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Representative James Murphy, Co-Chairman of the Joint Committee on Financial
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Dear Senator Welch and Representative Murphy:

On behalf of my colleagues I am forwarding an updated supplemental analysis for the 2015 CHIA report regarding An Act Relative to Insurance Coverage for PANDAS/PANS (H.920/S.613). This was requested by Adam Horgan and Lisa Pellegrini, legislative research staff members for the Joint Committee on Financial Services at the time of our discussions on PANDAS Awareness Day, October 10, 2019.

Thank you for your continued consideration.

Sincerely,

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**MEDICAL EFFICACY UPDATE:
AN ACT RELATIVE TO INSURANCE COVERAGE
FOR PANDAS/PANS (H.920/S.613)**

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HISTORY OF THE BILL

An Act Relative to Insurance Coverage for PANDAS/PANS (H.920/S.613) provides for insurance coverage of physician-recommended therapies, including intravenous immunoglobulin therapy (IVIG), for children suffering from Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS).¹ Passage of this bill would give physicians access to higher level treatment options for their most ill PANDAS and PANS patients. According to an actuarial assessment conducted by the Center for Health Information Analysis (CHIA) of the Commonwealth of Massachusetts in 2015, coverage would have a minimal impact on premiums.^{2,3} Recent literature, published in the four years following the initial CHIA report, recommends IVIG to treat a subset of patients with PANDAS and PANS and supports its efficacy. The present update summarizes these peer-reviewed studies, reviews, and international treatment guidelines.

PANDAS AND PANS

- PANS is a collection of disorders characterized by the abrupt onset of obsessive-compulsive disorder (OCD) or eating restrictions and a variety of cognitive, behavioral, neurological and somatic symptoms and signs. In most cases, neuroinflammation has been found to be the cause of the neuropsychiatric symptomatology.
- When PANS is triggered by prolonged infection with, or exposure to group A streptococcal (GAS) bacteria, it is known as PANDAS, or in severe cases, autoimmune encephalitis of the basal ganglia. Antigens on the strep bacteria's cell wall provoke the production of antibodies which cross-react with brain tissue, leading to neuroinflammation and the complex symptoms of PANDAS.
- PANDAS and PANS are most commonly recognized by the unusually abrupt and dramatic symptom onset. In addition to the primary symptoms of OCD or eating restrictions, children may experience personality changes, extreme emotional lability, severe separation anxiety, and neurologic signs, such as sensory abnormalities, motor and/or vocal tics, and cognitive changes. Other common symptoms include behavioral (developmental) regression, physical aggression, sleep difficulties, urinary frequency/enuresis, and a number of additional debilitating symptoms such as hallucinations and delusions.
- The diagnosis of PANDAS can be challenging because inciting streptococcal infections may be subclinical ("silent") and suspected only after the abrupt onset of this dramatic clinical picture. Although elevated GAS antibody tests are classically observed with immunologic complications of streptococcal infection, it is now recognized that these tests may be falsely negative rather frequently.⁴ Thus, the recognition of the clinical features of PANDAS and the response to appropriate therapy are important in the clinical management of these children despite limitations in laboratory assessment.

SUMMARY OF TREATMENT

In 2017, the PANS Research Consortium (PRC) published a guideline series in four parts with contributing experts from more than two dozen academic institutions across the United States.^{5,6,7,8} Researchers and clinicians from the National Institute of Mental Health (NIMH), Harvard, Yale, Georgetown, Columbia, Stanford and other academic institutions pooled their data and clinical experience with more than 1000

PANDAS and PANS patients to develop best practice recommendations. These can be summarized as: Treat the SYMPTOMS, remove the SOURCE, and modulate the IMMUNE SYSTEM to reduce neuroinflammation.⁵

Mild to moderate cases of PANDAS and PANS are often managed successfully with antibiotic and nonsteroidal anti-inflammatory therapy. More severely afflicted children frequently require prednisone and psychotropic medications. A small but significant subset, estimated to be 10-15% of referred children, fail to improve with these conventional measures and require immunomodulatory therapy with intravenous immunoglobulin (IVIG), therapeutic plasmapheresis (also known as plasma-exchange), or other modalities.⁷

CURRENT COVERAGE

Despite support of IVIG for severe cases of PANDAS and PANS in published studies and reviews and the PANS Research Consortium consensus, few insurers have recognized these recommendations and incorporated them into their policies. Tufts added coverage of IVIG for treatment of PANDAS for their Health Freedom plans on September 10, 2019.⁹ Families have also accessed treatment through MassHealth, which includes IVIG therapy in their covered services for PANDAS and PANS. In their documentation, MassHealth has designated IVIG as medically necessary when approving it for these children.

Between 2017 and 2019, Illinois, Minnesota, Arkansas, Delaware, and New Hampshire adopted legislation requiring insurance coverage for immunomodulating therapies, including IVIG, for PANDAS and PANS. Ten additional states have legislation pending or in development.

COST OF IMPLEMENTING THE BILL

Given the narrow subset of patients requiring IVIG calculated by the 2015 CHIA report, coverage of treatment would result in a slight increase in premiums for insurance holders in the Commonwealth of Massachusetts. According to the report, “requiring coverage for this benefit by fully-insured health plans would result in an average annual increase, over five years, to the typical member’s monthly health insurance premiums of between \$0.003 (0.001%) and \$0.039 (0.008%) per year.”² We ask for this cost to be considered in contrast to the enormous financial burden on patients with PANDAS and PANS, their families, communities, and insurers when effective treatment is delayed or unavailable.

MEDICAL EFFICACY: AN UPDATE BASED ON EMPIRICAL EVIDENCE

In the four years following the 2015 CHIA Report, consensus guidelines, systematic reviews, and IVIG treatment studies were published representing experts in psychiatry, infectious disease, general pediatrics, immunology, rheumatology, neurology, neuroimmunology, and basic science. The PANS Research Consortium immunomodulatory task force included recommendations for IVIG therapy for patients with PANDAS and PANS in their 2017 consensus guidelines.⁷

The authors believe that PANS patients presenting with severe symptoms and a chronic-static or chronic-progressive course require consideration of more intensive immunomodulatory approaches like those used for neuropsychiatric systemic lupus erythematosus (NPSLE), central nervous system (CNS) vasculitis, autoimmune encephalitis (AE), chronic-progressive MS, chronic-progressive Behçet's disease, and other persistent neuroinflammatory disorders.⁷

These guidelines further described the rationale for immunomodulatory therapy, including IVIG, in the treatment of PANDAS and PANS, in the context of its well-described predecessor and model, Sydenham chorea (SC).⁷

Accumulating evidence supports conceptualizing PANS as an immune-mediated brain disease, akin to SC and PANDAS, involving the caudate, putamen, and other basal ganglia structures. Data supporting this model come from epidemiological, clinical, paraclinical, translational, and basic science investigations of PANDAS and SC.⁷

Several literature reviews categorized PANDAS and PANS with pediatric neurological, neurodevelopmental, and neurodegenerative disorders in their determination of the medical efficacy of treatment with IVIG. A 2016 review acknowledged the wide use of IVIG despite the challenges and limitations of research in children with neurological and neurodevelopmental conditions such as PANDAS, SC, autoimmune encephalitis (AE), Myasthenia gravis, and Guillain-Barré syndrome (GBS). Their systematic analysis of data from previous studies supported IVIG treatment for many disorders, including PANDAS.¹⁰

We conclude that it is likely that IVIG improves recovery in selected patients with paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (level 2). We recommend that IVIG should be considered in selected patients with a diagnosis of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (grade B).¹⁰

Another systematic literature review determined that IVIG was effective in PANDAS and other neurodegenerative conditions including SC, Tourette's syndrome (TS), Multiple Sclerosis (MS), and acute disseminated encephalomyelitis (ADEM).¹¹ "In the studies we analyzed, IVIG was (sic) found to be efficient in the treatment of post-streptococcal neurodegenerative disorders, even if in PANDAS, plasma-exchange (PE) showed a higher efficiency."¹¹

In the American Academy of Allergy, Asthma, and Immunology's 2017 Work Group Report, the authors conducted a rigorous review of literature prior to June, 2015, that referenced immunoglobulin therapy for an exhaustive list of conditions, including primary and secondary immunodeficiency as well as autoimmune, atopic, infection-related, and neurologic diseases.¹² According to the report, IVIG is a treatment recognized for anti-inflammatory, immunomodulatory, and infection-fighting capabilities. Taking into account factors such as benefit versus risk, finite supply, and often limited research, their analysis determined whether IVIG would provide benefit for each diagnosis. Regarding PANDAS, the authors concluded, "immune-based therapies should be used only in cases in which it is clear that the neuropsychiatric symptoms are related to an autoimmune response, as supported by laboratory evidence and in conjunction with neuropsychiatric professionals."¹² Consistent with this stipulation of the appropriateness of IVIG for these disorders, the PANS Research Consortium recommends evaluating children for immunodeficiency because inflammatory and/or autoimmune diseases such as PANDAS and PANS are "more common in patients with immunodeficiency."⁶ In other words, children who have immunodeficiency are more at risk for PANDAS and PANS and such testing can confirm an inflammatory or autoimmune process underlying their illness.

The American Society for Apheresis (ASFA) included PANDAS in its guidelines published in the Journal of Clinical Apheresis (JCA) in its last two editions.^{13,14} Their 2019 issue provided apheresis indications, including plasmapheresis and IVIG when appropriate, for 84 different diseases based on an extensive review of the literature.¹⁴ When PANDAS was first included in the 2013 issue, the "strong recommendation" for treatment with therapeutic plasma exchange (TPE) by the ASFA set a new precedent given the rigorous, evidence-based methodology of this body.¹³ "In severely symptomatic patients with PANDAS or SC, immunomodulatory

therapies, such as IVIG...or TPE, have been shown to be effective in reducing symptom severity or shorten the course.” The strong endorsement of immunomodulatory therapies for PANDAS continues in the present edition.

A 2018 review published in the official journal of the European Paediatric Neurology Society evaluated treatment for immune-mediated movement disorders and classified IVIG as a first line therapy in the treatment of PANDAS and anti-NMDA encephalitis.¹⁵ The authors state that, although the pathophysiological processes differ in these conditions, “there are general themes that broadly apply including: early diagnosis and treatment is better, minimise the severity of disease, escalate treatment if the patient is not responding to initial treatments, and minimise relapse.”

Two papers, a treatment study and a literature review were published in quick succession in the Journal of Neurology and Neurosurgery in 2016.^{16,17} The treatment study found that up to 84% of pediatric patients exhibited benefit after IVIG and maintained this response even at 12 months.¹⁶ Children with low IgA, IgG, or IgG subclass at baseline were more likely to achieve and maintain 100% improvement at one year. The review expanded on an understanding of inflammatory autoimmune disease: “From immunodeficiency to autoimmunity, the dynamic immunologic basis of PANDAS highlights the broad potential of high-dose IVIG therapy.”¹⁷ Their literature search yielded a total of eight studies comprised of 145 children who met PANDAS criteria and received IVIG. On the basis of their systematic analysis, IVIG was deemed to be a “safe and useful adjunctive therapy in the treatment of refractory neuropsychiatric symptoms due to PANDAS and its variants.”

Additional recent treatment studies have documented that the response to IVIG is beneficial and appropriate for a subset of children with PANDAS. In an Italian study, 85% of “serious-severe” children with PANDAS showed a reduction or disappearance of the symptomatology following IVIG (1-2 cycles).¹⁸ For all pediatric participants in a blinded randomized control trial, a 62% mean decrease on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), maintained at 6 month follow-up, was indicative of improvement.¹⁹

A 2019 case study published in the British Medical Journal illustrates the profoundly debilitating symptoms of PANDAS in the acute phase and the significant and swift recovery possible when appropriate therapy is administered expeditiously.²⁰

A 6-year-old Indian boy residing in Bahrain was referred to us by his general practitioner (GP) after experiencing 4 days of irritability in the form of increased proneness to anger, which got worse with time, sleep disturbances, severe eating restrictions, parental separation anxiety, emotional lability, personality changes, loss of speech and intermittent eye blinking. The onset of these symptoms was abrupt...His mother further reported that he refused to eat on the day prior to his admission and was force fed...Additionally, he injured two of his teeth as a result of his agitated behaviour.²⁰

The patient’s medical workup revealed an antistreptolysin O (ASO) titer approximately five times above the normal upper limit. Following a diagnosis of PANDAS, the patient received one dose of immunoglobulin (12 hour infusion) and IV ampicillin over the course of his hospital stay. Within 48 hours, all of his symptoms resolved to normal, including behavior, activity level, appetite, and speech. Upon discharge, he was prescribed prophylactic penicillin. The authors concluded, “PANDAS can be rapidly cured with appropriate antibiotics and immunoglobulin administration.”²⁰

STANDARDS OF MEDICAL PRACTICE AND MEDICAL NECESSITY

Evidenced-based best practices drive the decision-making of physicians as to the efficacy of IVIG to meet the needs of a given patient, and should be the basis of insurers' decision-making when determining authorization. In formulating and adopting medical policies with respect to covered services, it is understood that insurers shall rely on "generally accepted standards of medical practice" or "standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community or otherwise consistent with the standards set forth in policy issues involving clinical judgment."^{21,22} This includes the recommendations of physician specialty societies and practicing specialists.

PANDAS Physicians Networks (PPN) in the US and UK represent physician specialty groups for practicing physicians in their respective countries. Their recommendations support a full range of treatment options for children with PANDAS and PANS, including IVIG. In particular, they underscore the favorable risk-benefit ratio for moderately severe to life-threatening cases "because the children's symptoms are causing significant impairment in daily functioning." The guidelines published by the PANS Research Consortium set standards of medical practice to support treating physicians who conclude that IVIG is medically necessary for children who are not responding to other therapies. The findings summarized in this update meet the criteria for medical necessity highlighted in the book, *Essential Health Benefits: Balancing Coverage and Cost*.^{21,22}

"Medically Necessary" or "Medical Necessity" shall mean health care services that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are: a) in accordance with generally accepted standards of medical practice; b) clinically appropriate, in terms of type, frequency, extent, site and duration, and considered effective for the patient's illness, injury or disease; and c) not primarily for the convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.²¹

PARITY

Although symptoms of these disorders often present as primarily psychiatric, they are a manifestation of a neurological condition. PANDAS and PANS rest at the intersection of mental and physical health, yet these branches of care are not fully aligned and therefore often do not work together in an efficient manner. The stakes are high for children with psychiatric symptoms regardless of their root cause. The cost and the stigma are often crippling for families.

Children with serious emotional disturbance are among the most fragile members of our society. ... Prompt coordinated services that support a child's continuation in the home can allow even the most disabled child a reasonable chance at a happy, fulfilling life. Without such services, a child may face a stunted existence, eked out in the shadows and devoid of almost everything that gives meaning to life.²³

U.S. District Court Judge Michael A. Ponsor, *Rosie D. v. Romney*, January 26, 2006

For families whose children have PANDAS and PANS, the risks are no less significant and the implications of lack of access to adequate treatment are no less serious than in any other mental or physical illness. For children with PANDAS and PANS, parity between mental health coverage and medical health benefits is critical as the most effective intervention is that which not only equates but coordinates behavioral health support with medical evaluation and treatment.

CONCLUSION

The efficacy of immunomodulatory treatment has been rigorously examined since 2015. Recent evidence overwhelmingly supports inclusion of IVIG in the levels of treatment available for children with PANDAS and PANS. Based on extensive systematic reviews from several specialty areas, treatment studies, and the consensus guidelines of the PRC and PPN, IVIG is indicated for the treatment of a small but significant subset of children who meet the criteria.

The current gap in health insurance coverage is causing disruption in physicians' medical practices, as well as an undue financial burden on patients, families, schools, insurers, and communities. When children are significantly impacted or in crisis, medical, mental health, and educational services are required to meet their needs. Parents miss work to care for their children and take them to appointments; insurers pay for ambulance transport, emergency room treatment, and psychiatric hospitalization; and schools place students in special classrooms, provide one-on-one classroom aides, and send tutors to homes when children are unable to attend school. Taking these factors into account, it is not only medically necessary, but cost-effective to provide appropriate treatment to these children without delay. Further, by effectively treating PANDAS, in which psychiatric symptoms stem from an organic illness, physicians can mitigate the lasting impact of infection, inflammation, and/or immune dysfunction on the developing brain, allowing children to recover and regain function in the home, school, and community.

IVIG for the treatment of children with PANDAS and PANS is almost universally denied by commercial Massachusetts insurers. As a result, physicians cannot exercise their best and full clinical judgement in order to provide sufficient care for the most severe patients whose symptoms are extremely impairing and often life-threatening. The appeals process is not structured to include a physician who is an expert in the management of these conditions, and clinicians are frustrated by their inability to objectively discuss IVIG approval with a knowledgeable expert. We ask the insurers' Physicians Advisory Committees and Medical Policy Review Boards to review recent evidence for the efficacy of IVIG in the treatment of PANDAS and PANS, and to support access to a full range of treatment.

Today, severely ill children wait indefinitely for appropriate medical intervention due to the gap in coverage for immune therapy in Massachusetts. Now is the time to change the clinical outcomes for children. Passage of An Act Relative to Insurance Coverage for PANDAS and PANS (H.920/S.613) will ensure that a full range of treatment options is widely available.

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