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Dear Chair Representative Prusak, Vice-Chairs, and Members of the Committee,

I am writing to express my strongest support for Oregon's House Bill 2390 to cover the cost of treatment for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS), including but not limited to intravenous immunoglobulin therapy and plasmapheresis. As a basic scientist, I know that passage of the bill will significantly improve the health and well-being of patients with PANDAS/PANS and ease the financial and emotional burdens of their families.

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is characterized by the abrupt and dramatic onset of obsessive-compulsive symptoms, restricted intake of food or fluids (sometimes to the point of starvation or dehydration), anxiety, depression and suicidality, emotional lability, personality changes, sensory hypersensitivity, cognitive deficits and physical symptoms, such as arthralgias, urinary dysfunction, and severe insomnia. As its name implies, PANS affect children, primarily those aged 4 - 9 years. When Group A streptococcal infections (such as strep throat) triggers symptoms, the disorder is known as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS). Recently, a number of studies have proven that PANS/PANDAS is a form of autoimmune encephalopathy—or inflammation of the brain. Treatment of PANS/PANDAS involves a three-pronged approach that utilizes psychiatric medications to provide symptomatic relief, antibiotics to eliminate the source of neuroinflammation and immune-modulating therapies to treat disturbances of the immune system. When these therapies are instituted promptly, many children recover completely and return to full functioning. Delays in obtaining treatment not only prolong the child's suffering needlessly but also increase the risk that the PANS/PANDAS symptoms will become entrenched, leading to long-term psychiatric, neurologic, and cognitive dysfunction.

Below, I outline several recent basic and clinical studies that demonstrate a very strong association of GAS with PANDAS and treatment strategies for PANDAS and PANS.

a) Basic studies in animal models of PANDAS/PANS have demonstrated that both cellular (Th17 lymphocytes) and humoral (antibodies) adaptive immunity, generated in response to multiple GAS infections, target the brain and trigger neuroinflammation, blood-brain barrier damage, neuroinflammation and neuronal dysfunction (Brimberg et al., 2012; Dileepan et al., 2016; Hoffman et al., 2004; Platt et al., 2020; Yaddanapudi et al., 2010). Moreover, Th17 lymphocytes, that are critical for pathogenesis in multiple autoimmune diseases such as Multiple Sclerosis,

Lupus, and Psoriasis, are also necessary for disease pathogenesis in rodent models for the PANDAS (Platt et al., 2020), suggesting a critical requirement for the adaptive cellular immune response in PANDAS pathogenesis in addition to the role of the humoral immune response.

b) Studies in sera of Sydenham's chorea, PANDAS and PANS have identified anti-neuronal autoantibodies targeting the basal ganglia, including the D1 and D2 dopamine receptors and recently cholinergic interneurons (Cox et al., 2013; Dale et al., 2012; Kirvan et al., 2003; Kirvan et al., 2006; Sinmaz et al., 2015; Xu et al., 2020). These antibodies induce neuronal dysfunction *in vitro* (Kirvan et al., 2003; Xu et al., 2020) and elicit behavioral abnormalities in rodents after adoptive transfer [reviewed in (Platt et al., 2017)], suggesting a critical role for the humoral immune response in the pathogenesis of these diseases. Moreover, the titer of these pathological antibodies is reduced in the sera of Sydenham's chorea, PANDAS or PANS patients during the convalescence period that corresponds with improved symptomatology (neurological and psychiatric manifestations) (Chain et al., 2020; Xu et al., 2020).

c) Recently, two large epidemiological cohort studies of children in Europe (N=1,068,000) (Orlovska et al., 2017) and Asia (N=28,600) (Wang et al., 2016) reported that children hospitalized with GAS infections had a 96% higher risk of neuropsychiatric disorders (Taiwan) (Wang et al., 2016), 51% higher risk for obsessive-compulsive disorder (OCD) and a 35% higher risk for tic disorders (Denmark) (Orlovska et al., 2017). These recent epidemiological studies together with previous findings that more than 25% of pediatric cases presenting with obsessive-compulsive disorders (OCD) and tic disorders (e.g. Tourette syndrome) originate as PANDAS (Swedo et al., 1998) strongly argue for a critical role of recurrent GAS infections in the etiology of PANDAS or PANS and that these diseases are rare similar in incidence to Lupus.

d) A recent clinical study has shown that in 41 pediatric subjects, followed for over a 24-month period, 65% of new GAS infections caused no symptoms, yet these subjects developed antibodies against GAS suggesting that **the majority of GAS infections are not detected in clinic** (Hysmith et al., 2017). This could result in missed opportunities for primary prevention of rheumatic fever and rheumatic heart disease, Sydenham's chorea or PANDAS with appropriate antimicrobial therapy.

e) The NIMH PANS consortium formed by a large number of experts from the disciplines of pediatrics, infectious disease, neurology, immunology and psychiatry have published the guidelines for treatment of PANDAS/PANS which rely on antibiotic therapy, steroids, IVIG, and psychiatric treatments (Thienemann et al., 2017; Frankovich et al., 2017: Cooperstock et al., 2017). The PANS Research Consortium has based its diagnosis and treatment guidelines on their experience of managing more than 1,000 patients in the U.S. The majority of the children are under age 13 and those who are left untreated can suffer dire consequences into young adulthood, including suicide.

f) PANDAS and PANS cases are increasingly being classified as a form of Autoimmune Encephalitis. The Mayo Clinic conducted a study in 2018 warning that more than 90,000 Autoimmune Encephalitis cases are being missed on an annual basis worldwide (Dubey et al., 2018). We contend that many PANDAS and PANS cases fall within that category as recently

discussed in detail in studies published in the American Academy of Neurology (Cellucci et al., 2020) and Lancet Psychiatry (Pollak et al., 2020). Furthermore, PANDAS and PANS are now considered as a form of basal ganglia encephalitis demanding attention and urgent care, as argued in recent editorial by esteemed physicians in Immunology, Neurology & Psychiatry of PANDAS/PANS. (Dale et al., 2017).

g) A Stage 3 Clinical Trial of IVIG will be conducted in January 2021, "A Superiority Study to Compare Panzyga Versus Placebo in Patients with PANS," Clinical Trials.gov, NCT04508530 in both Europe and USA in approximately 200 children to examine the effectiveness of IVIG in PANDAS and PANS children in a larger cohort.

Unfortunately, there are currently several barriers that delay or prevent treatment of PANS/PANDAS. At the outset, families are confronted with a paucity of physicians available to treat PANS/PANDAS. Oregon's House Bill 2390 would address this concern through providing insurance coverage for those whose severity requires it. Without such measures, many families must travel long distances to access treatment at great emotional and monetary expense. For others, the inability to travel due to financial circumstances or the severity of a child's illness postpones or precludes therapeutic interventions entirely.

Lack of insurance coverage for PANS/PANDAS further delays or, in some cases, completely prevents access to treatment. Particular difficulties are experienced with obtaining reimbursement for intravenous immunoglobulin (IVIG) and other immunotherapies. Insurers routinely deny insurance coverage, and a lengthy cycle of repeated denials and appeals frustrates both healthcare providers and families. More importantly, the denials/appeals process prolongs the patients' suffering and family trauma and increases the risk of serious neurological and psychological harm, long-term disability or even loss of life. Faced with continual denial of care, many families attempt to self-pay for the treatments, forcing them to take on heavy credit card debt, deplete retirement/college funds or sell their homes to raise funds to pay for a treatment that should be covered by insurance.

While I acknowledge that the cost of immunotherapies (particularly IVIG) is substantial, it is small in comparison with the cost of emergency interventions, in-patient psychiatric treatment, and/or pediatric hospitalizations for the complications of severe PANS/PANDAS, such as starvation/dehydration, aggressive behaviors, and self-injury or suicidality. Delayed or denied care also carries a risk of long-term care for serious neurological, emotional, and behavioral disabilities. In addition to the increased expenditures for medical care, untreated PANS/PANDAS also increase education-related costs, as children often require specialized, individualized instruction and significant accommodations for cognitive, neuropsychological, and psychological dysfunction.

In closing, I ask that you alleviate the burdens placed on families, physicians, and other community members who strive to serve the critical needs of children with PANS/PANDAS. Please enable their medical providers to make appropriate medical decisions free from administrative and time constraints posed by insurance coverage denials. I urge you to join your fellow legislators in Arkansas, Delaware, Indiana, Illinois, Minnesota, New Hampshire, Maryland, Massachusetts and require insurance coverage for PANS/PANDAS treatment. Your leadership on this important issue will help ensure children with PANS/PANDAS receive appropriate treatment, enabling them to experience all of the joys of childhood and reach their full potential.

Thank you for your time and consideration. Please feel free to contact me should you have any questions about this application.

Sincerely yours,

Dritan Agalliu Ph.D.

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