committee.	*Although observational before-and-after studies, such as the real-world studies you refer to, do appear to show benefit, this study design does not permit causal inference, and cannot control for confounding factors. More robust study designs exist, such as the randomized trial or, if that is not feasible, a matched-cohort or interrupted-time-series study.*

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B3	The RespirTech bronchiectasis registry has been a source of outcomes for our product, the methodology and results appearing in a recent peer-reviewed publication.[4] The results show a reduction in hospitalizations for bronchiectasis patients after the initiation of HFCWO (Figure 1).[4] The authors took specific measures to reduce the risk of bias: (1) registry findings were validated against objective patient chart data, (2) all data were housed and managed by an independent actuarial firm, and (3) all statistics were conducted by a 3d-party biostatistician. While pre-post studies are subject to regression to the mean, these concerns are mitigated by the large sample and the persistent character of the improvement. The data show the response to HFCWO is sustained for up to two years; regression to the mean, if present, would become evident by this point.	*See response to B2 regarding study designs.* *Fundamentally, a before-and-after study may have other limitations in addition to regression toward the mean. In the example of a registry, confounders can include, but are not limited to, the patient characteristics and family context of individuals who have access to HFCWO device therapy, and changes in clinical care aside from the HFCWO device therapy.*
B4	With a larger data set of over 12,000 patients, we extended the results to two years of follow-up, revealing a 72% reduction in hospitalization rate in the two years after initiating vest therapy (Figure 2).[5] Regarding potential cost savings, this works out to be a bit less than one-half of an avoided hospitalization per patient per year. The avoided cost of an expensive inpatient admission compares favorably with the purchase price of the device.	*See response to B2 regarding study designs.*
B5	Real-world evidence from two separate databases of cleared healthcare claims also demonstrates reductions in hospitalization in bronchiectasis patients following initiation of vest therapy. As an example, Weycker showed all-cause hospitalizations were reduced by 33% (n=865 patients).[6] A new study by Basavaraj presented at the 2021 ATS meeting reports that hospitalizations reduced by 73% in year one and by 64% in year two.[7]	*See response to B2 regarding study designs.*
B6	Claims data support the benefits of HFCWO therapy for neuromuscular patients. Analysis of claims data showed a 25% reduction in respiratory-related hospitalizations.[8] In addition, a peer-reviewed publication found a corresponding 20% reduction in inpatient admissions and a 44% reduction in inpatient days.[9]	*Although Lechtzin et al., 2016 is a peer-reviewed publication, the study design was before-after, and the McEvoy et al., 2020 reference cited in this row was presented at a conference and not published in a peer-*

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		reviewed journal. See response to B2 regarding study design.
B7	Concerning COPD, we bring to your attention a new systematic review and meta-analysis which found that the use of airway clearance devices can improve exacerbation frequency.[10] 18 randomized controlled trials of airway clearance devices for patients with stable COPD were evaluated and reported that using devices to support everyday management reduced future exacerbations by 50%.	*The single included study of HFCWO devices that reported exacerbations for patients with COPD in this meta-analysis was included and summarized in the coverage guidance. The other 17 studies included in this meta-analysis did not report exacerbations for patients with COPD in studies testing the effectiveness of HFCWO devices.*
B8	In terms of hospitalization outcomes from patients with COPD (n=219) within our registry, we found a 54.4% reduction in annualized hospitalization rate for respiratory causes.[11] In addition, a study of Optum claims data found that respiratory-related hospitalization was reduced by 17% in the year after receiving vest therapy.[12] Similarly, a 2017 study using MarketScan data showed that all-cause hospitalization was reduced by 40%.[6]	*All 3 references cited in this row were presented as conference submissions and not published in peer-reviewed journals.*
B9	In summary, this beneficial therapy should be available in the toolkit for physicians in the treatment of patients with bronchiectasis, COPD, and neuromuscular disorders. The difficulties of designing and performing true comparative studies in this area are considerable and the likelihood of new large-scale RCTs being conducted for these disease states is low. However, recent real-world evidence directly addresses critical outcomes identified by this committee. The outcomes for HFCWO have been demonstrated using multiple independent sources. The convergent findings from these studies, specifically as it relates to reducing hospitalizations and improving patient quality of life, should be considered so that this life-altering treatment is available to those who need it.	*Thank you for your comments.* *We reviewed the references that you provided and considered each for inclusion in the coverage guidance. Two references were excluded for not meeting the scope of the coverage guidance (Mikesell et al., 2017; Rubin, 2007). Six references were excluded because they were conference presentations (Barto et al., 2019a; Barto et al., 2019b; Weycker et al., 2017; Basavaraj et al., 2021; McEvoy et al., 2020a; McEvoy et al., 2020b). Three references were excluded due to ineligible study designs (noncomparative observational: Basavaraj et al., 2020; Barto et al., 2020; observational before-after: Lechtzin et al., 2016).*

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		Your work to address the evidence gaps is helpful and may motivate others to perform more rigorous research on these conditions. However, the subcommittee uses only peer-reviewed studies and generally requires between-group comparison for evidence of treatment effectiveness.
C1	Dear EbGS Committee Members, Hillrom appreciates the opportunity to provide comment on the coverage recommendation for high frequency chest wall oscillation (HFCWO). HFCWO therapy is an established technology that has served chronic respiratory patients for over 30 years. Hillrom strongly supports the EbGS Committee's guidance to recommend HFCWO coverage for patients with cystic fibrosis (CF). Hillrom also requests the committee consider HCFWO coverage for patients with neuromuscular disease (NMD) and bronchiectasis.	*Thank you for your comments. We have written responses to specific individual sections of your comment in the rows that follow.*
C2	HFCWO coverage for patients with CF has expanded across the payer continuum such that at least 45 of the Medicaid fee-for-service plans cover HFCWO for CF beneficiaries. HFCWO is considered standard of care for CF as evidenced by the CF foundation's estimate that 76% of the US CF population uses HFCWO for airway clearance.[1] This is largely attributable to assurance or reliable and consistent treatment, adherence to therapy, and patient preference. Accordingly, providing HFCWO coverage for the CF population would ultimately offset costs through reduced exacerbations and hospitalizations.	*We recognize that HFCWO device therapy is a commonly used treatment option for cystic fibrosis. Though the available evidence shows no difference in hospitalizations compared to chest physiotherapy, we are recommending coverage because of patient preferences and because chest physiotherapy may not be available or feasible for all patients.*
C3	Hillrom strongly encourages the committee also consider coverage for patients with NMD. Respiratory complications are the leading cause of morbidity and mortality for patients with NMD and HFCWO has been shown to reduce these complications. The rationale for the recommendation for coverage for patients with NMD starts that there is no evidence that HFCWO devices improve key outcomes compared to	*No economic studies met our inclusion criteria for this coverage guidance.* *See response to comment A5 regarding other payer coverage.*

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	standard treatments. Hillrom asserts that sufficient comparative clinical evidence is available that supports the HFCWO therapy on improved key outcomes over standard treatments. Multiple economic outcome studies from highly reputable sources support HFCWO as a cost-saving strategy. Further, including HFCWO coverage for patients with NMD is consistent with Medicare, many Medicaid departments, and an increasing number of commercial payers.	
C4	The Yuan and Landon clinical studies compared the efficacy of HFCWO to chest physiotherapy (CPT). Both studies demonstrated significantly decreased rates of hospitalization for intravenous antibiotics and superior oxygenation for patients using HFCWO as well as superior adherence to the therapy. The investigator-initiated Fitzgerald study demonstrated a 32% reduction in hospitalizations (P<.01) in neurologically impaired children with respiratory symptoms. These studies provide sufficient comparative evidence of the superior benefits of HFCWO over standard treatment for this population.	*The Yuan et al., 2010 reference has been added to the coverage guidance since the submission of this comment. The Landon et al., 2022 reference was excluded because it was a conference abstract. The Fitzgerald et al., 2014 reference reported a before-after study. Although observational before-and-after studies, such as the real-world studies you refer to, do appear to show benefit, this study design does not permit causal inference, and more robust study designs exist, such as the randomized trial or, if that is not feasible, a matched-cohort study.*
C5	In addition, multiple economic outcomes data studies confirm the positive impact of HFCWO therapy on healthcare costs for neuromuscular disorders, which supports the efficacy of HFCWO when compared to standard treatment. Most notable is the 2019 research article published by the National Institute for Health Care Excellence (NICE) which analysed the cost-effectiveness of HFCWO compared to CPT in patients with complex neurological disorders, including neuromuscular disease and cerebral palsy.[5] This analysis revealed that per 1000 patients, the Vest System results in 2,422 less hospitalizations, and 49,868 less bed days compared to CPT, resulting in $8 M in cost savings over a five-year time frame.[5]	*This reference was excluded because the cost effectiveness estimates produced for the health system in the UK are not directly related to cost effectiveness estimates for the health system in the US (Javanbakht et al., 2019). Additionally, this study included information from a before-after study and from the Yuan et al., 2010 study that we have incorporated into the coverage guidance.*

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C6	Another important economic data study, 2020 Pandya,[6] analysed the claimed of 1008 patients from the Optum healthcare claims repository. The study demonstrated a reduction of respiratory-related hospitalizations by 24.7% ($p<0.005$) in patients receiving HFCWO therapy. Similarly, Lechtzin demonstrated a 41.7% decrease in inpatients costs post intitation of HFCWO.[7] These studies are based on thousands of patient records and clearly show the benefit of HFCWO compared to standard treatment.	*The Pandya et al., 2020 reference was a conference presentation of a before-after study; the other 2 references also utilized a before-after design.*
C7	Additionally, Medicare, most Medicaid departments, and nearly all commercial payers include HFCWO coverage for NMD patients. As of October 1, 2008, all CMS jurisdictions revised the HFCWO Local Coverage Determination to include NMD while over 40 Medicaid departments cover NMD disease state. Consistent with the criteria considerations included in the guidance, payer coverage policies ensure appropriate utilization by requiring patients must either try and fail other airway clearance therapies or have the therapy by contra-indicated by the patient's prescriber.	*See response to comment A5 regarding other payer coverage.*
C8	Hillrom also strongly encourages the committee to approve coverage for patients with non-cystic fibrosis bronchiectasis. In a comparative study, bronchiectasis patients on HFCWO demonstrated superior improvement in dyspnea, pulmonary function tests, and quality of life compared to patients on PEP or CPT.[8] Additional analyses suggest that HFCWO therapy reduces the frequency of acute exacerbations, hospitalizations, antibiotic use and costs in patients with bronchiectasis.[9,10,11,12,13]	*The first reference (Nicolini et al., 2013) is already included in the coverage guidance. The Weycker et al., 2017 and Basavaraj et al., 2021 references are conference abstracts. The remaining 3 references (Barto et al., 2020; Seivert et al., 2018; Sievert et al., 2017) references report studies with noncomparative observational designs. The remaining references are addressed in the previous rows.*
D1	I personally know hundreds of families in the Northwest that have benefited from the use of the HFCWO device aka "The Shaker Vest" when experiencing respiratory distress. The scope of the current coverage guidance is limited to CF and bronchiecstasis. While it refers to other neuromuscular disease resulting in chronic lung disease, Rett Syndrome does not really fall into any of those categories.	*Thank you for your comments and for sharing the story of a patient's care. While individual stories provide context for the Subcommittee's decisions, the Subcommittee makes coverage decisions on a population-level basis and*

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	Rett Syndrome is like having a child with autism, cerebral palsy, Parkinson's epilepsy and an anxiety disorder all in one. Our daughter also experiences osteoporosis, scoliosis and uses a wheelchair. She is at constant risk for aspiration which can lead to pneumonia literally in a matter of hours. The majority (>80%) of people with Rett Syndrome experience a neurological scoliosis which can require titanium rods to assist with opening the chest cavity. Otherwise, the lung is crushed and tends to fester a chronic infection in one lobe that quickly turns acute. When O2 sats drop, the shaker vest is the first step to increase O2 saturation. In the year before her spinal surgery, [Redacted name] was hospitalized 6 times for pneumonia and this was always the protocol. O2 sats drop, use shaker vest, then on to cough assist, bi-pap, cpap and then trach in that order. If a family has a shaker vest at home, this can often be avoided and it also helps with home care after a hospital stay. During each of these stays the therapists made sure we had this device at home despite having both primary and secondary insurance denying it. We appealed the denial over the course of a year, eventually losing all appeals because this committee has determined that CPT is cost effective and only bronchiecstasis and CF are coverable conditions. We were also at Randall Children's Hospital. My personal experience is that these devices get covered if you go to OHSU but not if you go to Randall. Why the inconsistency? As a parent, the unequal coverage and prescription among hospital systems suggests to me there are magic buzzwords being used that I am not privy to. As a family we were repeatedly assured that we had to go through the appeal and denial process – but that we would be denied eventually due to the current HERC guidance – and that Hill-Rom would gift it to us after that process. That is how I learned that Oregon is the ONLY state that doesn't cover these devices. What is it that 49 other states saw that Oregon does not? At the end of the long and complicated process of applications, appeals and denials, we had to send the device back to the company or pay them	*must base these decisions on evidence and other factors with respect to the population in general.* *Health plans can and sometimes do make individual coverage exceptions for patient circumstances. Appeal and hearing processes are required by law, but outside the Subcommittee's purview.* *The draft coverage guidance recommends coverage for certain patients with cystic fibrosis.* *HERC's coverage decisions are intended primarily for health plans, including the Oregon Health Plan. The Children's In-Home Intensive Waiver program is a separate program, and decisions on which services that program provides are outside the scope of this report.*

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	$16,000 for the privilege of having it on hand. We made the decision as a family that if her sats drop, we will take her straight to the emergency room because we don't have a shaker vest at home, even though it's the first thing the ER will do after the X-ray confirms diminished breathing in the lower lobes – every single winter….we are just one family on the hundreds of families on the CIIS waivers. Reading this guidance the short version is that: It ONLY covers CF and bronchiectasis and other neuromuscular disease resulting in chronic lung disease. What if you had a MEDICALLY INVOLVED person (as defined by the Children's In Home Intensive Waiver) that resulted in multiple chronic and acute lung and respiratory-related incidents that were not considered 'disease'?	
D2	The current recommendation is "weak" but I find this term vague for a variety of reasons – is it weak because there no empirical evidence or independent analysis on the cost-benefit ratio on the reduction or avoidance of hospitalization? Or is it weak due to the small sample size? IS it weak because the population is limited in scope? Any of those reasons would keep the financial liability limited as well	*According to the subcommittee's methodology (Appendix A), a weak recommendation indicates that "The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors, but further research or additional information could lead to a different conclusion."* *The factors leading to the recommendation are described in the GRADE table.*
D3	CPT is as cost effective as the shaker vest with similar results and can be done by paid or unpaid caregivers for 20-40 minutes per day multiple times a day – try to do that for even 10 minutes on a girl with a T2-Pelvis titanium rod in her back and see how effective that is! It is exhausting and the CPT provider is in constant fear of injuring the patient.	*We did not identify any cost-effectiveness studies that met our inclusion criteria and also addressed the scope of this coverage guidance with information that is relevant to the US health system.* *See response to comment D1 regarding individual patient circumstances.*

HERC Coverage Guidance: High-Frequency Chest Wall Oscillation Devices
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	There is not enough evidence because the sample size is too small - but it always will be due to the population making it too small to fall under normal distribution confidence intervals – chicken and egg.	*Evidence is often insufficient, especially for rare conditions, which is why the subcommittee considers public comments and expert testimony, among other factors.*
D4	Evidence showing cost effectiveness has been presented as reduction or avoidance of hospital visits– this committee has disregarded such evidence because it was produced from the manufacturer. Has any analysis been done on any of the population covered by the CIIS waiver? This is the target population that would benefit from this device (even after they turn 18), allowing them to be treated in their home, saving the state money. You could extrapolate what 6 hospitalizations in one year cost the Oregon Health Plan even as secondary provider to determine the cost effectiveness of the shaker vest. I am not including the multiple times that we provided acute care at home during the same time period although there are many. While it would be a sound decision to expand the coverage guidance to people who meet the "medically involved" definition, it would also be financially prudent to cover the shaker vest if the initial expenditure of approximately $16k is less than the cost of even one nights hospitalization which is what the unintended consequence of the current guidance has been. Thank you for your consideration.	*The subcommittee bases decisions regarding effectiveness on peer-reviewed evidence. The Subcommittee does not disregard evidence produced from the manufacturer merely because it was produced by the manufacturer. Registry information from the manufacturers was excluded from the coverage guidance because the way that the information was gathered (a before-after study design) cannot account for competing hypotheses for why individuals using HFCWO device therapy improved or stabilized in terms of symptoms or health care utilization.* *Thank you for your comments.*

References Provided by Commenters

ID	References
A	Excluded from the coverage guidance Berry JG, Goodman DM, Coller RJ, et al. Association of home respiratory equipment and supply use with health care resource utilization in children. *J Pediat*. 2019;207:169-175.e162. doi: 10.1016/j.jpeds.2018.11.046. Daynes E, Jones AW, Greening NJ, Singh SJ. The use of airway clearance devices in the management of chronic obstructive pulmonary disease. A systematic review and meta-analysis of randomized controlled trials. *Ann Am Thorac Soc*. 2021;18(2):308-320. doi: 10.1513/AnnalsATS.202005-482OC McEvoy C, Pandya P, Weycker D, Hanson GL. Outcomes with high-frequency chest wall oscillation among patients with COPD using a large claims database. Presented at: CHEST 2020 Annual Meeting; October 18-21, 2020; Online. P1468.
B	Excluded from the coverage guidance Barto TL, Maselli DJ, Daignault S, et al. Real-life experience with high-frequency chest wall oscillation vest therapy in adults with non-cystic fibrosis bronchiectasis. *Ther Adv Respir Dis*. 2020;14:1753466620932508. (letter reference #4) Barto T, Maselli DJ, Daignault S, Hansen G. Outcomes of high frequency chest wall oscillation (HFCWO) in COPD patients without bronchiectasis. Presented at: CHEST 2019 Annual Meeting; October 19-23, 2019; New Orleans, LA. E1080. (letter reference #11) Barto T, Maselli DJ, Daignault S, Porter J, Kraemer C, Hansen G. Two years of high frequency chest wall oscillation (HFCWO) outcomes in a large registry of non-CF bronchiectasis patients. Presented at: American Thoracic Society Conference; May 21, 2019. (letter reference #5) Basavaraj A, Choate R, Addrizzo-Harris D, et al. Airway clearance techniques in bronchiectasis: analysis from the United States bronchiectasis and non-TB mycobacteria research registry. *CHEST*. 2020;158(4):1376-1384. (letter reference #3) Basavaraj A, Shah D, DeKoven M, et al. A pre-post analysis assessing the 3-year long-term impact of high frequency chest wall oscillation therapy on clinical outcomes, healthcare cost and utilization in adult patients with non-cystic fibrosis bronchiectasis in the US. ATS 2021 Abstract. 2021:A3944. (letter reference #7) Daynes E, Jones AW, Greening NJ, Singh SJ. The use of airway clearance devices in the management of chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized controlled trials. *Ann Am Thorac Soc*. 2021;18(2):308-320. doi:10.1513/AnnalsATS.202005-482OC (letter reference #10) Lechtzin N, Wolfe LF, Frick KD. The impact of high-frequency chest wall oscillation on healthcare use in patients with neuromuscular diseases. *Ann Am Thorac Soc.* 2016;13(6):904-909. (letter reference #9) McEvoy C, Pandya P, Weycker D, Hansen G. A Retrospective Real-World Cohort Study Demonstrating the Impact of HFCWO Therapy on Patients with Neuromuscular Disorders. Presented at: CHEST 2020 Annual Meeting; October 18-21, 2020; Online.P1943. (letter reference #8) McEvoy C, Pandya P, Weycker D, Hansen G. Outcomes with high-frequency chest wall oscillation among patients with COPD using a large claims database. Presented at: CHEST 2020 Annual Meeting; October 18-21, 2020; Online. P1468. (letter reference #12) Mikesell CL, Kempainen RR, Laguna TA, et al. Objective measurement of adherence to out-patient airway clearance therapy by high-frequency chest wall compression in cystic fibrosis. *Respir Care*. 2017;62(7):920-927. doi: 10.4187/respcare.05349 (letter reference #2)

ID	References
	Rubin BK. Designing clinical trials to evaluate mucus clearance therapy. *Respir Care*. 2007;52(10):1348-1358; discussion 1358-1361. (letter reference #1) Weycker D, Hansen GL, Seifer FD. Outcomes with high-frequency chest wall oscillation among patients with non-CF bronchiectasis or COPD. Presented at: American Thoracic Society Conference; May 21, 2017. P1122. (letter reference #6)
C	<u>Newly included in the coverage guidance</u> Yuan YN, Kane P, Shelton K, Matel J, Becker BC, Moss RB. Safety, tolerability, and efficacy of high-frequency chest wall oscillation in pediatric patients with cerebral palsy and neuromuscular diseases: an exploratory randomized controlled trial, *J. Child Neurol*. 2010;25(7):815–821. (letter reference #2) <u>Already included in coverage guidance</u> Nicolini A, Cardini F, Landucci N, Lanata S, Ferrari-Bravo M, Barlascini C. Effectiveness of treatment with high-frequency chest wall oscillation in patients with bronchiectasis. *BMC Pulm Med*. 2013;13:21. doi: 10.1186/1471-2466-13-21. (letter reference #8) <u>Excluded from the coverage guidance</u> Barto TL, Maselli DJ, Daignault S, et al. Real-life experience with high-frequency chest wall oscillation vest therapy in adults with non-cystic fibrosis bronchiectasis. *Ther Adv Respir Dis*. 2020;14:1753466620932508. (letter reference #9) Basavaraj A, Shah D, DeKoven M, et al. A pre-post analysis assessing the 3-year long-term impact of high frequency chest wall oscillation therapy on clinical outcomes, healthcare cost and utilization in adult patients with non-cystic fibrosis bronchiectasis in the US. ATS 2021 Abstract. 2021:A3944. (letter reference #13) CF Foundation Patient Registry Annual Data Report, 2019. (letter reference #1) Fitzgerald K, Dugre J, Pagala S, et al. High-frequency chest wall compression therapy in neurologically impaired children. *Respir Care.* 2014;59(1):107-112. doi: 10.4187/respcare.02446. (letter reference #4) Javanbakht M, Mashayekhi A, Montazeri M, Hemami MR, Branagan-Harris M. The Vest high frequency chest wall oscillation system compared with chest wall physical therapy for managing airway clearance in patients with complex neurological disorders: a UK-based cost-effectiveness analysis. *Open Pharmacoeconomics Health Econ J.* 2019;7:1-8. doi: 10.2174/1874129001907010001. (letter reference #5) Landon C, Goldie W and Evans JR. Airway clearance therapy utilizing high frequency chest wall oscillation (HFCWO) for medically fragile children [Abstract/Poster]. *J Am Med Dir Assoc.* 2002; 3(2):A17. (letter reference #3) Lechtzin N, Wolfe LF, Frick KD. The impact of high-frequency chest wall oscillation on healthcare use in patients with neuromuscular diseases. *Ann Am Thorac Soc.* 2016;13(6):904-909. (letter reference #7) Pandya P, McEvoy C. A retrospective real-world cohort study demonstrating the impact of HFCWO therapy on healthcare costs in patients with neuromuscular disorders. *CHEST.* 2020;156(4Suppl):A2292. doi: 10.1016/j.chest.2020.08.1943

ID	References
	Sievert C, Beaner C. Incidence of bronchiectasis-related exacerbation rates after high frequency chest wall oscillation (HFCWO) treatment — a longitudinal outcome-based study. *Respir Ther*. 2018;13(2):30-33. (letter reference #10) Sievert C, Beaner C. Cost-effective analysis of using high frequency chest wall oscillation (HFCWO) in patients with non-cystic fibrosis bronchiectasis. *Respir Ther*. 2017;12(1):45-49. (letter reference #11) Weycker D, Hansen GL, Seifer FD. Outcomes with high-frequency chest wall oscillation among patients with non-CF bronchiectasis or COPD. Presented at: American Thoracic Society Conference; May 21, 2017. P1122. (letter reference #12) Winfield NR, Barker NJ, Turner ER, Quin GL. Non-pharmaceutical management of respiratory morbidity in children with severe global developmental delay. *Cochrane Database Syst Rev.* 2014;2014(10):CD010382. doi: 10.1002/14651858.CD010382.pub2. (no letter reference number provided)
D	None provided

Health Evidence Review Commission (HERC)

Coverage Guidance: High-Frequency Chest Wall Oscillation Devices

DRAFT for EbGS Meeting 12/2/2021

HERC Coverage Guidance

High-frequency chest wall oscillation devices are recommended for coverage for patients with cystic fibrosis (*weak recommendation)* when there is documentation of frequent exacerbations requiring antibiotics, frequent hospitalization, or rapidly declining lung function measured by spirometry, despite either:

A) adequately provided standard care, including chest physiotherapy and positive expiratory pressure therapy, OR
B) documentation that chest physiotherapy and positive expiratory pressure devices are not tolerated or not available (e.g., inability of a caregiver to perform chest physiotherapy).

High-frequency chest wall oscillation devices are recommended for coverage for patients with non–cystic fibrosis bronchiectasis (weak recommendation) when the 4 criteria below are met:

A) The bronchiectasis is confirmed by computed tomography (CT) scan, AND
B) There is evidence of chronic lung infection, AND
C) The patient has experienced either:
    1) daily productive cough for at least 6 continuous months, OR
    2) frequent (> 2 times a year) exacerbations requiring antibiotic therapy, AND
D) The patient has received adequately provided standard care, including chest physiotherapy and positive expiratory pressure therapy OR chest physiotherapy and positive expiratory pressure devices are not tolerated, contraindicated, or not available (e.g., inability of a caregiver to perform chest physiotherapy).

High-frequency chest wall oscillation devices are recommended for coverage for patients with neuromuscular disease resulting in chronic lung disease (*weak recommendation)* when there is evidence of chronic lung infection, despite either:

A) adequately provided standard care, including chest physiotherapy and positive expiratory pressure therapy, OR
B) documentation that chest physiotherapy and positive expiratory pressure devices are not tolerated, contraindicated, or not available (e.g., inability of a caregiver to perform chest physiotherapy).

High-frequency chest wall oscillation devices are not recommended for coverage for patients with ~~bronchiectasis,~~ chronic obstructive pulmonary disease ~~or neuromuscular disease resulting in chronic lung disease~~ *(weak recommendation)*.

Note. Definitions for strength of recommendation are in Appendix A, GRADE Table Element Descriptions. Rationales for each recommendation appear below in the GRADE table.

Oregon Health Authority

Table of Contents

Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patient experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

The Health Evidence Review Commission (HERC) uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on diagnostic and clinical interventions, evidence is evaluated using an adaptation of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness could depend on the environment in which the intervention is implemented.

GRADE Table

HERC develops recommendations by using the concepts of the GRADE system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and assesses each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by HERC based on the assessment of two independent reviewers from the Center for Evidence-based Policy.

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence considering all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, statements regarding resource allocation, values and preferences, and other considerations are the assessments of HERC, as informed by the evidence reviewed, public testimony, and subcommittee discussion.

Recommendations for coverage are based on the balance of benefit and harms, resource allocation, values and preferences and other considerations. See Appendix A for more details about the factors that constitute the GRADE table.

GRADE Tables

Should high-frequency chest wall oscillation devices be recommended for coverage for children and adults with cystic fibrosis?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Hospitalizations *(Critical outcome)*	Compared to positive expiratory pressure: no significant difference. ●●○○ *(low confidence, based on 4 RCTs, n = 128)* Compared to conventional chest physiotherapy: No significant difference. ●●○○ *(low confidence, based on 4 RCTs, n = 128)*	Coverage of high-frequency chest wall oscillation would add significant cost compared to chest physiotherapy or positive expiratory pressure devices. However, in situations in which chest physiotherapy is not consistently available or tolerated and positive expiratory pressure devices are not effective or tolerated, the additional cost of the high-frequency chest wall oscillation device would be offset to the extent that it reduces hospitalizations and exacerbations.	Patients may prefer treatment options that can be self-administered, confer greater independence, and ensure reliable and consistent treatment.	Some patients may not be able to tolerate chest physiotherapy or positive expiratory pressure devices. Some patients may not have caregivers who are available or physically able to administer daily chest physiotherapy.
Mortality *(Critical outcome)*	No evidence			
Pulmonary Exacerbations Requiring Antibiotics *(Important outcome)*	Compared to positive expiratory pressure: significantly more exacerbations (median, 2.0; interquartile range, 1.0 to 3.0) than the positive expiratory pressure therapy group (median, 1.0; interquartile range, 0.0 to 2.0; *P* = .007) ●○○○ *(very low confidence, based on 1 RCT, n = 107)* Compared to chest physiotherapy: no significant difference (mean difference, -0.20; 95% CI, -2.32 to 1.92; *P* > .05). ●○○○ *(very low confidence, based on 1 RCT, n = 50)* Compared to other oral or external oscillatory devices: no significant difference ●○○○ *(very low confidence, based on 1 RCT, n = 16)*			

Should high-frequency chest wall oscillation devices be recommended for coverage for children and adults with cystic fibrosis?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Exercise Capacity *(Important outcome)*	No evidence	Chest physiotherapy must be provided by a trained caregiver for 20 to 40 minutes, one or more times per day; could be provided by a paid or unpaid caregiver.		
Breathlessness or Cough *(Important outcome)*	No evidence			

Balance of benefits and harms: Based on low-confidence evidence, high-frequency chest wall oscillation devices have similar outcomes to other chest clearance devices or chest physiotherapy for reducing hospitalizations or for reducing exacerbations for patients with cystic fibrosis. There are few harms found for high-frequency chest wall oscillation devices.
Rationale: High-frequency chest wall oscillation devices are not inferior to other alternatives, and have a low rate of harms, but much higher cost. However, we recommend coverage because some patients may need other treatment options. The recommendation is weak because of the low quality of the evidence.
Recommendation: High-frequency chest wall oscillation devices are recommended for coverage for patients with cystic fibrosis (*weak recommendation)* when there is documentation of frequent severe exacerbations requiring antibiotics and/or hospitalization, despite either: a) adequately provided standard care, including chest physiotherapy and positive expiratory pressure therapy, OR b) documentation that chest physical therapy and positive expiratory pressure devices are not tolerated or not available (e.g., inability of a caregiver to perform chest physiotherapy).

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation methodology; RCT: randomized controlled trial.

Should high-frequency chest wall oscillation devices be recommended for coverage for children and adults with non–cystic fibrosis bronchiectasis?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Hospitalizations *(Critical outcome)*	No evidence	Coverage of high-frequency chest wall oscillation would add significant cost compared to chest physiotherapy or positive expiratory pressure devices. However, in situations in which chest physiotherapy is not consistently available or tolerated and positive expiratory pressure devices are not effective or tolerated, the additional cost of the high-frequency chest wall oscillation device would be offset to the extent that it reduces hospitalizations and exacerbations.	Patients may prefer treatment options that can be self-administered, confer greater independence, and ensure reliable and consistent treatment.	Appointed expert opinion supported coverage of high-frequency chest wall oscillation devices for bronchiectasis, due to the pathophysiologic similarities of this condition to cystic fibrosis bronchiectasis, but only when there is evidence of chronic infection.
Mortality *(Critical outcome)*	No evidence			
Pulmonary Exacerbations Requiring Antibiotics *(Important outcome)*	Compared to standard pharmacological therapy alone: significantly fewer exacerbations over 12 months on average for 1 group that used high-frequency chest wall oscillation devices: • Respin11 group (mean, 0.52 exacerbations; SD, 0.14) • Pharmacological therapy with other device-delivered interventions (mean, 0.96 exacerbations; SD, 0.40) • Between-group difference, *P* < .001 Compared to standard pharmacological therapy alone: the treatment group that used the SmartVest HFCWO device did not have significantly fewer exacerbations when compared to the group that received standard pharmacological therapy • SmartVest group (mean, not reported; SD, not reported) • Pharmacological therapy with other device-delivered interventions (mean, 0.96 exacerbations; SD, 0.40) • Between-group difference, *P* > .05 ●○○○ *(very low confidence, based on 1 RCT, n = 42)*			
Exercise Capacity *(Important outcome)*	No evidence			

Should high-frequency chest wall oscillation devices be recommended for coverage for children and adults with non–cystic fibrosis bronchiectasis?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Breathlessness or Cough *(Important outcome)*	Compared to pharmacological therapy with other device-delivered interventions (e.g., positive expiratory pressure mask): significant reduction in symptoms as measured by the 12-point Breathlessness Cough Sputum Score scale (mean difference, -5.8; 95% CI, -7.21 to -4.39; N = 20; *P* < .05) ●○○○ *(very low confidence, based on 1 RCT, n = 20)* Compared to standard pharmacological therapy alone: significant reduction in symptoms as measured by the 12-point Breathlessness Cough Sputum Score scale: • Respin11 group (mean at 12 months post-baseline, 2.8; SD, not reported) • Pharmacological therapy with other device-delivered interventions group (mean at 12 months post-baseline, 6.1; SD, not reported) • Between-group difference, *P* < .001 ●○○○ *(very low confidence, based on 1 RCT, n = 42)* Compared to standard pharmacological therapy alone: The treatment group that used the SmartVest high-frequency chest wall oscillation device did not demonstrate a significant reduction in symptoms as measured by the 12-point Breathlessness Cough Sputum Score scale: • SmartVest group (mean at 12 months post-baseline, 4.5; SD, not reported) • Pharmacological therapy with other device-delivered interventions group (mean at 12 months post-baseline, 6.1; SD, not reported)			

Should high-frequency chest wall oscillation devices be recommended for coverage for children and adults with non–cystic fibrosis bronchiectasis?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
	• Between-group difference, *P* > .05 ●○○○ *(very low confidence, based on 1 RCT, n = 41)*			

Balance of benefits and harms: There is very low confidence evidence that high-frequency chest wall oscillation devices improve key outcomes for patients with non–cystic fibrosis bronchiectasis. However, expert opinion supports use in this population based on data extrapolated from cystic fibrosis, which is a similar condition, but only when there is evidence of chronic airway infection or chronic daily cough. There are few harms to high-frequency chest wall oscillation devices.

Rationale: The evidence is equivocal regarding whether high-frequency chest wall oscillation improves outcomes for patients with non–cystic fibrosis bronchiectasis, but we recommend coverage of these devices based on low risk of harms and the fact that they may result in cost offsets if they prevent hospitalizations. Expert testimony that pathophysiologic reasoning makes extrapolating evidence from the cystic fibrosis population reasonable. The recommendation is weak because of our very low confidence in the available evidence.

Recommendation: High-frequency chest wall oscillation devices are recommended for coverage for patients with non–cystic fibrosis bronchiectasis (weak recommendation) when the 4 criteria below are met:

A) The bronchiectasis is confirmed by CT scan, AND

B) There is evidence of chronic lung infection, AND

C) The patient has experienced either:

   a) daily productive cough for at least 6 continuous months, OR

   b) frequent (> 2 times a year) exacerbations requiring antibiotic therapy, AND

D) The patient has received adequately provided standard care, including chest physiotherapy and positive expiratory pressure therapy OR chest physiotherapy and positive expiratory pressure devices are not tolerated, contraindicated, or not available (e.g., inability of a caregiver to perform chest physiotherapy).

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation methodology; RCT: randomized controlled trial; SD: standard deviation.

Should high-frequency chest wall oscillation devices be recommended for coverage for children and adults with chronic obstructive pulmonary disease?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Hospitalizations *(Critical outcome)*	No evidence	Coverage of high-frequency chest wall oscillation would add significant cost compared to chest physiotherapy or positive expiratory pressure devices. However, in situations in which chest physiotherapy is not consistently available or tolerated and positive expiratory pressure devices are not effective or tolerated, the additional cost of the high-frequency chest wall oscillation device would be offset to the extent that it reduces hospitalizations and exacerbations.	Patients may prefer treatment options that can be self-administered, confer greater independence, and ensure reliable and consistent treatment.	Appointed expert did not recommend high-frequency chest wall oscillation devices for this population.
Mortality *(Critical outcome)*	No evidence			
Pulmonary Exacerbations Requiring Antibiotics *(Important outcome)*	No evidence			
Exercise Capacity *(Important outcome)*	No evidence			
Breathlessness or Cough *(Important outcome)*	Compared to standard pharmacological therapy without oscillatory devices: significantly greater improvement on the 12-point Breathlessness Cough Sputum Score scale over 4 weeks: • The Vest Airway Clearance System Model 205 group (baseline mean, 6.6; SD, 2.8; post-treatment mean, 5.2; SD, 2.2) • Standard pharmacological therapy group (baseline mean, 4.6; SD, 1.7; post-treatment mean, 5.5; SD, 2.1) • Between-group difference, *P* = .007 ●○○○ *(very low confidence, based on 1 RCT, n = 40)*			

Should high-frequency chest wall oscillation devices be recommended for coverage for children and adults with chronic obstructive pulmonary disease?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
	Compared to intrapulmonary percussive ventilation: significantly less improvement on the 12-point Breathlessness Cough Sputum Score scale over 4 weeks: • The Vest Airway Clearance System Model 205 group (baseline mean, 6.6; SD, 2.8; post-treatment mean, 5.2; SD, 2.2) • Intrapulmonary percussive ventilation group (baseline mean, 6.3; SD, 1.4; post-treatment mean, 3.1; SD, 1.7) • Between-group difference, $P < .01$ ●○○○ *(very low confidence, based on 1 RCT, n = 40)*			

Balance of benefits and harms: There is insufficient evidence that high-frequency chest wall oscillation devices improve key outcomes for patients with chronic obstructive pulmonary disease compared to alternatives. Expert opinion does not recommend use in this population. There are few harms to high-frequency chest wall oscillation devices.
Rationale: There is insufficient comparative evidence of benefit for this indication. It is a weak recommendation because of our very low confidence in the evidence.
Recommendation: High-frequency chest wall oscillation devices are not recommended for coverage for children and adults with chronic obstructive pulmonary disease *(weak recommendation).*

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. GRADE: Grading of Recommendations, Assessment, Development, and Evaluation methodology; RCT: randomized controlled trial; SD: standard deviation.

Should high-frequency chest wall oscillation devices be recommended for coverage for children and adults with pulmonary complications from neuromuscular disease resulting in chronic lung disease?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Hospitalizations *(Critical outcome)*	Compared to standard chest physiotherapy (pediatric patients with neuromuscular disease): there was a nonsignificant difference in the number of control group participants requiring hospitalizations (2/7) compared to the HFCWO device group (0/7; *P* > .05) ●○○○ *(very low confidence, based on 1 RCT, n = 14)*	Coverage of high-frequency chest wall oscillation would add significant cost compared to chest physiotherapy or positive expiratory pressure devices. However, in situations in which chest physiotherapy is not consistently available or tolerated and positive expiratory pressure devices are not effective or tolerated, the additional cost of the high-frequency chest wall oscillation device	Patients may prefer treatment options that can be self-administered, confer greater independence, and ensure reliable and consistent treatment. This group of conditions varies widely in severity and patients may have different preferences based on their condition.	Neuromuscular diseases are a broad range of conditions with very different pulmonary involvement. Many of these conditions have populations that are too small to meaningfully study. Appointed expert recommendation was for use in patients with neuromuscular disease who have evidence of chronic airway infection (defined as persistent culture positivity of organisms known to
Mortality *(Critical outcome)*	No evidence			
Pulmonary Exacerbations Requiring Antibiotics *(Important outcome)*	Compared to standard chest physiotherapy (pediatric patients with neuromuscular disease): There was nonsignificant difference between control group participants requiring antibiotics (3/7) compared to the HFCWO device group (2/7; *P* > .05) ●○○○ *(very low confidence, based on 1 RCT, n = 14)*			
Exercise Capacity *(Important outcome)*	No evidence			

Should high-frequency chest wall oscillation devices be recommended for coverage for children and adults with pulmonary complications from neuromuscular disease resulting in chronic lung disease?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Breathlessness or Cough *(Important outcome)*	Compared to no treatment (adult patients with ALS): significantly greater improvement in breathlessness (high-frequency chest wall oscillation group mean difference, -1.28; untreated group mean difference, 0.84; $P < .05$) Compared to no treatment (adult patients with ALS): no statistically significant differences in day or night cough or dyspnea ●○○○ *(very low confidence, based on 1 RCT, n = 35)*	would be offset to the extent that it reduces hospitalizations and exacerbations.		cause respiratory infection).

Balance of benefits and harms: There is no evidence that high-frequency chest wall oscillation devices improve key outcomes compared to standard treatments for patients with neuromuscular disease resulting in chronic lung disease. Expert testimony indicates patients with neuromuscular conditions and evidence of chronic airway infection benefit from these devices. There are few harms to high-frequency chest wall oscillation devices.

Rationale: There is insufficient comparative evidence of benefit for this population, but based on expert opinion and the potential to reduce exacerbations/costs, we recommend coverage for patients with neuromuscular disease when there is evidence of chronic airway infection. The disparate types of diseases and small populations within each disease make high-quality studies difficult to conduct and are not anticipated to be forthcoming. The recommendation is weak because of our very low confidence in the available evidence.

Recommendation: High-frequency chest wall oscillation devices are recommended for coverage for patients with neuromuscular disease resulting in chronic lung disease (*weak recommendation)* when there is evidence of chronic lung infection, despite either:

a) adequately provided standard care, including chest physiotherapy and positive expiratory pressure therapy, OR

b) documentation that chest physiotherapy and positive expiratory pressure devices are not tolerated, contraindicated, or not available (e.g., inability of a caregiver to perform chest physiotherapy).

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. ALS: amyotrophic lateral sclerosis; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation methodology; RCT: randomized controlled trial.

Background

Individuals with impaired airway clearance are unable to effectively clear mucus from their airways.[1] High-frequency chest wall oscillation (HFCWO) devices are designed to help those with impaired airway clearance clear mucus from their airways. Impaired airway clearance can be a characteristic of several respiratory disorders and neuromuscular diseases, including:

- Chronic obstructive pulmonary disorder (COPD)
- Cystic fibrosis
- Bronchiectasis, which is characterized by chronic cough, bronchial wall thickening, permanent expansion of the airway, and overproduction of thick mucus
- Multiple sclerosis
- Muscular dystrophy
- Spinal muscular atrophy
- Amyotrophic lateral sclerosis (ALS)

The Centers for Disease Control and Prevention estimate that 35,000 individuals have been diagnosed with cystic fibrosis in the US, and 16 million US individuals are living with COPD.[2,3] According to a claims-data analysis using information from 2013, aproximately 340,000 to 522,000 adults receive treatment for bronchiectasis in the US, and about half of patients diagnosed with bronichiectasis have comorbid COPD.[4]

Failing to adequately and regularly clear mucus from the airways can result in exacerbations and worsening of chronic lung disease that require antibiotic treatment, hospitalization and other interventions.[5] Therefore, a key element of managing these diseases is to keep airways clear of excess secretions. When patients are unable to mobilize mucus secretions on their own, airway clearance techniques for patients with many respiratory disorders can include:

- Chest physiotherapy
    - Can be administered by respiratory therapists, family members, or other informal caregivers
    - Has been the standard of care for first-line secretion clearance for individuals with excessive or retained mucus.[6]
    - Typically administered by a trained caregiver over 1 to 3 sessions per day, each lasting 20 to 30 minutes, depending on disease severity.[6]
    - May also be known as percussion and postural drainage.
- Breathing techniques
    - Typically taught to patients by pulmonary rehabilitation professionals.
    - Active cycle breathing techniques include breathing control, thoracic expansion exercises, and the forced expiration technique.[6]
    - Autogenic drainage involves breathing techniques in 3 phases (unstick, collect, and evacuate) at different lung volumes.
    - Breathing techniques do not require devices or assistance and can be self-administered.[6]
- Positive expiratory pressure devices
    - Increase resistance, prevent airway closure, and increase collateral ventilation.[6]

    - Some use oscillatory mechanisms to create vibrations when a patient breathes out.[6]
    - Examples include TheraPEP, Resistex PEP mask, Pari RC Cornet Mucus Clearing Device, Flutter, Acapella, Quake, and Aerobika.
    - The therapy from these devices can be self-administered without assistance.[6]
- Intrapulmonary percussive ventilation
    - A pneumatic device that uses high-frequency oscillatory ventilation through a mouthpiece.[6]
    - An example is the Percussionaire Corporation IPV Ventilator.[6]
- High-frequency chest wall oscillation (HFCWO) devices, which are described in the following section of this document.
    - Therapy from these devices can be self-administered.[6]

Indications

Children and adults with cystic fibrosis, bronchiectasis, COPD, or pulmonary complications from neuromuscular disease resulting in chronic lung disease might be prescribed HFCWO devices to assist in the clearance of mucus in airways as part of their treatment plan. HFCWO devices exert external force on the chest wall to assist in mobilizing mucus and use sound waves or pressure from inflation and deflation at variable intensities and frequencies to generate the force. They are much more expensive than the alternative forms of treatment but require less time from caregivers than chest physiotherapy.

Technology Description

We identified 1 nonwearable HFCWO device and 5 wearable HFCWO devices that are currently approved by the US Food and Drug Administration (FDA) and being manufactured for use in children and adults with cystic fibrosis, bronchiectasis, COPD, or pulmonary complications from neuromuscular disease resulting in chronic lung disease. See Table 1 for a description of each device.

Table 1. HFCWO Device Descriptions

Device Name FDA Approval Date	Manufacturer	Features	Indications
Frequencer V2 and V2x[7] January 26, 2011[8]	Dymedso	• Portable • Not wearable • 4 sizes of adaptors for patients of different sizes • Generates low frequency sound waves within the range of 20-65 Hz and offers an adjustable intensity based on the patient's condition	• Cystic fibrosis • Chronic bronchitis • COPD • Bronchiectasis • Ciliary dyskinesia syndromes • Asthma • Muscular dystrophy • Neuromuscular degenerative disorder • Post-operative atelectasis • Thoracic wall defects

Device Name FDA Approval Date	Manufacturer	Features	Indications
SmartVest SQL System[9] December 19, 2013[10]	Electromed	• Portable • Wearable • 8 different sizes • 16 pounds • Quiet (60 decibels) • 91% decompression (greater percent decompression than other vests) • Wireless capabilities that can connect usage to personal reports or to healthcare provider records	• Bronchiectasis • COPD • Cystic fibrosis • Neuromuscular conditions
The Vest Airway Clearance System Model 105[11] February 21, 2003[12]	Hill-Rom	• Portable • Wearable • 4 styles of garment for different body types (full garment, wrap garment, chest garment, C3 garment) • 17 pounds • Multiple programing options, including several languages • Can program a reminder to cough • Vest covers are washable and dryable • Offers at-home training • Wireless capabilities that can connect usage to personal reports or to healthcare provider records	• Bronchiectasis • COPD • Cystic fibrosis • Neuromuscular conditions • Primary ciliary dyskinesia • Post lung transplant • Spinal cord injury

Device Name FDA Approval Date	Manufacturer	Features	Indications
Respin11[13] July 13, 2012[14]	RespInnovation SAS	• Portable • Wearable • Vest plus control unit weight 11 kilograms • Several sizes for different sizes • Can target specific chest areas • Programmable with several protocols • Uses an air pressure piston which inflates and completely empties each cycle enabling the patient to breathe, speak and cough without restriction • Does not provide constant background pressure which manufacturer claims makes the therapy easy to tolerate and puts no pressure onto the patient's physiological state	• Bronchiectasis • COPD • Cystic fibrosis • Neuromuscular conditions • Emphysema
InCourage Vest[15] June 17, 2005[16]	Philips, via RespirTech	• Portable • Wearable • 17.5 pounds • Several sizes for different ages • Uses triangular waveform technology that manufacturer claims delivers a chest physiotherapy-like "thump" to the chest • Offers at-home training	• Bronchiectasis • COPD • Cystic fibrosis • Certain neuromuscular conditions
AffloVest[17] March 27, 2013[12]	International Biophysics Corporation	• Portable • Wearable • Available in 7 sizes • Battery-operated • Has eight mechanical oscillating motors that target all 5 lobes of the lungs, front and back, for fully mobile use • Programmable settings	• Bronchiectasis • COPD • Cystic fibrosis • Neuromuscular diseases

Device Name FDA Approval Date	Manufacturer	Features	Indications
		• Advertised as the lightest vest option (no weight specified)	

Abbreviations. COPD: chronic obstructive pulmonary disorder; FDA: US Food and Drug Administration; HFCWO: high-frequency chest wall oscillation.

Evidence Review

We identified 2 systematic reviews,[6,18] 4 randomized controlled trials (RCTs),[19-21,44] and a single ongoing RCT[22] for the comparative effectiveness of HFCWO devices for children and adults with cystic fibrosis, bronchiectasis, COPD, or pulmonary complications from neuromuscular disease resulting in chronic lung disease. We did not identify any studies of the comparative cost effectiveness of HFCWO devices.

Cystic Fibrosis

We identified a single systematic review that focused on airway clearance techniques in people diagnosed with cystic fibrosis, and included RCTs and quasi-randomized trials of HFCWO devices.[6] The review included external chest oscillating devices as well as oral oscillatory devices.[6] Morrison and colleagues abstracted information related to the scope of this coverage guidance: exercise tolerance and frequency of exacerbations with or without hospitalization.[6] Morrison and colleagues included 39 studies in the qualitative review and 19 studies in meta-analyses; they rated 85% of these studies as having unclear risk of bias.[6] They rated the quality of evidence summarized in the review as very low to low across outcomes.[6] We rated this systematic review as having low risk of bias, and the authors rated component studies as having unclear to high risk of bias.

The studies in this review did not report symptoms of breathlessness or cough, mortality, or exercise capacity for participants using HFCWO devices.

Exacerbations and Hospitalizations

The single RCT (N = 107) that compared HFCWO devices to positive expiratory pressure therapy reported that the average number of exacerbations requiring antibiotics during the 12-month study period was significantly higher in the HFCWO groups (median, 2.0; interquartile range, 1.0 to 3.0) than the positive expiratory pressure therapy group (median, 1.0; interquartile range, 0.0 to 2.0; $P = .007$).[6]

The single RCT (N = 50) that compared HFCWO devices to conventional physiotherapy for patients with cystic fibrosis admitted to a hospital for an acute exacerbation reported no significant difference between the groups for days of hospitalization or time to pulmonary exacerbation (mean difference, -0.20; 95% CI, -2.32 to 1.92).[6] The participants in this study were between 16 and 25 years of age, and 64.0% were identified as male.[6] Patients in the conventional physiotherapy group received therapy from a respiratory physiotherapist 3 times per day for approximately 30 minutes each time, along with the use of an inhaler prior to sessions with the physiotherapist.[6]

Neither of the 2 RCTs that compared HFCWO devices to breathing techniques for cystic fibrosis reported exacerbations or any other outcome scoped for this review.[6]

Only 1 of 6 studies comparing HFCWO devices to other external and oral oscillatory devices assessed exacerbations (N = 16); it reported that there were no significant differences between groups for frequency of hospitalizations or use of home intravenous therapies.[6]

Bronchiectasis

We identified a single systematic review focused on airway clearance techniques for people diagnosed with bronchiectasis,[18] and a single RCT (Nicollini et al., 2020; N = 60) that was published after the search dates of the systematic review.[19] We rated the systematic review as having a low risk of bias and the RCT as having a moderate risk of bias. The systematic review included 7 RCTs, but only 1 included RCT used HFCWO devices in the intervention group (Nicollini et al., 2013; N = 30).[23] This RCT was rated as having an unclear risk of bias by the authors of the systematic review. Both RCTs focused on adults.[19,23] Neither of these RCTs reported on mortality.

Exacerbations and Hospitalizations

In Nicollini and colleagues' 2020 RCT, both groups that used HFCWO devices had statistically significant improvement in exacerbations during the 12 months of the study compared to the average exacerbations per year prior to baseline.[19] Only the group that used the Respin11 HFCWO device had significantly fewer exacerbations during the 12-month study period, compared to the pharmacological comparison group that only received standard pharmacological care without HFCWO or chest physiotherapy (Respin11: mean, 0.52; standard deviation [SD], 0.14; control: mean, 0.96; SD, 0.40; between-group difference: $P < .001$).[19] The 2 HFCWO devices included in this study are described in Table 1.

Breathlessness or Cough

Nicollini and colleagues' 2013 RCT, identified in the systematic review, reported a statistically significant decrease in breathlessness, cough and sputum on the Breathlessness, Cough, and Sputum Scale (BCSS) in the group treated with HFCWO devices compared to a control group that received chest physiotherapy (mean difference, -5.8; 95% CI, -7.21 to -4.39; N = 20; $P < .05$).[23] This study summed the scores of items across 3 subscales, which makes it challenging to anchor this improvement in patient-response terms; publications that assess the clinical importance of change-scores for this scale rely on reporting the average score across subscales (i.e., mean-scores range from 0 to 4, and sum-scores range from 0 to 12 on this scale). This RCT also reported that use of HFCWO devices was associated with lower scores on a dyspnea scale compared to the group that received chest physiotherapy (mean difference, -1.7; 95% CI, -2.4 to -1; N = 20; $P < .05$). [23]

The additional Nicollini and colleagues' 2020 RCT also reported that the group using the Respin11 HFCWO device demonstrated statistically significant improvement on the BCSS compared to the control group that received pharmacological therapy and standard care without HFCWO (Respin11 mean at 12 months post-baseline, 2.8; SD, not reported; control mean at 12 months post-baseline, 6.1; SD, not reported; $P < .001$).19 The group that used the SmartVest HFCWO device did not demonstrate a significant improvement on the BCSS compared to the control group (SmartVest mean at 12 months post-baseline, 4.5; SD, not reported; control mean at 12 months post-baseline, 6.1; SD, not reported; $P > .05$).

Exercise Capacity

The Nicollini and colleagues' 2020 RCT used a 6-minute walk test to assess exercise capacity but did not report the results of the walk test.[19]

COPD

We identified a single RCT that reported on the safety and effectiveness of HFCWO devices compared to intrapulmonary percussive ventilation in patients with severe COPD, and rated this RCT as having a moderate risk of bias.[20] The listed authors overlapped with the 2 RCTs reviewed in the bronchiectasis section, and the design of all 3 RCTs was similar.[20] Participants in this study had severe or very severe (but stable) COPD and were followed for 4 weeks after being randomized into 3 groups: 1 group received 2 sessions per day (lasting 15 minutes per session) of intrapulmonary percussive ventilation with a respiratory physiotherapist using a percussive ventilator; 1 group received 2 sessions per day (lasting 20 minutes per session) of HFCWO with a respiratory physiotherapy; and 1 group received standard pharmacological therapy alone that the investigators termed "the best medical therapy."[20] Most participants were 70 years or older and had more than 2 exacerbations and 1 hospitalization per year.[20] This study did not report mortality, hospitalizations, exacerbations, or exercise capacity.[20]

Breathlessness or Cough

The average BCSS score for participants in the control group worsened over time, but average BCSS scores for participants in the intrapulmonary percussive ventilation and HFCWO groups improved; both treatment groups had statistically significantly lower BCSS scores when compared to the standard treatment group (control group baseline mean, 4.6; SD, 1.7; control group post-treatment mean, 5.5; SD, 2.1).[20] Symptoms were nearly halved in the group receiving intrapulmonary percussive ventilation (intrapulmonary percussive ventilation group baseline mean, 6.3; SD, 1.4; intrapulmonary percussive ventilation group post-treatment mean, 3.1; SD, 1.7).[20] The intrapulmonary percussive ventilation group BCSS scores were statistically significantly lower than HFCWO group scores after the 4 weeks of treatment (HFCWO group baseline mean, 6.6; SD, 2.8; HFCWO group post-treatment mean, 5.2; SD, 2.2; between-group difference, $P < .01$).[20] In other words, the participants in the intrapulmonary percussive ventilation group improved more on symptoms of breathlessness or cough on average, compared to participants who received HFCWO device therapy.

Pulmonary Complications from Neuromuscular Disease

We identified 2 RCTs that assessed the safety and effectiveness of HFCWO devices for individuals diagnosed with a neuromuscular disease with pulmonary complications.[21,44] One RCT focused on adults diagnosed with ALS.[21] Participants in this study were followed for 12 weeks after being randomized into groups that received HFCWO therapy (N = 19) or no treatment (N = 16).[21] We rated this RCT as having a high risk of bias. This study did not report mortality, exacerbations, hospitalizations, or exercise capacity.

The second RCT included 14 children various neuromuscular diseases (i.e., Duchenne muscular dystrophy, unown mitochondrial myopathy, congenital muscular dystrophy, mitochondrial thymidine kinase 2 deficiency, spinal muscular atrophy type 2, muscle-eye-brain disease, and giant axonal neuropathy).[44] None of the participating children had used cough-assistive devices or intrapulmonary percussive ventilation prior to the trial, but 10 relied on nocturnal noninvasive bilevel ventilation and 1

was dependent on a ventilator.[44] Participants were randomized to receive standard chest physiotherapy (N = 7) or to receive HFCWO device therapy (N = 7) for a mean of 5 months; follow-up periods varied nonsignificantly by participant and group assignment.[44] An additional 9 participants in this RCT were diagnosed with cerebral palsey, but did not have neuromuscular disease diagnoses;[44] we report outcomes from this study when the results were reported separately for participants with cerbral palsey and participants with neuromuscular disease (i.e., pulmonary exacerbations and hospitalizations). We rated this study as having a high risk of bias.

Exacerbations and Hospitalizations

The RCT that included children with neuromuscular disease reported hospitalization and pulmonary exacerbations that required antibiotics. There was a nonsignificant difference in the number of control group participants requiring hospitalizations (2/7) compared to the HFCWO device group (0/7; $P > .05$), and nonsignificant difference between control group participants requiring antibiotics (3/7) compared to the HFCWO device group (2/7; $P > .05$).[44]

Breathlessness or Cough

On average, participants in the HFCWO device group had a statistically significantly greater decrease in breathlessness (HFCWO group mean difference, -1.28; group receiving no care mean difference, 0.84; $P < .05$) in the RCT that included adults with ALS, but no statistically significant differences in day or night cough or dyspnea.[21] Among the 21 participants with impaired lung capacity (forced vital capacity of 40% to 70%) in this RCT, this pattern of improvement in breathlessness for participants using HFCWO devices was further accentuated (HFCWO group mean difference, -1.71; untreated group mean difference, 1.51; $P < .05$).[21]

Harms of HFCWO Devices

We reviewed the RCTs described above for information about harms and adverse events. We also searched the FDA's manufacturer and user facility device experience database (MAUDE) for reports of adverse events for each of the HFCWO devices listed in the technology description.

A single RCT comparing HFCWO devices to positive expiratory pressure therapy for patients with cystic fibrosis reported adverse events.[24] This RCT was included in the systematic review described in the cystic fibrosis section, and used the inCourage System from RespirTech for the HFCWO device.[6,24] The authors for this RCT reported that the number of adverse events was not statistically different between the 2 groups (HFCWO, 200 events; positive expiratory pressure, 163 events; $P > .05$).[23] However, the HFCWO device group had significantly more lower airway adverse events (mean, 2.46; SD, not reported) compared to the positive expiratory pressure group (mean, 1.72; SD not reported; $P = .023$).[24] Lower airway events included increased cough, chest infection, hemoptysis, decreased lung function and chest pain.[24]

Reports identified in the MAUDE database are listed in Table 2, by device.

Table 2. Adverse Events Reported in MAUDE by HFCWO Device

Device Name FDA Approval Date	Manufacturer	Adverse Event(s)

Frequencer V2 and V2x[7] January 26, 2011[8]	Dymedso	• No records
SmartVest SQL System[9] December 19, 2013[10]	Electromed	• No records
The Vest Airway Clearance System Model 105[11] February 21, 2003[12]	Hill-Rom	• No records
Respin11[13] July 13, 2012[14]	RespInnovation SAS	• No records
InCourage Vest[15] June 17, 2005[16]	Philips, via RespirTech	• 8 reports identified classified under injury event type ○ Rib bone fractures in 3 different patients ○ 1 vertebral fracture ○ 1 electromagnetic interference problem with a pacemaker ○ 1 hematoma ○ 1 pneumothorax ○ 1 pressure problem with co-occurring mastitis
AffloVest[17] March 27, 2013[12]	International Biophysics Corporation	• 1 report identified • Fractured ribs

Abbreviations. FDA: US Food and Drug Administration; HFCWO: high-frequency chest wall oscillation; MAUDE: manufacturer and user facility device experience database.

Comparative Cost Effectiveness of HFCWO Devices

We did not identify any comparative cost-effectiveness studies of HFCWO devices.

Ongoing Studies for HFCWO Devices

We identified a single ongoing comparative study for HFCWO devices in the Clinical Trials Registry. This pilot study will evaluate the use of the Vest system for treatment of bronchiectasis patients in the home setting.[25] This study is a nonblinded, multi-site, randomized controlled trial that anticipates enrolling 70 participants, and will compare the Vest HFCWO therapy to oscillating positive expiratory pressure (OPEP) therapy for adults aged 18 years and older diagnosed with bronchiectasis.[25] Assessed outcomes will include frequency of exacerbations within 12 months of study initiation, quality of life, and number of antibiotics used during exacerbations.[25] The anticipated study completion date was November 2020.[25]

Evidence Summary

For patients with cystic fibrosis, we have low confidence that HCWFO device therapy is equivalent to conventional chest physiotherapy and positive expiratory pressure devices for prevention of exacerbations requiring antibiotics and for reducing symptoms of coughing and breathlessness. There is no evidence regarding other outcomes.

For patients with bronchiectasis, we have very low confidence that HFCWO device therapy reduces hospitalizations from exacerbations and improves symptoms of breathlessness and cough compared to pharmacological therapy with other device-delivered interventions (e.g., positive expiratory pressure mask), and compared to pharmacological therapy without other devices. There is no evidence regarding other outcomes.

For patients with COPD, we have very low confidence that HFCWO device therapy is associated with less improvement in breathlessness and cough compared to intrapulmonary percussive ventilation. There is no evidence regarding other outcomes.

For patients with pulmonary complications from neuromuscular disease, we have very low confidence that HFCWO device therapy improves symptoms of breathlessness compared to no treatment or to standard chest physiotherapy. One study only included patients with ALS receiving HFCWO devices compared to no treatment, and the study that included children with neuromuscular disease likely had too few participants to identify whether there was a benefit to using HFCWO devices compared to standard chest physiotherapy. We have very low confidence that HFCWO device therapy does not improve day or night cough or dyspnea compared to receiving no treatment for patients with ALS. There is no evidence regarding other outcomes for other neuromuscular diseases resulting in chronic lung disease.

We identified few reports of adverse events or harms of HFCWO devices in the reviewed studies and the FDA's database for adverse event reporting for devices.

Policy Landscape

Payer Coverage Policies

We identified HFCWO device coverage policies for Washington State's Medicaid program, a local coverage determination from Medicare, and 4 private payers. Medicare's local coverage determination and all 4 private payer policies require documentation that standard treatments, such as chest physiotherapy, have failed or are not tolerated before covering HFCWO devices; these policies cover HFCWO devices for patients with cystic fibrosis and bronchiectasis, but coverage for neuromuscular diseases with pulmonary complications varies. None of these policies cover HFCWO devices for patients with COPD except when there is comorbid bronchiectasis.

Medicaid

The Washington Health Care Authority's (HCA) policy for respiratory care considers chest physiotherapy to be the standard of care for secretion clearance, but states that there are situations in which conventional chest physiotherapy is unavailable, ineffective, or not tolerated.[26] The HCA covers HFCWO air-pulse generator systems when medically necessary for a person with a diagnosis characterized by excessive mucus production and difficulty clearing secretions.[26] Other airway-clearance devices covered by the HCA include mechanical percussors, oscillatory positive expiratory pressure devices, positive expiratory pressure devices, and cough stimulating devices, including alternating positive and negative airway pressure devices, and replacement batteries.[26] Prior authorization is required, and the policy also states that the rental of a HFCWO device and generator includes all repairs and replacements, and that the manufacturer will replace the vest according to changes in user's size during the rental and purchase period.[26] The HFCWO device is considered to be purchased after 12 months of rental, and there is a limit

of 1 HFCWO device per client, per lifetime.[24] The fee schedule, which was last updated in October 2020, lists the maximum allowable monthly rental fee for a HFCWO device (HCPCS E0483) as $1,224.07, and the maximum allowable fee for replacement parts (HCPCS A7025) as $465.90.[27]

Medicare

The local coverage determination for HFCWO devices (L33785) for Medicare, last updated in 2020, provides the following criteria for medical necessity[28]:

- There is a diagnosis of cystic fibrosis; or
- There is a diagnosis of bronchiectasis that has been confirmed by a high resolution, spiral, or standard CT scan and which is characterized by daily productive cough for at least 6 continuous months and frequent exacerbations requiring antibiotic therapy (2 or more times per year); chronic bronchitis and COPD in the absence of a confirmed diagnosis of bronchiectasis do not meet this criterion; or
- The beneficiary has one of the following neuromuscular disease diagnoses: post-polio; acid maltase deficiency; anterior horn cell diseases; multiple sclerosis; quadriplegia; hereditary muscular dystrophy; myotonic disorders; other myopathies; or paralysis of the diaphragm; and
- There must be well-documented failure of standard treatments to adequately mobilize retained secretions.
- It is not reasonable and necessary for a beneficiary to use both a HFCWO device and a mechanical in-exsufflation device.
- Replacement supplies, HCPCS A7025 and A7026, used with beneficiary owned equipment, are covered if the beneficiary meets the criteria listed above for the base device, HCPCS E0483. If these criteria are not met, the claim will be denied as not reasonable and necessary.

Private Payers

Aetna updated its policy for HFCWO devices in March 2021 and anticipates re-review in January 2022. This policy provides the following criteria for medical necessity[29]:

- Patient has a well-documented failure of standard treatments to adequately mobilize retained secretions; and
- Patient has been diagnosed with bronchiectasis confirmed by CT scan, characterized by daily productive cough for at least 6 continuous months or by frequent (i.e., more than 2 times per year) exacerbations requiring antibiotic therapy; or
- Patient has been diagnosed with cystic fibrosis or immotile cilia syndrome; or
- Patient has been diagnosed with 1 of the following neuromuscular diseases: acid maltase deficiency; anterior horn cell diseases, including amyotrophic lateral sclerosis; hereditary muscular dystrophy; multiple sclerosis; myotonic disorders; other myopathies; paralysis of the diaphragm; post-polio; or quadriplegia regardless of underlying etiology.
- Lung transplant recipients, within the first 6 months post-operatively, who are unable to tolerate standard chest physiotherapy.
- Aetna considers continuous high-frequency chest wall oscillation therapy for the treatment of bronchitis, and secretion-induced atelectasis to be experimental and investigational because there is insufficient evidence of effectiveness.

- Aetna considers high-frequency chest compression systems experimental and investigational for other indications in members who do not meet medical necessity criteria above (e.g., alpha 1antitrypsin deficiency, cerebral palsy, childhood atelectasis, chronic inflammatory demyelinating polyneuropathy, coma, Cri-du-Chat syndrome, individuals with acute pneumonic respiratory failure receiving mechanical ventilation, interstitial lung disease, kyphosis, leukodystrophy, protein alveolar proteinosis, scoliosis, stiff-person (stiff-man) syndrome, and Zellweger syndrome; not an all-inclusive list) because their effectiveness for these indications has not been established.

Cigna updated its policy for HFCWO devices in March 2021 and anticipates reviewing this policy in September 2021. This policy provides the following criteria for medical necessity[30]:

- Patient has been diagnosed with cystic fibrosis and there is a failure, intolerance, or contraindication to home chest physiotherapy, or it cannot be provided; or
- Patient has been diagnosed with bronchiectasis confirmed by high-resolution computed tomography; has daily productive cough for at least 6 months or requires antibiotic treatment of exacerbations 2 or more times per year; and failure of standard treatments (e.g., pharmacotherapy, postural drainage, chest percussion, vibration) to mobilize secretions; or
- Patient has been diagnosed with neuromuscular disease; that disease is characterized by excessive mucus production, infection and difficulty clearing secretions; and there is a failure, intolerance, or contraindication to standard treatment (e.g., pharmacotherapy, postural drainage, daily chest percussion) and standard airway clearance device (e.g., mechanical percussors, positive expiratory pressure device).

Moda updated its policy for HFCWO devices in March 2021, and considers airway oscillating devices, mechanical percussors, positive expiration masks to be medically necessary to assist in mobilizing respiratory tract secretions for patients with cystic fibrosis, chronic bronchitis, bronchiectasis, immotile cilia syndrome, or asthma. Their policy requires prior authorization and provides the following criteria for medical necessity[31]:

- Face-to-face visit with provider within 6 months prior to the request;
- Documentation of failure of standard treatments to adequately mobilize retained secretions;
- Cannot request both HFCWO and mechanical in-exsufflation device; and
- One or more of the following conditions are met:
    - A high resolution, spiral, or standard CT scan documentation of bronchiectasis that is characterized by 1 or more of the following: at least 6 months of daily productive cough, or frequent exacerbations requiring antibiotic therapy (i.e., more than 2 times per year);
    - The patient does not have chronic bronchitis and COPD in the absence of confirmed diagnosis of bronchiectasis
    - Cystic fibrosis or immotile cilia syndrome
    - The patient has one of the following neuromuscular diseases: acid maltase deficiency; anterior horn cell diseases, including amyotrophic lateral sclerosis; hereditary muscular dystrophy; multiple sclerosis; myotonic disorders; other myopathies; paralysis of the diaphragm; post-polio; quadriplegia regardless of etiology; lung transplant recipients who are unable to tolerate standard chest physiotherapy, and who have submitted a request within the first 6 months post-operatively.

- Indications for which HFCWO is considered investigational include alpha 1-antitrypsin deficiency, childhood atelectasis, cerebral palsy, coma, kyphosis, leukodystrophy, scoliosis, and stiff-person syndrome.

Moda's policy specifically names the following devices but notes that the list is not all-inclusive: Frequencer, SmartVest, MedPulse Respiratory Vest System, The Vest Airway Clearance System, ABI Vest, Respin11 Bronchial Clearance System, and InCourage Vest/System.[31]

Regence BlueCross BlueShield updated their policy for oscillatory devices in July 2020 and anticipates starting a new review for their policy in June 2021. This policy required prior authorization and provides the following criteria for medical necessity for use of HFCWO devices[32]:

- Among patients with cystic fibrosis: demonstrated need for airway clearance and documentation that standard chest physiotherapy has failed, is not tolerated, or cannot be performed. Failure is defined as continued frequent severe exacerbations of respiratory distress.
- Among patients with chronic diffuse bronchiectasis: demonstrated need for airway clearance; documentation that standard chest physiotherapy has failed, is not tolerated, or cannot be performed; and high resolution or spiral chest tomography scan to document bronchiectasis, plus either daily productive cough for at least 6 continuous months, or exacerbations requiring antibiotic therapy 3 or more times per year.
- Among patients with COPD or conditions associated with other neuromuscular disorders, HFCWO devices are considered investigational.

Evidence-based Guidelines and Recommendations

National Institute for Health Care and Excellence (NICE)

The NICE guidelines published in 2017 for the diagnosis, treatment, and management of cystic fibrosis explicitly state that HFCWO devices should not be offered as an airway clearance technique for people with cystic fibrosis except in exceptional clinical circumstances.[33] There is a special cystic fibrosis team that decides when circumstances are exceptional; otherwise, the guidance states that based on published evidence, HFCWO is not as effective as other airway clearance techniques.[33]

We did not identify any NICE guidelines for the diagnosis, treatment, and management of bronchiectasis, COPD, or neuromuscular diseases that explicitly included HFCWO devices in the recommendations sections.

European Respiratory Society

The European Respiratory Society published guidelines in 2017 for the management of adult bronchiectasis from determinations made by a task force comprised of respiratory medicine, microbiology, physiotherapy, thoracic surgery, primary care, and patient advocates.[34] Systematic reviews of published evidence were conducted, reviewed, and debated by this task force during 4 in-person meetings that took place over 21 months, with additional communication by email and teleconference when drafting the final recommendations.[34] Any task force members with conflicts of interest were forced to abstain from all voting activities during the process of developing recommendations.[34] The guideline recommends that patients with bronchiectasis be taught to use an airway clearance technique 1 to 2 times daily by a trained physiotherapist, as a weak recommendation based on low quality of evidence.[34] HFCWO therapy was one of multiple airway clearance techniques

that the task force considered while making this recommendation, but there was no statement of which airway clearance technique might be superior to others.[34] There was a strong recommendation for use of pulmonary rehabilitation in patients with impaired exercise capacity.[34]

European Neuromuscular Centre (ENMC)

ENMC convened a meeting in March 2017 with 21 internationally recognized experts in airway clearance techniques for patients with neuromuscular disorders.[35] Several of the participating experts had received funding, honoraria, or expenses for travel paid for by manufacturers of devices that assist in airway clearance.[35] HFCWO devices were addressed in the review that the experts published after the meeting in the section related to peripheral airway clearance techniques, which also included discussion of intrapulmonary percussive ventilation, manual chest compression, and chest wall strapping.[35] Other sections of the review included information about manually assisted cough, assisted inspiration and expiration, mechanical insufflation-exsufflation.[35] The authors concluded that peripheral airway clearance techniques such as HFCWO therapy may be effective, and should be considered for use in management of chronic lung disease associated with neuromuscular disorders alongside manually assisted cough or other equipment to clear secretions from airways.[35] The authors noted that HFCWO devices are expensive in comparison to other available devices and techniques.[35]

American College of Chest Physicians

The American College of Chest Physicians published an expert panel report in 2018 on treating cough due to non–cystic fibrosis bronchiectasis and cystic fibrosis bronchiectasis with nonpharmacological airway clearance after conducting a systematic review of published evidence.[36] The authors were unable to make recommendations due to insufficient evidence, but provided the following consensus-based suggestions[36]:

- For children and adults with productive cough due to bronchiectasis related to any cause, we suggest that they be taught airway clearance techniques by professionals with advanced training in airway clearance techniques.
- For children and adults with productive cough due to bronchiectasis related to any cause, we suggest that the frequency of airway clearance should be determined by disease severity and amount of secretions.
- For children and adults with productive cough due to bronchiectasis related to any cause, we suggest that airway clearance techniques are individualized as there are many different techniques.

American Association for Respiratory Care (AARC)

AARC published clinical practice guidelines about the effectiveness of nonpharmacologic airway clearance therapies in hospitalized patients with impaired secretion clearance, based on a systematic review of published studies.[37] The guidelines provided focused recommendations for adult and pediatric patients without cystic fibrosis; adult and pediatric patients with neuromuscular disease, respiratory muscle weakness, or impaired cough; and postoperative adult and pediatric patients.[37] These guidelines note that HFCWO was not recommended for adult and pediatric patients with neuromuscular disease, respiratory muscle weakness, or impaired cough, due to insufficient evidence.[37] Airway clearance techniques were not recommended for routine treatment of COPD or post-operative care.[37] The authors

propose the following process questions when considering the use of airway clearance techniques in these populations[37]:

- Does the patient have difficulty clearing airway secretions? Are retained secretions affecting gas exchange or lung mechanics? Focus on patient's level of difficulty for mobilizing and expectorating secretions.
- Which therapy is likely to provide the greatest benefit with the least harm?
- What is the cost of the therapy in terms of the device cost and clinician time to apply or supervise the therapy? The authors note that this is especially relevant for devices or therapies to be used at home.
- What factors are important to the patient about performing airway clearance therapy? This is an important consideration, given the lack of high-quality evidence that any one technique is more effective than other techniques.

Recommendations and Guidelines from Professional Societies

American Thoracic Society

The American Thoracic Society published a clinical practice guideline in 2011 for the diagnosis and management of stable COPD in partnership with the American College of Physician, American College of Chest Physicians, and European Respiratory Society.[38] This guideline did not consider oscillation devices as part of standard management of COPD.[38]

Recommendations From Advocacy Organizations

American Lung Association

The American Lung Association does not list HFCWO devices as part of the management and treatment of cystic fibrosis, bronchiectasis, or COPD.[39-41]

Cystic Fibrosis Foundation

The Cystic Fibrosis Foundation promotes the use of clinical practice guidelines from a systematic review of the evidence that the foundation commissioned in 2009 to compare airway clearance techniques and devices.[42] The review concluded that airway clearance should be part of managing cystic fibrosis to maintain lung function and improve quality of life, and assessed that this could provide a moderate net benefit based on fair quality body of evidence.[43] No airway clearance technique or device was found to be superior to others, and the authors recommended that airway clearance technique be individualized to the patient in consideration of age, preference, and history of adverse events.[43]

References

1. Rogers DF, Barnes PJ. Treatment of airway mucus hypersecretion. *Ann Med.* 2006;38(2):116-125. doi: 10.1080/07853890600585795.
2. Centers for Disease Control and Prevention. Chronic obstructive pulmonary disease (COPD). 2021; https://www.cdc.gov/copd/index.html. Accessed May 3, 2021.
3. Centers for Disease Control and Prevention. Cystic fibrosis. 2021; https://www.cdc.gov/genomics/disease/cystic_fibrosis.htm. Accessed May 3, 2021.
4. Weycker D, Hansen GL, Seifer FD. Prevalence and incidence of noncystic fibrosis bronchiectasis among US adults in 2013. *Chron Respir Dis.* 2017;14(4):377-384. doi: 10.1177/1479972317709649.
5. Konstan M, Berger M. Current understanding of the inflammatory process in cystic fibrosis: onset and etiology. *Pediatr Pulmonol.* 1997;24(2):137-142.
6. Morrison L, Milroy S. Oscillating devices for airway clearance in people with cystic fibrosis. *The Cochrane database of systematic reviews.* 2020;4:CD006842. doi: https://dx.doi.org/10.1002/14651858.CD006842.pub5.
7. Dymedso. Frequencer. 2021; https://dymedso.com/frequencer/. Accessed April 21, 2021.
8. US Food and Drug Administration. Dymedso Frequencer V2 and Frequencer V2x airway clearance device. 2011; https://www.accessdata.fda.gov/cdrh_docs/pdf10/K103176.pdf. Accessed April 22, 2021.
9. Electromed Inc. The smart shoice for HFCWO therapy. 2021; https://smartvest.com/smart-choice-for-hfcwo-therapy/?gclid=EAIaIQobChMIz92Cqb-K7gIV2zizAB01yAGgEAAYASAAEgJoaPD_BwE. Accessed April 21, 2021.
10. US Food and Drug Administration. Special 510(k) summary. 2013; https://www.accessdata.fda.gov/cdrh_docs/pdf13/K132794.pdf. Accessed April 22, 2021.
11. Hill-Rom Inc. The Vest airway clearance system, model 105. 2021. Accessed April 21, 2021.
12. US Food and Drug Administration. 510(k) summary of safety and effetiveness. 2013; https://www.accessdata.fda.gov/cdrh_docs/pdf12/K122480.pdf. Accessed April 22, 2021.
13. respInnovation. RespIn 11 bronical clearance system. 2021; http://respin11.com/index.php/respin/respin-11. Accessed April 21, 2021.
14. US Food and Drug Administration. Premarket notification 510(k). 2012; https://www.accessdata.fda.gov/cdrh_docs/pdf12/K121170.pdf. Accessed April 22, 2021.
15. Philips, RespirTech. InCourage system airway clearance device. 2021; https://www.usa.philips.com/healthcare/product/HC500055/incourage-system-airway-clearance-device. Accessed April 22, 2021.
16. US Food and Drug Administration. 510(k) summary of safety and effectiveness. 2005; https://www.accessdata.fda.gov/cdrh_docs/pdf5/K051383.pdf. Accessed April 22, 2021.
17. International Biophysics Corportation. AffloVest mobile mechanial HFCWO vest therapy. 2020; https://www.afflovest.com/. Accessed Aprik 22, 2021.
18. Lee AL, Burge AT, Holland AE. Airway clearance techniques for bronchiectasis. *Cochrane Database Syst Revs.* 2015(11):CD008351. doi: 10.1002/14651858.CD008351.pub3.
19. Nicolini A, Grecchi B, Banfi P. Effectiveness of two high frequency chest wall oscillation techniques in patients with bronchiectasis: a randomized controlled preliminary study. *Panminerva Med.* 2020. doi: 10.23736/S0031-0808.20.03735-0.
20. Nicolini A, Grecchi B, Ferrari-Bravo M, Barlascini C. Safety and effectiveness of the high-frequency chest wall oscillation vs intrapulmonary percussive ventilation in patients with severe COPD. *International journal of chronic obstructive pulmonary disease.* 2018;13:617-625. doi: 10.2147/COPD.S145440.

21. Lange DJ, Lechtzin N, Davey C, et al. High-frequency chest wall oscillation in ALS: an exploratory randomized, controlled trial. *Neurology.* 2006;67(6):991-997.
22. Clinical Trials Registry. Clinical effectiveness of high frequency chest wall oscillation (HFCWO) in a bronchiectasis population. 2021; https://clinicaltrials.gov/ct2/show/NCT04271969. Accessed April 23, 2021.
23. Nicolini A, Cardini F, Landucci N, Lanata S, Ferrari-Bravo M, Barlascini C. Effectiveness of treatment with high-frequency chest wall oscillation in patients with bronchiectasis. *BMC Pulm Med.* 2013;13:21. doi: 10.1186/1471-2466-13-21.
24. McIlwaine MP, Alarie N, Davidson GF, et al. Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis. *Thorax.* 2013;68(8):746-751. doi: 10.1136/thoraxjnl-2012-202915.
25. Clinical Trials Registry. A pilot study to evaluate the use of the Vest system for treatment of bronchiectasis patients in the home setting. 2020; https://clinicaltrials.gov/ct2/show/NCT04017312. Accessed April 23, 2021.
26. Washington Apple Health (Medicaid). Respiratory care billing guide. 2019; https://www.hca.wa.gov/assets/billers-and-providers/Respiratory-care-bi-20190101.pdf.
27. Washington Health Care Authority. Provider billing guides and fee schedules. 2021; https://www.hca.wa.gov/billers-providers-partners/prior-authorization-claims-and-billing/provider-billing-guides-and-fee-schedules. Accessed April 30, 2021.
28. Centers for Medicare & Medicaid Services. Local coverage determination: high frequency chest wall oscillation devices (L33785). 2020; https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33785. Accessed Arpil 22, 2021.
29. Aetna. Chest physiotheray and airway clearance devices. 2021; http://www.aetna.com/cpb/medical/data/1_99/0067.html. Accessed April 22, 2021.
30. Cigna. Airway clearance devices in the ambulatory setting. 2021; https://chk.static.cigna.com/assets/chcp/pdf/coveragePolicies/medical/mm_Future/mm_0069_coveragepositioncriteria_airway_clearance_devices.pdf. Accessed April 22, 2021.
31. Moda. High frequency chest wall oscillation devices (HFCWO). 2021; https://www.modahealth.com/pdfs/med_criteria/HighFrequencyChestWallOscillationDevices.pdf. Accessed April 22, 2021.
32. Regence BlueCross BlueShield. Oscillatory devices for the treatment of cystic fibrosis and other respiratory conditions. 2020; http://blue.regence.com/trgmedpol/dme/dme45.pdf. Accessed April 22, 2021.
33. National Institute for Health and Care Excellence. Cystic fibrosis: diagnosis and management NG78. 2017; https://www.nice.org.uk/guidance/ng78/chapter/Recommendations#pulmonary-monitoring-assessment-and-management. Accessed April 30, 2021.
34. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J.* 2017;50(3). doi: 10.1183/13993003.00629-2017.
35. Chatwin M, Toussaint M, Goncalves MR, et al. Airway clearance techniques in neuromuscular disorders: a state of the art review. *Respir Med.* 2018;136:98-110. doi: 10.1016/j.rmed.2018.01.012.
36. Hill AT, Barker AF, Bolser DC, et al. Treating cough due to non-CF and CF bronchiectasis with nonpharmacological airway clearance: CHEST expert panel report. *Chest.* 2018;153(4):986-993. doi: 10.1016/j.chest.2018.01.014.
37. Strickland SL, Rubin BK, Drescher GS, et al. AARC clinical practice guideline: effectiveness of nonpharmacologic airway clearance therapies in hospitalized patients. *Respir Care.* 2013;58(12):2187-2193. doi: 10.4187/respcare.02925.

38. Qaseem A, Wilt T, Weinberger S, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med.* 2011;155:179-191. doi: 10.7326/0003-4819-155-3-201108020-00008.
39. American Lung Association. Treating COPD. 2021; https://www.lung.org/lung-health-diseases/lung-disease-lookup/copd/treating. Accessed April 30, 2021.
40. American Lung Association. Treating and managing bronchiectasis. 2021; https://www.lung.org/lung-health-diseases/lung-disease-lookup/bronchiectasis/treating-and-managing. Accessed April 30, 2021.
41. American Lung Association. Treating and managing cystic fibrosis. 2021; https://www.lung.org/lung-health-diseases/lung-disease-lookup/cystic-fibrosis/treating-and-managing. Accessed April 30, 2021.
42. O'Conner M, O'Sullivan B, Cystic Fibrosis Foundation. Cystic fibrosis airway clearance therapies clinical care guidelines. 2019; https://www.cff.org/Care/Clinical-Care-Guidelines/Respiratory-Clinical-Care-Guidelines/CF-Airway-Clearance-Therapies-Clinical-Care-Guidelines/. Accessed April 19, 2021.
43. Flume PA, Robinson KA, O'Sullivan BP, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. Respir Care. 2009;54(4):522-537.
44. Yuan N, Kane P, Shelton K, Matel J, Becker BC, Moss RB. Safety, tolerability, and efficacy of high-frequency chest wall oscillation in pediatric patients with cerebral palsy and neuromuscular diseases: an exploratory randomized controlled trial. *J Child Neurol*. 2010;25(7):815-821. doi: https://dx.doi.org/10.1177/0883073809350223.

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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Appendix A. GRADE Table Element Descriptions

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors., but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Appendix B. GRADE Evidence Profile

Certainty Assessment (Confidence in Estimate of Effect) for Cystic Fibrosis							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Certainty**
Hospitalizations							
4	RCTs	Serious	Not serious	Serious	Not serious	Small samples, short follow-up	Low ●●○○
Mortality							
0							
Pulmonary Exacerbations Requiring Antibiotics							
3	RCT	Serious	Not serious	Serious	Serious	Small samples, short follow-up	Very low ●○○○
Exercise Capacity							
0							
Breathlessness or Cough							
0							

Abbreviation. RCT: randomized controlled trial.

Certainty Assessment (Confidence in Estimate of Effect) for Bronchiectasis							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Certainty**
Hospitalizations							
0							
Mortality							
0							
Pulmonary Exacerbations Requiring Antibiotics							
1	RCT	Serious	Unable to rate (single study)	Not serious	Serious		Very low ●○○○
Exercise Capacity							
0							
Breathlessness or Cough							
1	RCT	Serious	Unable to rate (single study)	Not serious	Serious		Very low ●○○○

Abbreviation. RCT: randomized controlled trial.

Certainty Assessment (Confidence in Estimate of Effect) for COPD							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Certainty**
Hospitalizations							
0							
Mortality							
0							
Pulmonary Exacerbations Requiring Antibiotics							
0							
Exercise Capacity							
0							
Breathlessness or Cough							
1	RCT	Moderate	Unable to rate (single study)	Serious	Serious	Short intervention period and follow-up	Very low ●○○○

Abbreviation. RCT: randomized controlled trial.

Certainty Assessment (Confidence in Estimate of Effect) for Pulmonary Complications From Neuromuscular Disease Resulting in Chronic Lung Disease							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Certainty**
Hospitalizations							
0							
Mortality							
0							
Pulmonary Exacerbations Requiring Antibiotics							
0							
Exercise Capacity							
0							
Breathlessness or Cough							
1	RCT	Serious	Unable to rate (single study)	Serious	Serious	Small sample, short follow-up	Very low ●○○○

Abbreviation. RCT: randomized controlled trial.

Appendix C. Methods

Scope Statement

Populations

Children and adults with cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disorder, or pulmonary complications from neuromuscular disease resulting in chronic lung disease

Population scoping notes: Patients without any of the above conditions are excluded.

Interventions

High-frequency chest wall oscillation devices approved for use in the US

Intervention exclusions: None

Comparators

Home physiotherapy, mechanical percussors, positive expiratory pressure masks, airway clearance devices (e.g., oscillating devices, intrapulmonary percussive ventilation), or other types of high-frequency chest wall oscillation devices not approved for use in the US

Outcomes

Critical: Hospitalizations, mortality

Important: Frequency of pulmonary exacerbations requiring antibiotics, changes in exercise capacity, symptoms of breathlessness or cough

Considered but not selected for GRADE Table: Sputum volume or weight, forced expiratory volume, forced vital capacity, total lung capacity

Key Questions

KQ1: What is the comparative effectiveness of high-frequency chest wall oscillation devices?

KQ2: Does the comparative effectiveness of high-frequency chest wall oscillation devices vary by:

a. Disease type

b. Patient characteristics

c. Device characteristics

KQ3: What are the harms of high-frequency chest wall oscillation devices?

KQ4: What is the comparative cost effectiveness of high-frequency chest wall oscillation devices?

Contextual Questions

CQ1: What resources are required to use the interventions and comparators?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2015.

The following core sources were searched:

Agency for Healthcare Research and Quality (AHRQ)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Online Library)
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

An Ovid MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms *chest wall oscillation, high frequency chest wall oscillation, high frequency Chest wall compression, Frequencer, SmartVest, MedPulse Respiratory Vest, Vest Airway Clearance System, ABI Vest, Respin11, bronchial clearance, InCourage Vest,* and *Afflovest*. The search was limited to publications in English published since 2015. In addition, a MEDLINE® search was conducted for randomized controlled trials published after the search dates of the identified systematic reviews for cystic fibrosis and bronchiectasis. An additional search for randomized controlled trials published since 2006 was conducted for chronic obstructive pulmonary disorder and neuromuscular diseases with pulmonary complications leading to chronic lung disease, because no systematic reviews were identified for these populations. The searches were limited to publications in English.

Searches for clinical practice guidelines were limited to those published since 2015. A search for relevant clinical practice guidelines was also conducted using MEDLINE® and the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Centers for Disease Control and Prevention (CDC), Community Preventive Services
National Institute for Health and Care Excellence (NICE)
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, randomized controlled trials, or clinical practice guidelines.

Appendix D. Applicable Codes

HCPCS	
A7025	High frequency chest wall oscillation system vest, replacement for use with patient owned equipment, each
A7026	High frequency chest wall oscillation system hose, replacement for use with patient owned equipment, each
E0467	Home ventilator, multi-function respiratory device, also performs any or all of the additional functions of oxygen concentration, drug nebulization, aspiration, and cough stimulation, includes all accessories, components and supplies for all functions
E0480	Percussor, electric or pneumatic, home model
E0481	Intrapulmonary percussive ventilation system and related accessories
E0482	Cough stimulating device, alternating positive and negative airway pressure
E0483	High frequency chest wall oscillation system, includes all accessories and supplies, each
E0484	Oscillatory positive expiratory pressure device, non-electric, any type, each
E0656	Segmental pneumatic appliance for use with pneumatic compressor, trunk
E0657	Segmental pneumatic appliance for use with pneumatic compressor, chest
ICD-10-CM	
B91	Sequelae of poliomyelitis
D81.810	Biotinidase deficiency
D84.1	Defects in the complement system
E84	Cystic fibrosis
G12	Spinal muscular atrophy and related syndromes
G14	Post-polio syndrome
G35	Multiple sclerosis
G71.0-G71.1	Primary disorders of muscles
G72	Other and unspecified myopathies
G73.7	Myopathy in diseases classified elsewhere
G82.5	Quadriplegia
G95	Syringomyelia and syringobulbia
J44	Chronic obstructive pulmonary disease
J47	Bronchiectasis
J98.6	Disorders of diaphragm
M33	Dermatopolymyositis
M34.82	Systemic sclerosis with myopathy
M35.03	Sicca syndrome with myopathy
Q33.4	Congenital bronchiectasis

Note. Inclusion on this list does not guarantee coverage.

Section 3.0

Coverage Guidances

Health Evidence Review Commission (HERC)

Coverage Guidance: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

DRAFT for EbGS Meeting 12/2/2021

HERC Coverage Guidance

[Option 1]

Tonsillectomy, adenoidectomy, adenotonsillectomy, and prophylactic antibiotic therapy are not recommended for coverage to treat pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS) (*weak recommendation*).

Up to 3 monthly immunomodulatory courses of intravenous immunoglobulin (IVIG) therapy or therapeutic plasma exchange are recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met:

a) Two or more less-intensive therapies (e.g., appropriate course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) have been tried and were not effective, AND
b) A consultation with and recommendation by 2 pediatric subspecialists (e.g., pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist)

A reevaluation at 3 months by both pediatric experts is required for continued therapy of IVIG or plasma exchange. This evaluation must include objective clinical testing, which must be performed pretreatment and posttreatment to demonstrate significant clinical improvement.

Note: Other treatments (corticosteroids, SSRIs, NSAIDs, short-course antibiotics, and behavioral therapies) were included in an initial version of this report. These therapies were determined to be beyond the scope of a HERC coverage guidance, as these therapies are commonly used for many indications and are not typically subject to utilization control. Only treatments subject to coverage criteria were retained for the final version of this report.

[Option 2]

The following are not recommended for coverage to treat pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS) (*weak recommendation*):

a) Prophylactic antibiotic therapy
b) Tonsillectomy, adenoidectomy, or both
c) Intravenous immunoglobulin (IVIG) therapy
d) Therapeutic plasma exchange

Note: Other treatments (corticosteroids, SSRIs, NSAIDs, short-course antibiotics, and behavioral therapies) were included in an initial version of this report. These therapies were determined to be beyond the scope of a HERC coverage guidance, as these therapies are commonly used for many indications and are not typically subject to utilization control. Only treatments subject to coverage criteria were retained for the final version of this report.

Note. Definitions for strength of recommendation are in Appendix A, GRADE Table Element Descriptions. Rationales for each recommendation appear below in the GRADE tables.

Oregon Health Authority

Table of Contents

Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patients' experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on diagnostic and clinical interventions, evidence is evaluated using an adaptation of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness could depend on the environment in which the intervention is implemented.

GRADE Tables

HERC develops recommendations by using the concepts of the GRADE system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and assesses each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. Assessments of confidence are from the published systematic reviews and meta-analyses, where available and judged to be reliable. The level of confidence in the estimate is determined by HERC based on the assessment of 2 independent reviewers from the Center for Evidence-based Policy.

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, statements regarding resource allocation, values and preferences, and other considerations are the assessments of HERC, as informed by the evidence reviewed, public testimony, and subcommittee discussion.

Recommendations for coverage are based on the balance of benefit and harms, resource allocation, values and preferences and other considerations. See Appendix A for more details about the factors that constitute the GRADE table.

GRADE Tables

Should prophylactic antibiotics be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	In a single RCT (N = 37) comparing penicillin to placebo for 4 months, there was no significant difference in neuropsychiatric symptoms between children when they received penicillin or placebo. The cross-over design meant that each participant was in both the intervention and control group for the analysis. In a second RCT comparing prophylactic azithromycin (N = 17) to placebo (N = 14) for 4 weeks, the azithromycin group had a significantly greater reduction OCD severity, but no significant difference in number of obsessions and compulsions. Significantly more children were classified as responding at a clinically significant level in the azithromycin group (7/17) than in the placebo group (1/14). In a third RCT that tested prophylactic antibiotic therapy for 1 year, significantly more (5/11) children who received penicillin demonstrated significant reduction in symptoms compared to (1/12) children who received azithromycin. Compared to the year before baseline, children in both groups had fewer exacerbations during the trial year. ●○○○ *(very low confidence, based on 3 RCTs, n = 91)*	Antibiotics are inexpensive and readily available. Treatment of complications of long-term or frequent antibiotic use would add cost.	Some parents would want any treatment that might help their child's symptoms. However, other parents would have concerns about the risks and side effects of long-term or frequent antibiotic use.	Long-term or frequent antibiotic use is associated with a range of negative consequences, including but not limited to *C. difficile* infection, gut flora disruption, diarrhea, and increased antibiotic resistance leading to reduced ability to treat other infections with antibiotics. Most health plan cover short-term antibiotics without prior authorization criteria but may scrutinize or not cover long-term prescriptions.
Hospitalizations *(Critical outcome)*	No evidence identified.			

Should prophylactic antibiotics be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Harms *(Important outcome)*	The few harms that were reported included heart rate irregularity (9/12) for children who received azithromycin, and loose stool (no statistics reported). ●○○○ *(very low confidence, based on 1 RCTs, n = 23)*			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			

Balance of benefits and harms: We have very low confidence that prophylactic antibiotic use is helpful in PANDAS/PANS, given the small sample sizes in the included studies. There are concerning known harms of frequent or long-term antibiotic use.
Rationale: Prophylactic antibiotic therapy is not recommended for coverage for PANDAS/PANS (*weak recommendation*) because of insufficient comparative evidence that prophylactic antibiotic use leads to any measurable benefit for these conditions. The known risks of prophylactic or long-term antibiotic use outweigh potential benefits in these conditions.
Recommendation: Prophylactic antibiotic therapy is not recommended for coverage for PANDAS/PANS (*weak recommendation*).

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; RCT: randomized controlled trial.

Should tonsillectomy and/or adenoidectomy be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	No difference in neuropsychiatric symptoms between surgery and nonsurgery groups among children diagnosed with PANDAS. ●●○○ *(low confidence, based on 2 comparative cohort studies, n = 232)*	Tonsillectomy and adenoidectomy are invasive procedures requiring general anesthesia and specialty surgical care.	Parents would not value an invasive surgery with risks as well as the risks of general anesthesia for a procedure that has no evidence of benefits.	Tonsillectomy and/or adenoidectomy frequently have coverage limitations, such as multiple streptococcal infections in one year. This procedure has historically been overused.
Hospitalizations *(Critical outcome)*	No evidence identified.			
Harms *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			

Balance of benefits and harms: We have low confidence that that there is no benefit from tonsillectomy and/or adenoidectomy for PANDAS/PANS, and this procedure has known harms.
Rationale: Tonsillectomy and/or adenoidectomy are not recommended for coverage (*weak recommendation*) for treatment of PANDAS/PANS because these procedures have known harms and because evidence shows that these procedures do not improve the outcomes in this condition.
Recommendation: Tonsillectomy and/or adenoidectomy are not recommended for coverage (*weak recommendation*) for treatment of PANDAS/PANS.

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Abbreviations. PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome.

Should IVIG be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	<u>Compared to Saline Placebo</u> Among children meeting the criteria for PANDAS and OCD in an RCT, 7/18 had a significant decrease in symptoms 6 weeks after receiving 2 consecutive days of IVIG infusions, and 4/17 children in the placebo group had a significant decrease in symptoms. When comparing the IVIG group and placebo group, there were no statistically significant differences. During an open-label phase of this same trial, 17/24 children meeting the criteria for PANDAS and OCD had a significant decrease in symptoms 12 to 18 weeks after receiving 2 consecutive days of IVIG infusions on 1 or 2 occasions. Another RCT compared children who received IVIG (N = 9) to children who received saline placebo (N = 10) 1 month after treatment reported that the IVIG group improved significantly more on most measures compared to the placebo group. One year after treatment, the improvements in the IVIG group were maintained, but the placebo group was not followed to determine whether the IVIG group's symptoms remained significantly better than the placebo group's symptoms. <u>Compared to plasma exchange</u> No significant difference 1 month or 1 year after treatment between children receiving IVIG (N = 9) or plasma exchange (N = 10); both groups had	IVIG is expensive and requires the cost of an infusion center, nursing care, and possible hospitalization. Treatment for side effects of IVIG would add cost. IVIG is a scarce resource and shortages have been reported in the past.	Parents would value any treatment that would improve their child's symptoms. However, many parents would value avoiding a treatment with known side effects that has little evidence of effectiveness.	IVIG is a blood product with the inherent risks that accompany accepting any form of blood product. IVIG therapy has a significant rate of mild side effects including fever, body aches, nausea, rash, and fatigue. Severe side effects include thrombosis, renal dysfunction, and acute renal failure, and life-threatening allergic reaction. IVIG can interfere with vaccine effectiveness for vaccines given

Should IVIG be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
	significant improvement in symptoms compared to baseline at both 1-month and 1-year follow-ups ●○○○ *(very low confidence, based on 2 RCTs, N = 54)*			within several months of IVIG. Several products on the market are FDA-approved for people under the age of 19.
Hospitalizations *(Critical outcome)*	No evidence identified.			
Harms *(Important outcome)*	1/33 children who received IVIG infusions had an allergic reaction to the IVIG infusion that resolved without complication. 31/33 children reported mild or moderate adverse events such as nausea, vomiting, headache, fever, joint pain, tiredness, stomach pain, or decreased appetite. ●○○○ *(very low confidence, based on 2 RCTs, N = 64)*			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			

Balance of benefits and harms: There were mixed results from 2 very small trials regarding the clinical effectiveness of IVIG. Outside of PANDAS, no evidence met inclusion criteria for PANS. IVIG has a significant rate of known harms.
Rationale: Option 1: Expert opinion and lower-quality observational data indicate there may be benefit for some patients with these conditions, but recommended treatment protocols and criteria for treatment vary widely. Due to the severe impact of symptoms associated with PANDAS/PANS on child health, growth and development, and the lack of known effective treatments, coverage of IVIG is recommended when recommended by 2 pediatric sub-specialists and after less-intensive therapies were not effective.

Should IVIG be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Option 2: Because the potential benefits of IVIG do not outweigh its high costs and known harms, treatment of PANDAS/PANS with IVIG is not recommended (*weak recommendation*).				
Recommendation: Option 1: Up to 3 monthly immunomodulatory courses of IVIG are recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met: a) Two or more less-intensive therapies (e.g., appropriate course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) have been tried and were not effective, AND b) A consultation with and recommendation by 2 pediatric subspecialists (e.g., pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist) A reevaluation at 3 months by both pediatric experts is required for continued therapy of IVIG. This evaluation must include objective clinical testing, which must be performed pretreatment and posttreatment to demonstrate significant clinical improvement. **Option 2:** IVIG is not recommended for coverage for treatment of PANDAS/PANS (*weak recommendation*).				

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Abbreviations. IVIG: intravenous immunoglobulin; OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; RCT: randomized controlled trial.

Should therapeutic plasma exchange be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	Compared to saline placebo In the same RCT that is described in the IVIG table, the plasma exchange group (N = 10) was compared to the same placebo group (N = 10) 1 month after treatment. The plasma exchange group improved significantly more on most measures compared to the placebo group. One year after treatment, the improvements in the plasma exchange were maintained, but the placebo group was not followed to determine whether the plasma exchange group's symptoms remained significantly better than the placebo group's symptoms. Compared to intravenous immunoglobulin No significant difference 1 month or 1 year after treatment between children receiving IVIG (N = 9) or plasma exchange (N = 10); both groups had significant improvement in symptoms compared to baseline at both 1-month and 1-year follow-ups ●○○○ *(very low confidence, based on 1 RCT, N = 29)*	Plasma exchange is an expensive therapy which requires a monitored infusion in a clinical setting. Children in the studies included in this review required multiple treatment sessions.	Parents would value any treatment that would improve their child's symptoms. However, many parents would value avoiding a treatment with known side effects that has little evidence of effectiveness.	High rates of patients undergoing plasma exchange report side effects, including fever, chills, and muscle cramps. Known complications of plasma exchange include circuit clotting, low or high blood pressure, nausea, vomiting, itchy skin, hives, low calcium levels in the blood, venous access malfunction, infections, thrombosis, and anaphylactic shock.
Hospitalizations *(Critical outcome)*	No evidence found.			
Harms *(Important outcome)*	All children who received plasma exchange (10/10) experienced mild side effects such as nausea, vomiting, anxiety, or fever. ●○○○ *(very low confidence, based on 1 RCT, N = 29)*			

Should therapeutic plasma exchange be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Function or quality of life for patient *(Important outcome)*	No evidence found.			
Function or quality of life for patient *(Important outcome)*	No evidence found.			

Balance of benefits and harms: The comparative evidence that plasma exchange is effective for treating PANDAS is very limited and shows no clear benefit. The harms of this treatment are generally mild but serious complications can occur.

Rationale: Option 1: Expert opinion and lower-quality observational data indicate there may be benefit for some patients with these conditions, but recommended treatment protocols and criteria for treatment vary widely. Due to the severe impact of symptoms associated with PANDAS/PANS on child health, growth and development, and the lack of known effective treatments, coverage of plasma exchange is recommended when recommended by 2 pediatric sub-specialists and after less-intensive therapies were not effective.

Option 2: Plasma exchange is not recommended for treatment of PANDAS/PANS *(weak recommendation)* as the benefits have not been demonstrated and do not outweigh the known harms and cost.

Recommendation: Option 1: Up to 3 monthly immunomodulatory courses of therapeutic plasma exchange is recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met:

a) Two or more less-intensive therapies (e.g., appropriate course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) have been tried and were not effective, AND
b) A consultation with and recommendation by 2 pediatric subspecialists (e.g., pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist)

A reevaluation at 3 months by both pediatric experts is required for continued therapy of plasma exchange. This evaluation must include objective clinical testing, which must be performed pretreatment and posttreatment to demonstrate significant clinical improvement.

Option 2: Plasma exchange is not recommended for treatment of PANDAS/PANS *(weak recommendation).*

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. IVIG: intravenous immunoglobulin; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; RCT: randomized controlled trial.

Background

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS are conditions associated with a sudden onset of changes or regression in behaviors and experiences prior to puberty in multiple domains, such as motor, neurological, psychiatric, and biological systems.[1-3] Care providers and researchers from multiple disciplines (including microbiology, neurology, neuroimmunology, immunology, child psychiatry, infectious diseases, rheumatology, and pediatrics) have contributed to publications seeking to define these conditions.[3] These conditions have an abrupt onset of symptoms and may include exacerbations, sudden worsening of symptoms in short bursts, in a sawtooth-like pattern.[1-3]

In PANDAS, the triggering mechanism for these changes is hypothesized to be a beta-hemolytic streptococcal infection within 6 months of symptom onset, and is characterized by sudden onset of obsessive-compulsive disorder (OCD), along with verbal or motor tics.[2,4] However, some researchers suggest that tying the diagnosis to streptococcus infection to the exclusion of other etiologies has limited the exploration of other disease pathways that could inform diagnosis and treatment of symptoms.[5,6] The prevalence of PANDAS is not known, but some studies suggest that males are more likely than females to be diagnosed with PANDAS.[7]

PANS is characterized by sudden onset of OCD, with or without severe eating restrictions, and 2 or more other symptoms in neurological, behavioral, or cognitive domains.[3] PANDAS can be considered a subset of PANS. These symptoms could result from multiple disease pathways or other disorders, including but not limited to streptococcus, varicella, or bacterial pneumonia infections.[3,8] The prevalence of PANS is not known.

Two other conditions with similar symptoms are pediatric infection-triggered autoimmune neuropsychiatric disorders (PITAND) and childhood acute neuropsychiatric syndromes (CANS).[8,13]

The natural histories of PANDAS and PANS are still being studied, but early signals suggest that 60% to 80% of pediatric patients have a significant reduction in symptoms over time, similar to childhood-onset OCD.[14] The American Academy of Child and Adolescent Psychiatry published a practice parameter for assessing and treating childhood-onset OCD; they noted some clinical experts believe a small subset of children that have been diagnosed with OCD or Tourette disorder might have clinical exacerbations linked to streptococcal infection.[15] The authors report that more males than females are diagnosed with pediatric OCD, typically diagnosed between the ages of 7 and 12 years; earlier onset is associated with comorbid psychiatric diagnoses (e.g., mood disorders, attention deficit disorder, anxiety disorders, phobias).[15]

There is some discussion about whether PANDAS and PANS is related to pediatric autoimmune encephalitis, which is also characterized by abrupt onset of similar abnormal behavioral symptoms and disruptions in multiple biological systems (e.g., gastrointestinal, nervous).[1,10,11,19] Autoimmune encephalitis in children is characterized by a sudden onset of symptoms including seizures, irritability, aggression, and abnormal movements, and could be associated with an acute infection or presence of a tumor.[1,9,10] The prevalence of pediatric autoimmune encephalitis is not known, but a population study of adults and children suggested the incidence rate of autoimmune encephalitis was 0.8 per 100,000, and that males had more than twice the prevalence of females.[12] Autoimmune encephalitis is a life-threatening condition usually treated in a hospital setting.[1,11] Because of the differences in diagnostic

criteria and disease process between autoimmune encephalitis and PANDAS/PANS, the scope of this report excludes autoimmune encephalitis.

Diagnostic Criteria and Tests

Table 1 presents diagnostic criteria and tests by condition, and includes information from publications summarized in the Evidence Review and Clinical Practice Guidelines sections of this coverage guidance.[3,9,13,16-30]

Table 1. Proposed Diagnostic Criteria, Tests and Processes

Proposed Diagnostic Criteria	Proposed Diagnostic Tests and Processes
PANDAS[2]	
Presence of OCD, symptoms similar to attention deficit hyperactive disorder, or tics	In patients with OCD, complete blood count, erythrocyte sedimentation rate, C-reactive protein, metabolic panel, urine analysis, pharyngeal swab and anti-streptococcal antibodies. Positive results from the pharyngeal swab and anti-streptococcal antibodies indicate exposure to the streptococcal infection do not differentiate between the state of carrier and acute infection. For children with neurological and psychiatric symptoms, physical or neurological examination require the analysis of the cerebrospinal fluid and neuroimaging exams.
Onset of symptoms occurs between the ages of 3 and 12 (or prior to puberty)	
Symptoms had sudden onset, or existing symptoms worsened for a short period	
Confirmed culture or antibodies related to a streptococcal infection temporally associated with onset of symptoms	
Neurological anomalies such as hyperactivity, choreiform motor movements, bedwetting, anxiety, emotional lability, developmental regression or mood changes	
Rule out Sydenham's chorea, Tourette syndrome, OCD, central nervous system vasculitis, autoimmune encephalitis, and neuropsychiatric lupus	Differential diagnosis.
PANS[3,20]	
Sudden onset of OCD or eating restrictions, and at least 2 of the following: • Anxiety (particularly separation anxiety) • Emotional lability or depression • Irritability, aggression, and/or severely oppositional behaviors • Deterioration in school performance (related to attention-deficit/hyperactivity disorder-like behaviors, memory deficits, and cognitive changes) • Sensory or motor abnormalities • Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency	Complete medical and psychiatric history, physical examination, laboratory testing of blood and possibly cerebrospinal fluid, and selected paraclinical evaluations, such as magnetic resonance imaging, electrocardiogram/ echocardiography, electroencephalography, and polysomnography.

Proposed Diagnostic Criteria	Proposed Diagnostic Tests and Processes
Rule out Sydenham chorea, autoimmune encephalitis, neuropsychiatric lupus, central nervous system vasculitis, and other conditions that better account for the symptoms	Differential diagnosis.

Abbreviations. OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome.

We identified 4 publications that specifically presented or summarized evidence for diagnostic criteria and tests related to PANDAS or PANS.[4,7,31,32] Nielsen and colleagues performed a systematic review and meta-analysis of studies on the association between streptococcal infections and exacerbations of neuropsychiatric symptoms.[32] The authors concluded that although children diagnosed with PANDAS had more neuropsychiatric exacerbations than children with streptococcal infections without a follow-up diagnosis of PANDAS, these exacerbation were not significantly temporally associated with streptococcal infections.[32]

Baj and colleagues reviewed published literature in search of distinguishing features of patients diagnosed with PANDAS and concluded that despite more than 20 years of research into this condition, it remains challenging to differentiate PANDAS from OCD or tic disorders.[7] Their observations of characteristics that appear to be different for children diagnosed with PANDAS include[7]:

- some alterations of cortico-basal ganglia circuitry, due to the effect of antibodies produced in response to the condition on various neuronal proteins, including tubulin, lysoganglioside, and dopamine receptors;
- deposits of antibodies which are also accumulated in the striatal interneurons;
- significantly enlarged volumes of corpus striatum, caudate, putamen, globus pallidus, and basal ganglia; and
- significant alterations to the gut microbiota.

Gamucci and colleagues described the clinical, neuropsychological, and biological characterization of PANDAS and PANS, and recommended 4 categories of tools to add in the diagnostic process.[4] Proposed neuropsychological tests to assess motor and vocal tics, obsession and compulsion[4]:

- Children's Yale–Brown Obsessive Compulsive Scale for presence and severity of motor and vocal tics; and
- Yale Global Tic Severity Scale for presence and severity of child's obsession and compulsion.

Proposed neuropsychological tests to assess anxiety[4]:

- Multidimensional Anxiety Scale for Children (MASC) for the presence and types of child's anxiety symptoms for ages 8 to 19 years.

Proposed neuropsychological tests to assess short-term memory and attention[4]:

- Digit Span subtest Wechsler Intelligence Scale for Children for verbal short-term memory for ages 6 to 16 years;
- Coding subtest Wechsler Intelligence Scale for Children for visual-motor dexterity and nonverbal short-term memory for ages 6 to 16 years; and

- Symbol Search subtest Wechsler Intelligence Scale for Children for accuracy, attention and concentration for ages 6 to 16 years.

Proposed neuropsychological tests to assess processing speed[4]:

- Processing Speed Index Wechsler Intelligence Scale for Children (WISC III-IV) for speed of cognitive processes and response output on visual-motor tasks for ages 6 to 16 years

In addition to the scales proposed by Gamucci and colleagues above, Leibold and colleagues validated a Global Impairment Score scale to measure impairment in children and adolescents as part of the diagnostic process for PANS.[31] This scale was designed to be answered by a child's caregiver, and is scored on a scale of 0 to 100.[31]

For additional measures proposed in guidelines, please refer to the Clinical Practice Guidelines section of this coverage guidance.

Treatments

Table 2 presents treatments by condition and includes information about treatments from the publications summarized in the evidence review and clinical practice guidelines sections of this coverage guidance.[3,9-11,13,16-30] Not all treatments in Table 2 have been evaluated in studies with prospective comparative designs; the evidence review portion of this coverage guidance will synthesize findings from comparative studies related to treatments and outcomes.

Table 2. Treatments Proposed for PANDAS and PANS

Treatments	PANDAS	PANS
Antibiotics		
Amoxicillin	X	X
Aripiprazole		X
Azithromycin	X	
Penicillin	X	
Surgical Interventions		
Tonsillectomy	X	
Adenoidectomy	X	
Intravenous Immunoglobulin and Plasma Exchange		
Intravenous immunoglobulin	X	X
Plasma exchange	X	X
SSRIs		
Fluoxetine	X	
NSAIDs		
Naproxen sodium	X	
Antipsychotics		
Pimozide	X	
Risperidone		X
Corticosteroids		
Dexamethasone		X
Prednisone	X	

Treatments	PANDAS	PANS
Behavioral Interventions		
Cognitive behavioral therapy	X	

Abbreviations. NSAID: nonsteroidal anti-inflammatory drug; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; SSRI: selective serotonin reuptake inhibitor.

Evidence Review

We identified 2 systematic reviews, 5 RCTs with 6 publications, and 2 comparative cohort studies that reported interventions for children diagnosed with PANDAS or PANS.[13,22-30] Table 3 summarizes key characteristics of each included study. Given the varied study designs, treatments, and outcomes collected, neither of the systematic reviews included a meta-analysis section.

Sigra and colleagues included in their systematic review any report of any treatments for children with PANDAS, PANS, CANS, or PITAND published in English that also reported outcomes; this expansive inclusion criteria resulted in 5 RCTs, 7 observational survey study, and 65 case reports.[22] We rated this systematic review itself as having a low risk of bias, although it is important to note that the review authors concluded that there is not enough rigorous research about treatments for children with PANDAS, PANS, CANS, or PITAND, and the existing studies themselves have a high risk of bias. Sigra and colleagues concluded there was insufficient evidence to clearly recommend specific treatments for children with these diagnoses, but that psychiatric behavioral interventions, immunomodulatory therapies, and antibiotics likely have roles in the treatment of these disorders and should be more systematically investigated.[22]

In addition to summarizing comparative evidence regarding antibiotics, tonsillectomy, IVIG, and therapeutic plasma exchange, Sigra and colleagues sumarized noncomparative evidence for behavioral therapy, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs). The first draft of this coverage guidance included the latter interventions, although it was not possible to make a clear determination of effectiveness or harms of these interventions due to the lack of comparative evidence.

Farhood and colleagues included in their systematic review 13 studies testing treatments for PANDAS that also reported outcomes related to change in symptoms, and excluded case reports; 3 included studies were RCTs, and 10 had retrospective designs.[25] We rated this review as having a high risk of bias. This review included studies of adenotonsillectomy, antibiotic therapy, intravenous immunoglobulin (IVIG) therapy, and cognitive behavioral therapy.[25] The authors suggested that immunoglobulin therapy might be effective for certain populations, and that psychotherapy and antibiotic therapies were likely low-risk interventions.[25] However, the authors concluded that the study designs left results open to question due to inability to account for confounding factors, such as co-occurring treatments, and were unable to strongly recommend any specific course of treatment.[25] All of the studies included in Farhood and colleagues' systematic review were also included in Sigra and colleagues' systematic review. Given the later search and publication dates and the lower risk of bias for Sigra and colleagues' review, we restrict our summary of review findings to the Sigra review in the following sections.

The RCTs all had fewer than 40 participating children, so the number of children in each treatment and placebo group was also small during comparative stages of the trials. These RCTs compared antibiotics

to placebo and had moderate to high risk of bias,[23,28,29] or compared IVIG to placebo or plasma exchange and had low to high risk of bias.[24,30] At the end of the trial phase, the investigators of 3 of the RCTs offered the active treatment under consideration to the children who had been in the group receiving a placebo, which makes the long-term follow-up of participants in these trials an open-label observation follow-up (range, 4 weeks to 57 months).[13,23,24,29]

The number of children included in the 2 comparative cohort studies was larger (more than 100), and both studies focused on surgical interventions for symptom relief for children diagnosed with PANDAS.[26,29] We rated both studies as having a high risk of bias, primarily due to an inability to account for confounding factors.

The following sections organize findings from these studies by type of intervention. First, we summarize relevant RCTs and comparative cohort studies, and then we compare those findings with conclusions from the systematic reviews that included results from noncomparative study designs such as case reports.

Table 3. Characteristics of Included Studies

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
Systematic Reviews				
Sigra et al., 2018[22] 5 RCTs, 7 observational survey studies, and 65 case reports Not applicable	Studies in which patients with PANDAS, PANS, CANS, or PITAND were given treatment, that presented outcome data, and were written in English	No exclusion criteria explicitly listed	Cognitive behavior therapy, antibiotics, tonsillectomy, corticosteroids, therapeutic plasma exchange, IVIG, rituximab, nonsteroidal anti-inflammatory drugs	Low
Farhood et al., 2016[25] 3 RCTs and 10 retrospective designs Not applicable	Studies testing treatments for PANDAS and reported outcomes, and were written in English or Spanish	Review articles, single case reports, and studies of natural history or diagnostic strategies	Tonsillectomy, adenoidectomy, antibiotics, IVIG, cognitive behavioral therapy, or SSRIs	High
RCTs				
Murphy et al., 2017[23] N = 31 2 and 4 weeks	Children with an acute onset or acute relapse within 6 months of evaluation (abrupt, dramatic overnight onset) of moderate or worse OCD symptoms and presence of a sudden and severe co-occurrence of at least 2 neuropsychiatric symptoms.	Children with a gradual onset or duration of OCD symptoms of more than 6 months; who were receiving extended-course antibiotics (i.e., not a typical treatment course of antibiotics for an infection, or prophylactic antibiotics) and/or other immune therapy for PANS; with a primary diagnosis of tics; who were receiving exposure-based cognitive behavioral therapy; who had a history of nonresponse to a prior antibiotic trial; or who had a diagnosis of moderate to severe autism spectrum disorder,	Azithromycin and probiotics versus placebo with probiotics for 4 weeks; after this all participants were offered azithromycin	Moderate

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
		intellectual disability, and/or chronic neurological disease.		
Williams et al., 2016[24] Leon et al., 2018[13] N = 35 3 and 6 months during the trial, and a 57-month observational follow-up	Children who were 4 to 13 years of age in first episode of PANDAS symptoms and documentation that symptoms first appeared within 6 to 8 weeks of streptococcal infection or exposure; who had a sudden onset or exacerbation of OCD (reaching peak severity and impairment within 24 to 48 hours); and had at least 3 neuropsychiatric symptoms (which meets criteria for PANS).	Children with a history of Sydenham chorea or acute rheumatic fever; who had symptoms consistent with autism spectrum disorder or schizophrenia; who had severe physical, behavioral, or psychiatric symptoms that would prevent study participation; or prior corticosteroid or immunomodulatory therapy for PANDAS	IVIG versus placebo for 6 weeks; participants in the placebo group were then given the opportunity to receive IVIG; 31 participants received at least 1 dose of IVIG over the course of the study	Low risk for original trial, and high risk for long-term follow-up
Snider et al., 2005[28] N = 23 12 months	Children with a tic disorder and/or OCD; who had a history of a sudden onset of symptoms or an episodic course with abrupt symptom exacerbations interspersed with periods of partial or complete remission; who had onset of neuropsychiatric symptoms prior to puberty; and who had documentation of a temporal association between a preceding streptococcal infection and the onset or exacerbation of neuropsychiatric symptoms.	No specific exclusion criteria listed.	Azithromycin versus penicillin for 12 months	High

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
Garvey et al., 1999[29] N = 37 4 months	Children between 4 and 15 years of age with a tic disorder and/or OCD; who had history of a sudden onset of symptoms or an episodic course with abrupt symptom exacerbations interspersed with periods of partial or complete remission (a sawtooth, rather than a waxing and waning course); who had an onset of symptoms prior to puberty; and evidence of a temporal association between a preceding streptococcal infection and the onset or exacerbation of neuropsychiatric symptoms.	Children who had tics or OCD of such a severity that hospitalization was considered; who required treatment for severe, active comorbid major psychiatric disorders; who had with autism, pervasive developmental delay, or "mental retardation"[a]; or who had neurologic diagnoses other than tics and Tourette syndrome, serious concurrent or chronic medical disorders, and a personal history of penicillin allergy.	Penicillin versus placebo for 4 months; cross-over design meant that all participants received penicillin during the 8 months of the study	High
Perlmuter et al., 1999[30] N = 29 1 month and 12 months	Children ages 5 to 14 years with a tic disorder and/or OCD; onset of neuropsychiatric signs and symptoms before puberty; a history of sudden onset of signs and symptoms, or an episodic course characterized by abrupt exacerbations and periods of partial or complete remission; evidence of, and association between, streptococcal infection and onset or exacerbation of signs and symptoms; and current exacerbation severe	Children with a history of Sydenham's chorea or rheumatic fever, autism, schizophrenia or other psychotic disorder, a neurological disorder other than a tic disorder, an autoimmune disorder, or other medical illness. Immunoglobulin concentrations were measured, and children were excluded from the study if they had IgA deficiency (a contraindication to IVIG administration).	Plasma exchange, IVIG, or placebo for 2 weeks	High

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
	enough to cause significant distress and interfere with the child's social functioning in at least 2 spheres (home, school, social relations).			
Comparative Cohort Studies				
Pavone et al., 2014[26] N = 120 Every 2 months for 2 years	Children with a tic disorder and/or OCD; who had infection-related symptom flare-ups, history of dramatic onset of either OCD or tics, new onset anxiety, sensory or motor abnormalities, behavioral regression, deterioration in school performance, emotional lability, or urinary symptoms (all these neuropsychiatric phenomena were in temporal association to streptococcal pharyngeal tonsillitis). The surgical group (n = 56) were referred to surgery based on a clinical history of recurrent inflammation in addition to the symptoms above.	No specific exclusion criteria listed	Surgery versus no surgery; surgery group had 25 tonsillectomies and 31 adenotonsillectomies	High
Murphy et al., 2013[27] N = 112 Not reported	Children with a tic disorder and/or OCD; and with infection-related symptom flare-ups, history of dramatic onset of either OCD or tics, new onset anxiety, sensory or motor	Children with a psychotic disorder, significant medical illness, or non-tic neurologic disorder	Surgery versus no surgery; surgery group had 4 tonsillectomies, 10 adenoidectomies, and 22 had both procedures	High

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
	abnormalities, behavioral regression, deterioration in school performance, emotional lability, or urinary symptoms. Participants on stable doses of psychotropic medication for their condition were not excluded. The surgical group comprised children who had a tonsillectomy and/or adenoidectomy procedure, and were matched to nonsurgery participants on age and sex.			

Note. This language was taken directly from the study; the coverage guidance authors recognize this language is no longer acceptable.
Abbreviations. CANS: childhood acute neuropsychiatric syndromes; IgA: immunoglobulin A; IVIG: intravenous immunoglobulin; OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; PITAND: pediatric infection-triggered autoimmune neuropsychiatric disorders; RCT: randomized controlled trial; SSRI: selective serotonin reuptake inhibitor.

Antibiotics

We identified 3 RCTs that tested antibiotics as a primary intervention for children diagnosed with PANDAS or PANS.[23,28,29] As a reminder, children meeting the criteria for PANDAS also meet the criteria for PANS. Conclusions from both systematic reviews agreed with author conclusions of these 3 RCTs: there is some evidence that antibiotic prophylaxis might reduce exacerbations of neuropsychiatric symptoms for children diagnosed with PANDAS.[22,25]

Azithromycin

Murphy and colleagues conducted a double-blind RCT with 31 participants randomized to receive azithromycin prophylaxis (N = 17) for 4 weeks or to receive a placebo (N = 14) for 4 weeks; participants in the placebo group were then given the option to begin taking azithromycin, which launched the open-label observational portion of the study.[23] Both groups also received twice daily probiotics.[23] We rated the outcomes from the trial portion of this study as having a moderate risk of bias; no outcomes were reported for the open-label portion.

When comparing scores on the OCD Clinical Global Impressions Severity scale (which has a scale of 1 to 7), participants who received azithromycin reported statistically significantly greater reductions in symptom frequency 4 weeks after baseline (azithromycin group mean, 4.06; azithromycin group standard deviation [SD], 0.23; placebo group mean, 4.93; placebo group SD, 0.25; effect size, 0.11; $P = .003$). The effect size for the difference in symptoms between the azithromycin and placebo groups suggests that there was only a very small difference between the 2 groups, and that the difference was not likely to be clinically significant. No significant difference was found between the group on the Children's Yale-Brown Obsessive Compulsive Scale, and no difference between groups for the severity of symptoms.[23]

Investigators also assessed whether participants responded to their assigned therapy, using a 30% or greater reduction in symptoms to judge whether a participant responded. In the azithromycin group, 52.9% (9 of 17) were categorized as responders, and 21.4% (3 of 14) were categorized as responders in the placebo group.[23]

The authors reported that among participants with greater tic severity scores at baseline (measured as 1 standard deviation greater than average number of tics), participants in the azithromycin group were significantly more likely to have at least a 30% reduction in tic symptoms during the 4-week trial than control group participants (no statistics reported; $P < .05$).[23] If there is a treatment benefit to azithromycin, this suggests that it might have greater benefit for children with more severe tics.

Penicillin

Garvey and colleagues conducted a double-blind, balanced crossover study with 37 participants randomized to receive either penicillin prophylaxis or a placebo for 4 months.[29] After the first 4 months passed, the treatment assignment was reversed for 4 months; therefore, participants were followed for 8 months.[29] There was no wash out period between the reversal of treatment assignment.[29] We rated this study as having a high risk of bias. No statistically significant difference was reported between treatment groups for exacerbations of neuropsychiatric symptoms, with 38 exacerbations during the placebo phase and 35 exacerbations during the penicillin phase.[29] There were no clinically meaningful differences in depression or anxiety symptoms between the treatment phases.[29] Of the 27 parents who

provided global ratings of their child's behaviors, 22 reported an improvement of behavior during the penicillin phase; 18 of these parents correctly identified this as the active treatment phase when rating their child's behavior.[29] There were no statistically significant differences in neuropsychiatric symptoms between the penicillin and placebo phases, as measured by the Children's Yale-Brown Obsessive Compulsive Scale (P = .16) or the Yale Global Tic Severity Scale (P = .28).

Azithromycin Versus Penicillin

Snider and colleagues conducted a double-blind RCT with 23 participants randomized to receive either azithromycin or penicillin prophylaxis for 12 months.[28] We rated this study as having a high risk of bias. The authors reported that both antibiotic therapies reduced the number of streptococcal infections during the study year compared to the year prior to the study (mean reduction of about 2 infections per year), with no significant difference between the 2 groups (mean for both groups, 0.1; SD for both groups, 0.3; P > .05). Parent and child reports at baseline and the end of the study were reviewed and rated by the study authors to determine the presence and frequency of exacerbations of neuropsychiatric symptoms.[28] Both groups reported decreased neuropsychiatric exacerbations, but the participants who received penicillin reported significantly fewer exacerbations of neuropsychiatric symptoms (penicillin group mean, 0.5; penicillin group SD, 0.5; azithromycin group mean, 0.9; azithromycin group SD, 0.5; P < .01).[28]

Tonsillectomies and Adenoidectomies

We identified 2 comparative cohort studies that examined the association of tonsillectomies and adenoidectomies with change in symptoms for children diagnosed with PANDAS, and both compared children with PANDAS who had either or both of these surgeries (N = 88) to children with PANDAS who had received neither surgery (N = 140).[26,27] Both studies specifically named PANDAS as the diagnosis of focus.[26,27] We rated both of these studies as having a high risk of bias. Both systematic reviews agreed with the conclusions of the authors from these 2 studies that tonsillectomy and adenoidectomy do not appear to reduce neuropsychiatric symptom severity or exacerbations.[22,25] We did not identify any studies that tested the surgical interventions of tonsillectomies and adenoidectomies for the broader diagnosis of PANS.

In a prospective comparative cohort study including 120 participants, Pavone and colleagues reported that there was no significant difference in symptom remission rates between the surgery and nonsurgery groups (relative risk [RR], 1.39; 95% confidence interval [CI], 0.75 to 2.55; P = 0.29).[26] The authors also reported no significant difference in days to first symptom relapse (surgery group mean, 45.1; surgery group SD, 17.8; nonsurgery group mean, 39.3; nonsurgery group SD, 14.2; P = .09).[26]

Murphy and colleagues conducted a prospective comparative cohort study including 112 children who met the criteria for an OCD or tic diagnosis, and were divided into a group meeting the criteria for PANDAS and a group that did not meet criteria for PANDAS, according to a temporal relationship with a streptococcal infection.[27] The authors reported no significant difference in OCD or tic severity between the surgery and nonsurgery groups among children with or without a PANDAS diagnosis, as measured by the Children's Yale-Brown Obsessive Compulsive Scale (surgery group mean, 17.9; surgery group SD, 9.9; nonsurgery group mean, 18.7; nonsurgery group SD, 10.5; P = .71) or the Yale Global Tic Severity Scale (surgery group mean, 33.4; surgery group SD, 23.5; nonsurgery group mean, 33.6; nonsurgery group SD, 21.6; P = .97).[27] The authors also reported that there was no relationship between surgery status and

age of onset of OCD or tic symptoms (surgery group mean, 5.9 years; surgery group SD, 2.1 years; nonsurgery group mean, 6.5 years; nonsurgery group SD, 2.7 years; P = .32).[27] There was no statistically significant relationship between surgery status and duration of symptoms (surgery group mean, 2.5 years; surgery group SD, 2.1 years; nonsurgery group mean, 3.3 years; nonsurgery group SD, 2.5 years; *P* = .09).[27]

Both comparative cohort studies concluded that the surgical interventions had no effect on severity of symptoms or symptom progression.[26,27]

IVIG

We identified a single RCT that tested IVIG versus placebo,[13,24] and a single RCT that tested IVIG versus a placebo or plasma exchange.[30] Both RCTs reported that they enrolled children who met the diagnostic criteria for PANDAS and OCD.[24,30]

IVIG Versus Saline Placebo

Williams and colleagues randomized 35 children to receive IVIG or an intravenous saline placebo for 2 consecutive days at trial start.[24] All children were prescribed prophylactic antibiotics for the duration of the 6 months of this study, and penicillin was reported as the most commonly prescribed antibiotic (no number reported).[13] The investigators then offered the opportunity to children who had received the placebo to enter an open-label phase in which they received IVIG along with the children in the intervention group who were judged to be nonresponders to the treatment 6 weeks after the first infusion.[24] The investigators defined responding to treatment before the trial began as a 30% or greater decrease in symptoms as measured by the Children's Yale Brown Obsessive Compulsive Scale, or by a "much" or "very much" improved rating on the Clinical Global Impressions Improvement scale.[24] We rated the first phase of this trial as having a low risk of bias, and the 6- to 12-week open-label phase and the 24-week follow-up with any associated outcomes as having a high risk of bias.

At the conclusion of the 6-week blinded trial phase, there were no significant differences between the intervention and control groups for neuropsychiatric symptoms, as measured by changed in scores between baseline and 6-week follow-up on the Clinical Global Impressions Improvement scale and the Children's Yale Brown Obsessive Compulsive Scale.[24]

- Seven of the participants in the intervention group (38.9%; intervention group N = 18) were classified as responders to the treatment, meaning that they either demonstrated a 30% or greater decrease in symptoms as measured by the Children's Yale Brown Obsessive Compulsive Scale, or by a "much" or "very much" improved rating on the Clinical Global Impressions Improvement scale.[24] In the placebo group, 4 children were classified as having a significant decrease in symptoms (23.5%; placebo group N = 17).[24]
- There was not a significant difference in the number of children in each group who had a significant improvement in symptoms (*P* = .40).[24] The authors also reported that was no significant difference in the average change in symptoms between the intervention group and placebo group, as measured by the Clinical Global Impressions Improvement scale (*P* = .12) or the Children's Yale-Brown Obsessive Compulsive Scale (*P* = .44).[24]

During the nonblinded, open-label phase, 24 participants received IVIG.[24] This included 10 of 18 participants who were originally randomized to the intervention group and who were classified as

nonresponders at the end of the 6-week blinded phase; these participants therefore received doses of IVIG on 2 consecutive days twice: at baseline and 6 weeks after baseline.[24] Of the participants in the open-label phase, 17 (70.8%) were classified as responding to the treatment by 24 weeks.[24] However, there was no comparator group for this phase of the study and the authors did not report follow up at 24 weeks for the group of initial responders in the blinded phase of the RCT.

Leon and colleagues conducted additional follow-up interviews by telephone for all 35 original study participants for up to 5 years.[13] The authors reported that after the trial, 6 participants had tonsillectomy, 11 participants were diagnosed with new psychiatric conditions (i.e., attention-deficit/hyperactivity disorder, depression, anxiety, phobia, or chronic tic disorder), and 24 (68.6%) had experienced an exacerbation of symptoms.[13] Those exacerbations were treated with a variety of approaches, including additional IVIG, antibiotics, psychiatric medications, and cognitive behavioral therapy; treatments were often combined and used at the same time.[13]

IVIG Versus Plasma Exchange or Saline Placebo

Perlmutter and colleagues randomized 29 children who met the diagnostic criteria for PANDAS or OCD to receive IVIG, plasma exchange, or a saline placebo.[30] The authors compared symptoms at baseline to the same symptoms measured 1 month after treatment.[30] Participants in the plasma exchange group (N = 10) received 5 or 6 exchange transfusions, which required 85 to 121 minutes per transfusion.[30] Participants in the IVIG group (N = 9) received infusions during 2 days at the start of the trial; participants in the control group received a saline placebo (N = 10).[30] On average, participants in both the plasma exchange group and IVIG group reported significant reduction in symptoms from baseline to 1 month and between baseline and the 1-year follow-up, as measured by obsessive-compulsive symptoms, psychosocial functioning (i.e., anxiety, depression, and emotional lability), and global functioning.[30]

The authors reported comparisons of the change in symptoms for the 2 intervention groups to the change in symptoms for the saline placebo group between baseline and 1-month follow-up.[30] In comparison with the changes in scores in the saline placebo group (N = 10) 1 month after treatment, the IVIG group's (N = 9)[30]:

- scores for obsessions and compulsions decreased (45% vs. 3%; $P < .05$);
- scores for tics did not decrease significantly (19% vs. 12%; $P > .05$);
- sum of obsessions, compulsions, and tics decreased (45% vs. 6%; $P < .05$);
- scores for global impairment improved (26% vs. 1%; $P < .05$);
- scores for psychosocial functioning did not significantly improve (20% vs. 0%; $P > .05$); and
- scores for global severity improved significantly (26% vs. 1%; $P < .05$).

One year after treatment, all 9 participants who received IVIG were successfully followed and readministered the measures described above; 7 of 9 were judged to be "much" or "very much" improved in a global assessment of symptoms by their parents.[30] There were no comparisons made between the control group and the intravenous exchange group 1 year after baseline.[30]

The authors noted that there was not a statistically significant difference between the IVIG and plasma exchange groups for improvement in any symptoms at 1 month or 1 year after treatment.[30] They reported that scores for both active intervention groups remained significantly improved from baseline for obsessions and compulsions, psychosocial functioning, and global severity.[30] However, the

participants who received IVIG did not show a statistically significant improvement in tics at 1 year after baseline when compared to their own scores.

Plasma Exchange

We identified a single RCT that tested plasma exchange versus placebo or IVIG for children who met the criteria for PANDAS and OCD; this study conducted by Perlmutter and colleagues is also described in the section that describes studies of IVIG.[30] We rated this study as having a high risk of bias. In comparison with the placebo group (N = 10) 1 month after treatment, the plasma exchange group's (N = 10)[30]:

- scores for obsessions and compulsions decreased (58% vs. 3%; *P* < .05);
- scores for tics decreased (49% vs. 12%; *P* <.05);
- sum of obsessions, compulsions, and tics decreased (54% vs. 6%; *P* < .05);
- scores for global impairment improved (36% vs. 1%; *P* < .05);
- scores for psychosocial functioning did not significantly improve (30% vs. 3%; *P* > .05); and
- scores for global severity improved (26% vs. 1%; *P* < .05).

One year after baseline, 8 of 10 participants who received plasma exchange were successfully followed and readministered the measures described above; 7 of 8 were judged to be "much" or "very much" improved in a global assessment of symptoms by their parents.[30] There were no comparisons made between the control group and the intravenous exchange group 1 year after treatment.[30]

The authors noted that there was not a statistically significant difference between the IVIG and plasma exchange groups for improvement in any symptoms at 1 month or 1 year after treatment.[30] They reported that scores for both active intervention groups remained significantly improved from baseline for obsessions and compulsions, psychosocial functioning, and global severity.[30] In addition to those measures, the participants who received plasama exchange also remained signifcantly improved on the measure of tics when compared to their scores at baseline.[30]

Harms

Sigra and colleagues' systematic review of any treatment for PANDAS, PANS, CANS or PITAND reported that adverse events reported in included studies were typically mild to moderate in nature, including nausea, vomiting, headache and stomachache.[22]

Antibiotics

Murphy and colleagues reported that some participants who received prophylactic azithromycin had loose stools (no number reported), and 9 out of 12 children who received azithromycin had heart rate irregularities.[23]

Other known adverse events associated with long-term antibiotic therapy include skin rashes, gastrointestinal disturbance, increased risk of childhood-onset chronic conditions (e.g., asthma, obesity, attention deficit hyperactivity disorder), and contribute to antibiotic resistance.[34,35] Use of azithromycin may also result in changes in the electrical activity of the heart that can lead to fatal irregular heart rhythm.[36]

Tonsillectomy and Adenoidectomy

Although the included studies did not report harms, adverse events associated with tonsillectomy and adenoidectomy may include hemorrhage, complications from anesthesia, and infection.[37,38]

IVIG

Williams and colleagues reported that a single participant appeared to have an allergic reaction to the IVIG infusion, but that the reaction resolved without complication. The authors also reported that several participants noted minor discomforts during treatment, such as joint pain, headache, stomach pain, tiredness, and anxiety.[24] Perlmutter and colleagues reported that 6 of 9 children receiving immunoglobulin infusions reported experiencing 1 or more of the following: nausea, vomiting, mild to moderately severe headache, and low grade fever.[30] All of these symptoms were resolved with hydration therapy, paracetamol, or diphenhydramine.[30] No long-term adverse events were reported, and none of the studies mentioned intending to collect information about long-term adverse events.[13,24,30]

The FDA categorized IVIG as a biologic agent, and 8 of the 12 products listed are approved for use in children under 18 years of age (ASCENIV, Flebogamma, Gammagard Liquid, Gammagard S/D, Gammaplex, Gamunex-C, PANZYGA, and Privigen).[39] None of the approved indications include PANDAS or PANS for these products, and the age range for approved use vary by product.[39] The package inserts for IVIG products include black box warnings for thrombosis, renal dysfunction, and acute renal failure.[40]

Plasma Exchange

Perlmutter and colleagues reported that 7 of 10 children who received plasma exchange reported pallor, dizziness, and nausea during the first exchange transfusions; 2 of these children also experienced vomiting.[30] Three additional children reported feeling anxious during the exchange transfusions.[30]

Known complications of plasma exchange include circuit clotting, low or high blood pressure, nausea, vomiting, itchy skin, hives, low calcium levels in the blood, venous access malfunction, infections, thrombosis, anaphylactic shock, and high fever.[41-44]

Ongoing Studies

We identified 3 ongoing studies that might provide upcoming information about diagnosis and treatment of PANDAS or PANS.[33,45,46]

A single double-blinded RCT plans to enroll 44 children diagnosed with PANDAS to test the effectiveness of taking naproxen sodium twice daily for 8 weeks on the severity of OCD symptoms, as measured by the second edition of the Children's Yale-Brown Obsessive-Compulsive Scale.[33] Enrolled participants will be between 6 and 15 years of age with first OCD symptom onset within 18 months prior to trial start date, and have symptoms that significantly interfere with daily life.[33] The estimated primary completion date is October 2022.[33]

A single RCT plans to enroll 92 children from 6 to 17 years of age with a confirmed diagnosis of PANS or PANDAS, and will randomize participants to receive IVIG therapy or a placebo; the participant, care provider, investigator, and outcomes assessor will all be blinded.[46] The estimated study start date is August 30, 2021, and the estimated primary completion date is March 2023.[46] The primary outcome

measure will be the Children's Yale-Brown Obsessive Compulsive Scale at 9 weeks after treatment, which will be measured as a secondary outcome at week 18 along with Clinical Global Impression assessment, the Parent Obsessive-Compulsive Impact Scale, the Child Obsessive-Compulsive Impact Scale, the Swanson, Nolan, And Pelham Scale - Version IV (SNAP-IV; measures symptoms and behaviors that could impact child's behaviors at school), and the Parent Tic Questionnaire.[46]

This study will exclude children whose symptoms had first onset more than 6 months before the trial start date, children with current relapse of symptoms whose first onset was more than 12 months before the trial start date; who have a contraindication for IVIG; who have severely restricted food intake, whose body mass index is 40 or greater; who have symptoms of autism or schizophrenia, bipolar disorder, or other psychotic disorder; who have serious or unstable mental illness; who have been treated with corticosteroids or began cognitive behavioral therapy within the 8 weeks prior to randomization; who have a history of rheumatic fever; who have had prior immunomodulatory treatment; who had taken antibiotics or antivirals for an acute infection within 1 week of randomization; who have severe liver disease; who have known hepatitis B, hepatitis C, or HIV infection; pregnant or lactating women or women unwilling to comply with contraception protocol; or who participated in another interventional trial within 3 months of randomization or during the course of this study.[46]

A single observational matched cohort study plans to enroll 500 children diagnosed with PANS who have not yet received any treatment, whose symptoms began within 1 month of enrollment date, and who are 18 years of age or younger.[45] The investigators plan to match these children with healthy children without a PANS diagnosis to examine immunologic, neurologic, genomic, and behavioral differences between the 2 cohorts.[45] This study began in 2013 and has an estimated primary completion date of March 2028.[45] Outcome measures include the following, measured every 2 to 4 weeks for up to 12 years: Global Impairment Score, Children's Yale-Brown Obsessive Compulsive Scale, Columbia Impairment Score, Caregiver Burden Inventory, and neurological findings (e.g., irregular movements).[45]

Evidence Summary

The origins and progression of symptoms associated with PANDAS and PANS are still being studied and documented; there are few published studies that tested whether antibiotic therapy, surgical interventions, IVIG, or plasma exchange might improve symptoms in children diagnosed with these conditions. It is also difficult to know how long any improvements in symptoms last after children receive the treatments we reviewed in this coverage guidance, because they often receive multiple treatments (simultaneously or 1 after another). Additionally, it is hard to distinguish whether patterns of exacerbation and resolution of symptoms can be directly attributed to infections and treatments, or if there is an underlying pattern of increase of symptoms followed by a decrease of symptoms that would occur without these treatments. It is not clear how long any treatment benefit might be sustained before another exacerbation, or whether any treatment alone or in combination with other treatments can prevent or shorten the length of exacerbations.

- We have very low confidence that prophylactic antibiotic therapy reduces exacerbations of neuropsychiatric symptoms. Risks for long-term antibiotic use include skin rashes, gastrointestinal disturbance, increased risk of childhood-onset chronic conditions (e.g., asthma, obesity, attention deficit hyperactivity disorder), and contribute to antibiotic resistance.[34,35]
- We did not identify any evidence testing antibiotics in response to current psychiatric exacerbation.

- We have low confidence that surgical interventions such as tonsillectomy and adenoidectomy do not reduce neuropsychiatric symptom exacerbations. Harms of tonsillectomy and adenoidectomy may include hemorrhage, complications from anesthesia, and infection.[37,38]
- We have very low confidence that IVIG decreases neuropsychiatric symptoms. It is not clear how long any treatment benefit might be sustained. There is an ongoing trial of IVIG for children with PANS or PANDAS that might have published results in 2023 or 2024. The package inserts for IVIG products include serious warnings for thrombosis, renal dysfunction, and acute renal failure.[40]
- We have very low confidence that plasma exchange decreases neuropsychiatric symptoms. It is not clear how long any treatment benefit might be sustained. Known complications of plasma exchange transfusions include high fever, blood clots, infection, minor or severe allergic reactions, and high or low blood pressure.[41-44]

The very low and low confidence we have in the findings above means that findings from new comparative studies that test treatments for PANDAS or PANS could change the recommendations that we make for which treatments should be covered for children diagnosed with PANDAS or PANS.

Clinical Practice Guidelines

We identified 6 publications that included recent guidelines for the diagnosis and treatment of individuals with PANDAS or PANS.[3,16-18,20,21] We rated all the guidelines as having poor methodological quality.

PANS/PANDAS Clinical Research Consortium

The most recent clinical guidelines written and published in the US for treating PANS was written by members of the PANS/PANDAS Research Consortium at workgroup meetings partially sponsored by the National Institutes of Health.[3] The workgroups reviewed literature, reviewed more than 1,000 cases of children diagnosed with PANDAS/PANS, and then prepared summaries to be reviewed by review panels of clinical experts who either worked with children suspected of having PANDAS/PANS or were experts in child psychiatry, pediatrics, infectious diseases, microbiology, neurology, neuroimmunology, immunology, and rheumatology.[3] Not all experts agreed on all treatments proposed in the guidelines, so the guideline committee opted to describe multiple treatment options beyond the treatments that had the highest consensus.[3] The authors of the committee summary stated that they expect the guidelines to be altered over time in response to the initiation and completion of new controlled clinical trials testing the efficacy of treatments.[3]

As an overview, the guidelines recommend a 3-pronged approach to treating PANS[3,16,17,20]:

- “treating the symptoms with psychoactive medications, psychotherapies (particularly cognitive behavioral therapy), and supportive interventions;
- removing the source of the inflammation with antimicrobial interventions; and
- treating disturbances of the immune system with immunomodulatory and/or anti-inflammatory therapies” (pp. 562; Swedo et al., 2017).

The guidelines presented the following 6 principles for the identification and treatment of PANS:

1. Establish that PANS is the correct ‘‘diagnosis of exclusion’’ by completing a comprehensive diagnostic evaluation.[21]

2. Provide symptomatic relief with psychiatric medications and behavioral interventions, prioritizing treatment of symptoms causing the greatest distress and interference.[20]
3. Treat underlying infections and consider use of therapeutic or prophylactic antibiotics.[17]
4. Treat symptoms resulting from neuroinflammation or postinfectious autoimmunity with anti-inflammatory or immunomodulatory therapies, chosen on the basis of symptom severity and disease trajectory.[16]
5. Evaluate effectiveness of the treatment regimen at frequent intervals, making modifications as warranted by improvement or worsening of symptoms.[3]
6. Treatment can be tapered downward or stopped when symptoms resolve. However, treatment may be necessary again at some point in the future, given the relapsing–remitting nature of PANS symptoms.[3]

Clinical Guidance About PANS From Nordic Countries

The Nordic Pediatric Immunopsychiatry group published guidance for diagnosis and management of suspected PANS in 2021, and included pediatric neurologists, child psychologists, and child psychiatrists from Denmark, Norway, Sweden and Great Britain.[18] The authors intended this guidance to propose a standard set of diagnostic criteria for PANDAS and PANS, and to propose a standard process for diagnostic evaluation.[18]

The authors agreed to adopt the clinical criteria proposed by Chang and colleagues for PANS that was published in 2015[18,21]:

1. Abrupt, dramatic onset (culmination within 72 hours) of OCD or severely restricted food intake.
2. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least 2 of the following 7 categories (see reference for full description):
    - Anxiety,
    - Emotional liability and/or depression,
    - Irritability, aggression and/or severely oppositional behaviors,
    - Behavioral (developmental) regression,
    - Deterioration in school performance,
    - Sensory or motor abnormalities and
    - Somatic signs and symptoms, including sleep disturbances, enuresis or increased urinary frequency.
3. Symptoms are not better explained by a known medical disorder, such as Sydenham's chorea, systemic lupus erythematosus, Tourette disorder or others.

The authors agreed to adopt Swedo and colleagues' diagnostic criteria for PANDAS that were published in 1998[18,47]:

1. Presence of OCD and/or a tic disorder: The patient must meet lifetime diagnostic criteria (DSM-III- R or DSM- IV) for OCD or a tic disorder.
2. Pediatric onset: Symptoms of the disorder first become evident between 3 years of age and the beginning of puberty.
3. Episodic course of symptom severity: Clinical course is characterized by the abrupt onset of symptoms or by dramatic symptom exacerbations. Symptoms usually decrease significantly between episodes and occasionally resolve completely between exacerbations.

4. Association with group A Beta- hemolytic streptococcus infection: Symptom exacerbations must be temporally related to group A Beta- hemolytic streptococcus infection, that is associated with positive throat culture and/or significantly elevated anti- group A Beta- hemolytic streptococcus antibody titers.
5. Association with neurological abnormalities: During symptom exacerbations, patients will have abnormal results on neurological examination. Motoric hyperactivity and adventitious movements (including choreiform movements or tics) are particularly common.

In addition to the criteria listed above, the authors further proposed a definition of severe symptoms and required that the child meet at least 1 major criteria and 1 minor criteria.[18] The major criteria included: total Children's Yale- Brown Obsessive Compulsive Scale score ≥24; reduced intake of food or fluid, leading to less urine production (less than 3 urinations daily) or weight loss (more than 10%); and severe tics (Yale Global Tic Severity Scale total tic severity score ≥40 but <50).[18] Minor criteria included being absent from school at least 50% of class days during 1 month, and inability to participate in leisure activities or loss of social contact.[18]

The authors then proposed a standard clinical work-up, which is described in Table 4.

Table 4. Nordic Pediatric Immunopsychiatry Group's Proposed Clinical Work-Up for PANS

Examination	Instrument or Analysis	Description
Psychiatric		
General	Achenbach System of Empirically Based Assessment (ASEBA),19 Mini international neuropsychiatric interview (M.I.N.I.- KID) or equivalent	General assessment of psychiatric conditions
	Child and Adolescent Trauma Screen (CATS)	Trauma screening
	Children's Global Assessment Scale (C- GAS)	Assessment of general functioning
	Clinical Global Impression- Severity Scale (CGI- S)	Clinician- rated severity of the patient's illness at time of assessment
	Pediatric Quality of Life Inventory (PedsQL)	Assessment of quality of life
	Optional: Work and Social Adjustment Scale (WSAS) 2	Measure of impaired functioning
	Optional: KIDSCREEN	Assessment of subjective health and well- being
Symptom-specific	Children's Yale- Brown Obsessive Compulsive Scale (CY- BOCS)	OCD inventory
	The Screen for Child Anxiety Related Disorders (SCARED)	Screening for child anxiety related disorders
	Yale Global Tic Severity Scale (YGTSS)	Tics inventory
	Kiddie Schedule for Affective Disorders and Schizophrenia (Kiddie- SADS)	Interview screening for psychiatric diagnoses

Examination	Instrument or Analysis	Description
	ADHD rating scale (ADHD- RS)	Questionnaire related to inattention, hyperactivity and impulsivity
	Behavior Rating Inventory of Executive Function (BRIEF)	Behavior Rating Inventory of Executive Function
Infectious		
General	Throat: bacterial culture	No description
	Blood: complete blood cell count with differential count, antistreptolysin- O and anti-deoxyribonuclease B antibodies	No description
Symptom-specific	Throat: Mycoplasma Polymerase Chain Reaction (PCR)	No description
	Nasopharynx: Aspirate PCR panel	Common viral airway infections such as influenza virus and enterovirus
	Urine analysis and culture	No description
Extended workup	Cerebrospinal fluid cell count, protein, glucose, lactate; Epstein- Barr-virus/cytomegalovirus/varicella zoster virus/ herpes simplex virus/Mycoplasma/ enterovirus/influenza virus immunoglobulin G and immunoglobulin M +Polymerase Chain Reaction (PCR); Borrelia burgdorferi immunoglobulin G and immunoglobulin M (paired with serum)	No description
Immunological		
General	Blood: erythrocyte sedimentation rate (ESR), antiphospholipid antibodies (anticardiolipin and beta2 glycoprotein 1 antibodies), antinuclear antibodies (antidsDNA, ANA IIF, anti- ENA screen: Anti- SSA, anti- SSA, anti- SSB, anti- Sm, anti-Scl−70, anti- Jo1, anti- Centromer B (- CENP- B) and anti- U1- RNP), immunoglobulins subclasses, tissue- transglutaminase IgA and deamined gliadinpeptide IgG (Celiac disease), neuronal antibodies, Myelin oligodendrocyte glycoprotein (MOG) antibodies, antithyroperoxidase (TPO), thyroid stimulating hormone (TSH) receptor antibodies, TSH, T3 and free T4, complement C3 and C4, angiotensin- converting enzyme (ACE), Vitamin- D, Vitamin B12, ferritin, cupper, ceruloplasmin, cytokines	No description
Extended work-up	Cerebrospinal fluid Lumbar opening pressure, neuronal antibodies (standard panel),	No description

Examination	Instrument or Analysis	Description
	immunoglobulin G, index and electrophoresis for oligoclonal bands (paired with serum), and cytokines	
Toxicological		
Symptom-specific	Drug screening	No description
Metabolic		
Symptom-specific	Urine metabolic screening	No description
Radiological		
Extended work-up	Cerebral MRI including contrast: structural, diffusion and FLAIR sequences	No description
Neuropsychological		
Extended work-up	Standard or sleep electroencephalogram	No description

Note. This table is reproduced from Tables 3 and 4 on pages 4 and 5 of the Nordic Pediatric Immunopsychiatry group's published guidance for diagnosis and management of suspected PANS.[18] *Abbreviations. FLAIR: fluid attenuated inversion recovery; MRI: magnetic resonance imaging; OCD: obsessive-compulsive disorder; PANS: pediatric acute-onset neuropsychiatric syndrome.*

The authors recommended that verified or strongly suspected bacterial infections should be treated at the discretion of the provider for a maximum of 14 days; however, they do not recommend prophylactic antibiotic therapy.[18] They further recommended that any other treatment occur within ongoing clinical research or under the guidance of centers that specialize in the care of children with suspected PANS.[18] Such treatments for children with severe symptoms might begin with oral nonsteroidal anti-inflammatory drugs, proceed to steroids if ineffective, and finally proceed to IVIG.[18] The authors state that plasma exchange, and cytostatic and immunomodulatory drugs are only clinically indicated when a child has been diagnosed with autoimmune encephalitis.[18]

Policy Landscape

Payer Coverage Policies

We did not identify coverage policies for Washington State's Medicaid program or national or local coverage determinations for Medicare related to PANDAS or PANS.

We identified coverage policies related to PANDAS and PANS from 2 private payers (Aetna and Cigna), but we did not identify coverage policies related to PANDAS or PANS for BlueCross BlueShield or for Moda.

Private Payers

Aetna considers parenteral immunoglobulins, rituximab, and plasma exchange to be investigational or experimental for PANDAS.[48-50]

Cigna considers plasma exchange, immune globulin, and rituximab to be investigational or experimental for PANDAS and PANS in policies last updated in 2021.[51-53] These coverage policies consider plasma

exchange to be medically necessary as a primary therapy for autoimmune encephalitis characterized by the presence of the n-methyl D-aspartate receptor antibody.[53]

Recommendations from Others

We did not identify policy statements or recommendations for PANDAS or PANS from the American Neurology Association, the American Academy of Pediatrics, the American Association of Immunologists, the Infectious Diseases Society of America, or the American Psychiatric Association.

PANDAS Physician Network

The PANDAS Physician Network maintains a website with tools such as flowcharts for diagnosing and treating PANS and PANDAS, and for classifying symptoms into mild, moderate, or severe cases.[54] The authors recommend that children with moderate or severe symptoms be treated by an experienced team of multidisciplinary providers or a PANS/PANDAS specialist.[54] To summarize the proposed elements of the treatment guidelines (please note that this list is simplified)[54]:

1. Start with 14 days of antibiotic consider the appropriateness of prophylactic antibiotic therapy; lengthen therapy if infection is not resolved or symptoms persist.
2. Consider 5 to 7 days of nonsteroidal anti-inflammatory drugs.
3. Ensure family access to cognitive behavioral therapy, and parenting management techniques.
4. Consider steroid course if no improvement from first 3 steps.
5. Escalate to IVIG therapy if first 4 steps have not resolved symptoms.
6. If symptoms do not resolve, consider a second course of IVIG or evaluate the need for plasma exchange, and prescribe prophylactic antibiotic therapy.

References

1. Garg D, Mohammad SS, Sharma S. Autoimmune encephalitis in children: an update. *Indian Pediatr.* 2020;57(7):662-670.
2. Dop D, Marcu IR, Padureanu R, Niculescu CE, Padureanu V. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (Review). *Experimental Ther.* 2021;21(1):94. doi: 10.3892/etm.2020.9526.
3. Swedo SE, Frankovich J, Murphy TK. Overview of treatment of pediatric acute-onset neuropsychiatric syndrome. *J Child Adolesc Psychopharmacol.* 2017;27(7):562-565. doi: 10.1089/cap.2017.0042.
4. Gamucci A, Uccella S, Sciarretta L, et al. PANDAS and PANS: clinical, neuropsychological, and biological characterization of a monocentric series of patients and proposal for a diagnostic protocol. *J Child Adolesc Psychopharmacol.* 2019;29(4):305-312. doi: 10.1089/cap.2018.0087.
5. Hyman SE. PANDAS: too narrow a view of the neuroimmune landscape. *Am J Psychiatry.* 2021;178(1):5-7. doi: 10.1176/appi.ajp.2020.20111598.
6. Wald ER. A pediatric infectious disease perspective on pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection and pediatric acute-onset neuropsychiatric syndrome. *Pediatr Infect Dis J.* 2019;38(7):706-709. doi: 10.1097/INF.0000000000002295.
7. Baj J, Sitarz E, Forma A, Wroblewska K, Karakula-Juchnowicz H. Alterations in the nervous system and gut microbiota after beta-hemolytic streptococcus group a infection-characteristics and diagnostic criteria of pandas recognition. *Int J Mol Sci.* 2020;21(4):21. doi: 10.3390/ijms21041476.
8. Zibordi F, Zorzi G, Carecchio M, Nardocci N. CANS: childhood acute neuropsychiatric syndromes. *Europ J Paediatr Neurol.* 2018;22(2):316-320. doi: 10.1016/j.ejpn.2018.01.011.
9. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* 2016;15(4):391-404. doi: 10.1016/S1474-4422(15)00401-9.
10. Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry.* 2021;92(7):757-768. doi: 10.1136/jnnp-2020-325300.
11. Cellucci T, Van Mater H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm.* 2020;7(2). doi: 10.1212/NXI.0000000000000663.
12. Dubey D, Pittock S, Kelly C, et al. The incidence and prevalence of autoimmune encephalitis and a comparison to infectious encephalitis: a population-based study. *Neurology.* 2018;90.
13. Leon J, Hommer R, Grant P, et al. Longitudinal outcomes of children with pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS). *Eur Child Adolesc Psychiatry.* 2018;27(5):637-643. doi: 10.1007/s00787-017-1077-9.
14. Wilbur C, Bitnun A, Kronenberg S, et al. PANDAS/PANS in childhood: controversies and evidence. *Paediatr Child Health.* 2019;24(2):85-91. doi: 10.1093/pch/pxy145.
15. Geller D, March JS, Walter J, et al. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry.* 2012;51(1):98-113. doi: 10.1016/j.jaac.2011.09.019.
16. Frankovich J, Swedo S, Murphy T, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part II—use of immunomodulatory therapies. *J Child Adolesc Psychopharmacol.* 2017;27(7):574-593. doi: 10.1089/cap.2016.0148.
17. Cooperstock MS, Swedo SE, Pasternack MS, Murphy TK, for the PPC. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part III—treatment and prevention of infections. *J Child Adolesc Psychopharmacol.* 2017;27(7):594-606. doi: 10.1089/cap.2016.0151.

18. Pfeiffer HCV, Wickstrom R, Skov L, et al. Clinical guidance for diagnosis and management of suspected pediatric acute-onset neuropsychiatric syndrome in the Nordic countries. *Acta Paediatr.* 2021;13:13. doi: 10.1111/apa.15875.
19. Mooneyham GC, Ferrafiat V, Stolte E, Fuchs DC, Cohen D. Developing consensus in the assessment and treatment pathways for autoimmune encephalitis in child and adolescent psychiatry. *Front Psychiatry.* 2021;12:638901. doi: 10.3389/fpsyt.2021.638901.
20. Thienemann M, Murphy T, Leckman J, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part i-psychiatric and behavioral interventions. *J Child Adolesc Psychopharmacol.* 2017;27(7):566-573. doi: 10.1089/cap.2016.0145.
21. Chang K, Frankovich J, Cooperstock M, et al. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. *J Child Adolesc Psychopharmacol.* 2015;25(1):3-13. doi: 10.1089/cap.2014.0084.
22. Sigra S, Hesselmark E, Bejerot S. Treatment of PANDAS and PANS: a systematic review. *Neurosci Biobehav Rev.* 2018;86:51-65. doi: 10.1016/j.neubiorev.2018.01.001.
23. Murphy TK, Brennan EM, Johnco C, et al. A double-blind randomized placebo-controlled pilot study of azithromycin in youth with acute-onset obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol.* 2017;27(7):640-651. doi: 10.1089/cap.2016.0190.
24. Williams KA, Swedo SE, Farmer CA, et al. Randomized, controlled trial of intravenous immunoglobulin for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *J Am Acad Child Adolesc Psychiatry.* 2016;55(10):860-867 e862. doi: 10.1016/j.jaac.2016.06.017.
25. Farhood Z, Ong AA, Discolo CM. PANDAS: a systematic review of treatment options. *Int J Pediatr Otorhinolaryngol.* 2016;89:149-153. doi: 10.1016/j.ijporl.2016.08.008.
26. Pavone P, Rapisarda V, Serra A, et al. Pediatric autoimmune neuropsychiatric disorder associated with group a streptococcal infection: the role of surgical treatment. *Int J Immunopathol Pharmacol.* 2014;27(3):371-378. doi: 10.1177/039463201402700307.
27. Murphy TK, Lewin AB, Parker-Athill EC, Storch EA, Mutch PJ. Tonsillectomies and adenoidectomies do not prevent the onset of pediatric autoimmune neuropsychiatric disorder associated with group A streptococcus. *Pediatr Infect Dis J.* 2013;32(8):834-838. doi: 10.1097/INF.0b013e31829062e2.
28. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biol Psychiatry.* 2005;57(7):788-792. doi: 10.1016/j.biopsych.2004.12.035.
29. Garvey MA, Perlmutter SJ, Allen AJ, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biol Psychiatry.* 1999;45(12):1564-1571. doi: 10.1016/s0006-3223(99)00020-7.
30. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet.* 1999;354(9185):1153-1158. doi: 10.1016/S0140-6736(98)12297-3.
31. Leibold C, Thienemann M, Farhadian B, Willett T, Frankovich J. Psychometric properties of the pediatric acute-onset neuropsychiatric syndrome global impairment score in children and adolescents with pediatric acute-onset neuropsychiatric syndrome. *J Child Adolesc Psychopharmacol.* 2019;29(1):41-49. doi: 10.1089/cap.2018.0029.
32. Nielsen MO, Kohler-Forsberg O, Hjorthoj C, Benros ME, Nordentoft M, Orlovska-Waast S. Streptococcal infections and exacerbations in PANDAS: a systematic review and meta-analysis. *Pediatr Infect Dis J.* 2019;38(2):189-194. doi: 10.1097/INF.0000000000002218.

33. Clinical Trials Registry. Trial of naproxen sodium for the treatment of OCD in children with PANDAS. 2020; https://www.clinicaltrials.gov/ct2/show/NCT04015596. Accessed August 4, 2021.
34. Ahmed H, Davies F, Francis N, Farewell D, Butler C, Paranjothy S. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials. *BMJ Open.* 2017;7(5):e015233. doi: 10.1136/bmjopen-2016-015233.
35. Aversa Z, Atkinson EJ, Schafer MJ, et al. Association of infant antibiotic exposure with childhood health outcomes. *Mayo Clin Proc.* 2021;96(1):66-77. doi: 10.1016/j.mayocp.2020.07.019.
36. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med.* 2012;366(20):1881-1890. doi: 10.1056/NEJMoa1003833.
37. Erwin DZ, Heichel PD, Wright LB, et al. Post-tonsillectomy hemorrhage control with nebulized tranexamic acid: A retrospective cohort study. *Int J Pediatr Otorhinolaryngol.* 2021;147:110802. doi: 10.1016/j.ijporl.2021.110802.
38. Dhaduk N, Rodgers A, Govindan A, Kalyoussef E. Post-tonsillectomy bleeding: A national perspective. *Ann Otol Rhinol Laryngol.* 2021;130(8):941-947. doi: 10.1177/0003489420987438.
39. US Food and Drug Administration. Immune globulins. 2020; https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins. Accessed August 16, 2021.
40. Octapharma. PANZYGA package insert. 2021; https://www.fda.gov/media/115397/download. Accessed August 16, 2021.
41. Sik G, Demirbuga A, Annayev A, Akcay A, Citak A, Ozturk G. Therapeutic plasma exchange in pediatric intensive care: Indications, results and complications. *Ther Apher Dial.* 2020;24(2):221-229. doi: 10.1111/1744-9987.13474.
42. Veerachit OLT, Siritho S, Prayoonwiwat N. Retrospective study of the adverse events of the treatment for an acute attack of neuromyelitis optica spectrum disorder. *Ther Apher Dial.* 2020;24(4):453-460. doi: 10.1111/1744-9987.13456.
43. Abe Y, Kusaoi M, Tada K, Yamaji K, Tamura N. Successful treatment of anti-MDA5 antibody-positive refractory interstitial lung disease with plasma exchange therapy. *Rheumatology (Oxford).* 2020;59(4):767-771. doi: 10.1093/rheumatology/kez357.
44. Lu J, Zhang L, Xia C, Tao Y. Complications of therapeutic plasma exchange: a retrospective study of 1201 procedures in 435 children. *Medicine (Baltimore).* 2019;98(50):e18308. doi: 10.1097/MD.0000000000018308.
45. Clinical Trials Registry. Neurobiologic, immunologic, and rheumatologic markers in youth with PANS. 2016; https://clinicaltrials.gov/ct2/show/NCT02889016. Accessed August 4, 2021.
46. Clinical Trials Registry. Study to compare the effect of panzyga versus placebo in patients with pediatric acute-onset neuropsychiatric syndrome. 2021; https://clinicaltrials.gov/ct2/show/NCT04508530. Accessed August 16, 2021.
47. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry.* 1998;155(2):264-271.
48. Aetna. Medical clinical policy bulletins: parenteral immunoglobulins. 2021; https://www.aetna.com/cpb/medical/data/200_299/0206.html. Accessed July 21, 2021.
49. Aetna. Medical clinical policy bulletins: Rituximab. 2021; https://www.aetna.com/cpb/medical/data/300_399/0314.html. Accessed July 21, 2021.
50. Aetna. Medical clinical policy bulletins: plasmapheresis plasma exchange therapeutic apheresis. 2021; https://www.aetna.com/cpb/medical/data/200_299/0285.html. Accessed July 21, 2021.

51. Cigna. Drug and biologic coverage policy: immune globulin. 2021; https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/ph_5026_coveragepositioncriteria_Immune_Globulin_Intravenous_IGIV.pdf. Accessed July 21, 2021.
52. Cigna. Drug and biologic coverage policy: rituximab for non-oncology indications. 2021; https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/ph_5108_coveragepositioncriteria_rituximab_rituxan.pdf. Accessed July 21, 2021.
53. Cigna. Medical coverage policy: plasmapheresis. 2021; https://static.cigna.com/assets/chcp/pdf/coveragePolicies/medical/mm_0153_coveragepositioncriteria_plasmapheresis.pdf. Accessed July 21, 2021.
54. PANDAS Physician Network. Clinician resources for PANS/PANDAS. 2021; https://www.pandasppn.org/. Accessed August 16, 2021.

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Appendix A. GRADE Table Element Descriptions

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors., but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Appendix B. GRADE Evidence Profile

Quality Assessment (Confidence in Estimate of Effect) for Antibiotics							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
3	RCTs	Moderate to High	Not serious	Not serious	Serious	Small sample sizes, short follow-up	Very Low ●○○○
Hospitalizations							
Harms							
1	RCT	High	Unable to rate	Not serious	Serious	Small sample sizes, short follow-up	Very Low ●○○○
Function or Quality of Life for Patient							
0							
Function or Quality of Life for Parent							
0							

Abbreviation. RCT: randomized controlled trial.

Quality Assessment (Confidence in Estimate of Effect) for Tonsillectomy or Adenoidectomy							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
2	Comparative cohort	High	Not serious	Serious	Not serious	None	Low ●●○○
Hospitalizations							
0							
Harms							
0							
Function or Quality of Life for Patient							
0							
Function or Quality of Life for Parent							
0							

Quality Assessment (Confidence in Estimate of Effect) for IVIG							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
2	RCTs	High	Not serious	Not serious	Not Serious	Very small samples, incomplete reporting	Very low ●○○○
Hospitalizations							
Harms							
2	RCTs	High	Not serious	Not Serious	Not Serious	Very small samples, incomplete reporting	Very low ●○○○
Function or Quality of Life for Patient							
Function or Quality of Life for Parent							

Abbreviation. RCT: randomized controlled trial.

Quality Assessment (Confidence in Estimate of Effect) for Plasma Exchange							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
1	RCT	High	Not serious	Not serious	Not Serious	Very small sample, incomplete reporting	Very low ●○○○
Hospitalizations							
Harms							
1	RCT	High	Not serious	Not Serious	Not Serious	Very small sample, incomplete reporting	Very low ●○○○
Function or Quality of Life for Patient							
Function or Quality of Life for Parent							

Abbreviation. RCT: randomized controlled trial.

Appendix C. Methods

Scope Statement

Populations

Children diagnosed with:

- Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS),
- Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

Population scoping notes: Patients without either of the above conditions are excluded

Interventions

Therapeutic plasma exchange; intravenous immunoglobulin (IVIG); antibiotics; tonsillectomy and/or adenoidectomy

Intervention exclusions: Behavioral interventions, selective serotonin reuptake inhibitors, nonsteroidal inflammatory drugs

Comparators

Usual care or other interventions

Outcomes

Critical: Change in psychiatric symptom scores (e.g., Children's Yale-Brown Obsessive Compulsive Scale, Clinical Global Impressions-Improvement, Yale Global Tic Severity scale); Hospitalizations, including institutionalization or emergency visits

Important: Harms; standardized measures of function or quality of life for patients and caregivers

Considered but not selected for the GRADE table: None

Key Questions

KQ1: What is the effectiveness of treatments for PANDAS/PANS as compared to the named comparators?

KQ2: Does the comparative effectiveness of treatments for PANDAS/PANS differ by:

a. Patient characteristics
b. Condition characteristics
c. Intervention
d. Provider characteristics (e.g., Center of Excellence)

KQ3: What are the harms of interventions for PANDAS/PANS in children?

Contextual Questions

CQ1: What are the evidence-based criteria available for the diagnosis of PANDAS/PANS, and what are the diagnostic accuracy of available criteria or tests?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2015.

The following core sources were searched:

Agency for Healthcare Research and Quality (AHRQ)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Online Library)
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

An Ovid MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms *paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection, pediatric acute-onset neuropsychiatric syndrome, pediatric infection triggered autoimmune neuropsychiatric disorder, childhood acute onset neuropsychiatric syndrome, paediatric acute-onset neuropsychiatric syndrome, autoimmune encephalitis*. The search was limited to publications in English published since 2012. In addition, a MEDLINE® search was conducted for randomized controlled trials and comparative cohort studies.

Searches for clinical practice guidelines were limited to those published since 2015. A search for relevant clinical practice guidelines was also conducted using MEDLINE® and the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Centers for Disease Control and Prevention (CDC), Community Preventive Services
National Institute for Health and Care Excellence (NICE)
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, randomized controlled trials, comparative cohort studies, or clinical practice guidelines.

Appendix D. Applicable Codes

Coding note: PANS does not have ICD-10-CM index entries; PANDAS is indexed to D89.89.

CODES	DESCRIPTION
ICD-10-CM Codes	
D89.89	Other specified disorders involving the immune mechanism, not elsewhere classified
D89.9	Disorder involving the immune mechanism, unspecified
G04.81	Other encephalitis and encephalomyelitis
CPT Codes	
Behavioral therapy	
90832	Psychotherapy, 30 minutes with patient
90833	Psychotherapy, 30 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90834	Psychotherapy, 45 minutes with patient
90836	Psychotherapy, 45 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90837	Psychotherapy, 60 minutes with patient
90838	Psychotherapy, 60 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90839	Psychotherapy for crisis; first 60 minutes
Intravenous immunoglobulin therapy	
90283	Immune globulin (IgIV), human, for intravenous use
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
99601	Home infusion/specialty drug administration, per visit (up to 2 hours)
Plasma exchange	
36514	Therapeutic apheresis; for plasma pheresis
Tonsillectomy and adenoidectomy	
42820	Tonsillectomy and adenoidectomy; younger than age 12
42821	Tonsillectomy and adenoidectomy; age 12 or over
42825	Tonsillectomy, primary or secondary, younger than age 12
42826	Tonsillectomy, primary or secondary, age 12 or over
42830	Adenoidectomy, primary; younger than age 12
42831	Adenoidectomy, primary; age 12 or over
42835	Adenoidectomy, secondary; younger than age 12
42836	Adenoidectomy, secondary; age 12 or over
HCPCS Level II Codes	
Intravenous immunoglobulin therapy	
J1459	Injection, immune globulin (privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1555	Injection, immune globulin (cuvitru), 100 mg
J1556	Injection, immune globulin (bivigam), 500 mg
J1557	Injection, immune globulin, (gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1558	Injection, immune globulin (xembify), 100 mg
J1559	Injection, immune globulin (hizentra), 100 mg
J1561	Injection, immune globulin, (gamunex-c/gammaked), non-lyophilized (e.g., liquid), 500 mg
J1562	Injection, immune globulin (vivaglobin), 100 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg

J1568	Injection, immune globulin, (octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (gammagard liquid), non-lyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (flebogamma/flebogamma dif), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg
S9338	Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
SSRIs, NSAIDs, and corticosteroids	
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1 mg
J0702	Injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg
J1700	Injection, hydrocortisone acetate, up to 25 mg
J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg
J1720	Injection, hydrocortisone sodium succinate, up to 100 mg
J2650	Injection, prednisolone acetate, up to 1 ml
J7510	Prednisolone oral, per 5 mg
J7512	Prednisone, immediate release or delayed release, oral, 1 mg
J8540	Dexamethasone, oral, 0.25 mg
J7624	Betamethasone, inhalation solution, compounded product, administered through DME, unit dose form, per mg
J1130	Injection, diclofenac sodium, 0.5 mg

Note. Inclusion on this list does not guarantee coverage.