# TABLE OF CONTENTS

**ILLINOIS PANDAS/PANS ADVISORY COUNCIL MEMBERSHIP** ........................................ 3

**ILLINOIS PANDAS/PANS ADVISORY COUNCIL** ............................................................ 3

**UNDERSTANDING PANDAS/PANS** .................................................................................. 4
  Epidemiology/Demographics ......................................................................................... 4
  Clinical Presentation ..................................................................................................... 5
  Clinical Management .................................................................................................... 5
  Etiology and Disease Mechanisms for PANDAS (Post-streptococcal symptoms) .......... 6

**PANDAS/PANS BURDEN IN ILLINOIS** ........................................................................ 7

**STANDARD DIAGNOSTIC AND TREATMENT GUIDELINES** ....................................... 8
  Absolute Criteria ....................................................................................................... 8
  Major Criteria ............................................................................................................ 8
  Minor Criteria Group 1 ............................................................................................... 8
  Minor Criteria Group 2 ............................................................................................... 8
  Diagnostic Formulas ................................................................................................... 8
  Additional Supporting Evidence .................................................................................. 9

**INCREASING CLINICAL AWARENESS** ..................................................................... 11

**OUTREACH** ............................................................................................................... 11

**NETWORK OF EXPERTS** ............................................................................................ 11

**RECOMMENDATIONS FOR THE FUTURE** ................................................................. 12
  ENACT STANDARD PRACTICE GUIDELINES ............................................................ 12
  DEVELOP MECHANISMS TO INCREASE PUBLIC AWARENESS ............................... 12
  PROVIDE OUTREACH TO EDUCATORS AND PARENTS ............................................ 13
  INCREASE UNDERSTANDING OF THE BURDEN ON ILLINOIS .................................. 13

**CITATIONS** .................................................................................................................. 14
ILLINOIS PANDAS/PANS ADVISORY COUNCIL MEMBERSHIP

- Dr. Anette Mnabhi, DO, Synergy Health Care, Co-Chair
- Dr Natalie Drummond, MD, Whole Child Pediatrics, Co-Chair
- Laura Vaught, Legislative Liaison, Illinois Department of Public Health
- Illinois Representative Patti Bellock
- Diana Brown, District 45, Psychologist
- Kathleen M. Casey, RN, PEL-CSN, Illinois Association of School Nurses
- Dr. Pamela Campbell, MD, Division Chief Child Psychiatry, Southern Illinois University
- Illinois Representative Deb Conroy
- Illinois Senator Tom Cullerton
- Catherine Drury, PANDAS/PANS Parent
- Jessica Gerdes, MS, RN, NCSN, Principal Consultant/School Health, Illinois State Board of Education
- Wendy Nawara, MSW, Executive Director, PANDAS/PANS Advocacy and Support
- Dr. Greg Sharon, MD, Immunologist, Asthma and Allergy Center
- Tiffany Tumminaro, LCSW, CADC, Life Care Counseling
- Dr. Anjum Usman, MD, True Health Medical Center
- Dr. Susan Swedo, Principal Investigator, Pediatrics and Developmental Neuroscience, National Institute of Mental Health

ILLINOIS PANDAS/PANS ADVISORY COUNCIL

The Illinois PANDAS/PANS Advisory Council was created in 2015 in accordance with Public Act 99-0320 to:

- To make recommendations concerning standard practice guidelines for PANDAS/PANS
- To develop mechanisms to increase clinical awareness of PANDAS/PANS
- To provide outreach to educators and parents
- To develop of a network of volunteer experts on PANDAS/PANS to serve as resources within the State.

The Illinois Department of Public Health (IDPH) has managed oversight and support of the 15-member commission since 2015. The priorities of the council have been to adopt a standard of care that medical providers in the state can access and to educate citizens, health providers, mental health providers, medical students, and education professionals on PANDAS/PANS.

The council consists of physicians, who are board certified in immunology, pediatrics, psychiatry, osteopathy, and family medicine and have expertise and experience in the diagnostics and treatments of Pediatric Autoimmune Neuropsychiatric Disorders and/or Autism Spectrum Disorders; other health and mental health care professionals with expertise and experience in the diagnostics and treatments of Pediatric Autoimmune Neuropsychiatric Disorders; certified members of the School Health and Special Education Divisions of the State Board of Education; representatives of organizations or groups that advocate on behalf of children and families suffering from PANDAS/PANS and/or Autism Spectrum Disorders; a principal investigator from the National Institute of Mental Health; legislators; and parents of children who have been diagnosed with PANDAS/PANS.

The council met six times in 2016.
UNDERSTANDING PANDAS/PANS

PANDAS = Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections¹
PANS = Pediatric Acute-onset Neuropsychiatric Syndrome²

For nearly thirty years, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) has been studied extensively at the National Institute of Mental Health (NIMH) and elsewhere across the U.S. and internationally.³ More recently, a consortium of clinicians, researchers, and scientists has dedicated considerable time and effort to clinical care and study of children with PANDAS and the larger cohort of patients with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).² A medically treatable cause can be found for most cases of PANDAS and PANS. Preliminary data suggest that with appropriate treatment early in the course of illness, and effective use of antibiotics prophylaxis, we may be able to prevent up to 25-30% of childhood mental illnesses.⁴ Evidence consists demonstrating that Group A streptococcal infections (GAS) are the causal factor in PANDAS. Antibody studies demonstrate that children with PANDAS have antibodies that invoke bioactivity to produce the acute symptomatology.⁵⁻⁸ Animal studies show the transference of antibodies from an originally infected mouse to a naïve, healthy mouse to produce the same behavioral abnormalities and OCD symptoms.⁹⁻¹⁰ This demonstrates that PANDAS/PANS is an immune mediated antibody process. Placebo-controlled trials of antibiotic therapies demonstrate significant benefits for both PANDAS and PANS, and trials of prophylactic antibiotics have shown that preventing strep infections leads to reduction or cessation of the neuropsychiatric exacerbations.¹¹ In mild cases with positive strep cultures, a single course of antibiotics given to eradicate the strep infection can be effective in eliminating the psychiatric and behavioral symptoms. Additionally, a growing body of evidence indicates that PANDAS/PANS are autoimmune encephalitic disorders.¹²⁻¹³ In more moderate to severe presentations of PANDAS/PANS, and when considered medically necessary, physicians must rely on immunomodulatory measures, including steroids, intravenous immunoglobulin (IVIG), and therapeutic plasmapheresis (TPA) to halt this neuroinflammatory process.

Children with PANDAS/PANS who do not receive appropriate treatment remain chronically ill and the progression of the disease may exacerbate symptomatology to the extent that they are unable to attend school, participate in the community and in some cases may require institutional care. In the most severe cases, lack of appropriate medical interventions can result in the progression of clinically associated symptoms, which may result in death due to suicide or complications due to anorexia.

Epidemiology/Demographics

- Peak age at onset = 6.5 years²
- Boys outnumber girls approximately 2:1²
- 1 in 250 children have impairing symptoms (estimates from clinic populations²,¹⁴)
- 5 – 10% of grade-school aged children have observable GAS-related neurologic and behavioral symptoms¹⁴
Clinical Presentation
PANDAS and PANS are defined by an unusually abrupt onset of obsessive-compulsive disorder (OCD) or eating restrictions/anorexia.1-2 Comorbidity is present in all children, with most having symptoms in at least four categories1-2,15:
- Anxiety (particularly separation anxiety)
- Emotional lability and/or depression
- Irritability, aggression, and/or severely oppositional behaviors
- Behavioral (developmental) regression
- Deterioration of school performance
- Sensory or motor abnormalities
- Somatic signs and symptoms, including sleep disturbances, enuresis & urinary frequency

The course is relapsing/remitting, with exacerbations preceded by infections (particularly Group A strep) and psychosocial stressors.

Although early recognition and treatment can eradicate symptoms, children who fail to receive appropriate diagnosis and treatment have increasingly severe episodes, with resultant distress and loss of function (unable to participate in extracurricular activities; stop seeing friends; unable to attend school or even leave a “safe” room in their house). Severe cases often require prolonged psychiatric hospitalizations and may end in death (by suicide, starvation/dehydration, or accidents caused by impulsive behaviors).

Clinical Management
Early recognition and prompt treatment of occult GAS infections can produce complete symptom remission.16

Antibiotics may help PANS patients, even in the absence of documented GAS infection6 Immunomodulatory therapies, such as steroids, IVIG or therapeutic plasmapheresis, are helpful for severe, debilitating symptoms.17-19

A – IVIG vs. Placebo vs. Plasmapheresis
Improvements: 45%, 0% and 58% respectively

B – 20% reduction in caudate size following immunomodulatory treatment
Etiology and Disease Mechanisms for PANDAS (Post-streptococcal symptoms)

It is understood that 65-100% of patients with Sydenham Chorea have obsessive-compulsive symptoms, with that rate increasing with recurrences. OCD symptoms are often more persistent and difficult to treat than the chorea.

The postulated etiology of Sydenham Chorea and PANDAS is shown in the figure below.

Group A streptococci are “molecular mimics” that cause the immune system to produce antibodies which misrecognize host antigens as foreign. This temporary loss of tolerance may become permanent if blood-brain barrier is breached (which GAS exotoxins can do) or if the immune system is repeatedly activated.

Evidence for an etiologic role of GAS (Group A Strep) infections in PANDAS comes from:

- Clinical observations showing 1:1 correlation between (occult) GAS infections and neuropsychiatric symptom exacerbations
- Epidemiologic studies demonstrating association between GAS infections and choreiform movements, tics and problem behaviors
- Treatment of GAS infections improves OCD/tic symptoms
- Prevention of GAS infections reduces number and severity of neuropsychiatric symptom exacerbations
- Cross-reactive antibodies present during acute illness, but not during convalescence
- Animal models show that repeated GAS infections in lymphoid tissues, such as tonsils and adenoids, stimulate T-cell production and immune activation in Central Nervous System

Evidence for immune dysfunction in PANDAS comes from:

- Efficacy of immunomodulatory therapies, such as IVIG and plasmapheresis
- Cross-reactive antibodies produce cell signaling, as evidenced by activation of CaM KII
• Animal models have demonstrated that PANDAS sera/antibodies produce neuropsychiatric symptoms, even by passive transfer\textsuperscript{10,28-30}

**PANDAS/PANS BURDEN IN ILLINOIS**

The true incidence of PANDAS/PANS is currently unknown. A pediatrician member of the PANDAS/PANS Collaborative Consortium practicing in Illinois considers PANDAS/PANS to affect 1-2\% of the pediatric population\textsuperscript{31}, while PANDAS Network reports the incidence at 1 in 200 children\textsuperscript{32}.

The CDC reports that 1 in 7 US children between the ages of 2 and 8 years have a mental, behavioral or developmental disorder. When these issues persist into adulthood especially as a result of misdiagnosis or inadequate care, the risk of poor school outcomes, decreased employment, additional health concerns, early mortality and the great cost of caring for people with the disorders is heightened.\textsuperscript{33}

In accordance with the Illinois Mental Health 2013-2018 Strategic Plan, children suffering from PANDAS/PANS meet the definition of having a serious emotional disturbance, which is defined as the “unique needs of children and adolescents under age 18 who have, in the past year, been diagnosed with a mental, emotional, or behavioral disorder resulting in functional impairment that substantially interferes with or limits the child’s role or functioning in family, school, or community activities.”\textsuperscript{34}

As already mentioned, NIMH has estimated 25-30\% of childhood mental illness may be preventable through appropriate treatment of PANDAS/PANS.\textsuperscript{4} If we compute this estimation with the data suggested by the Illinois Mental Health Strategic Plan, in 2012 approximately 43,750-52,500 children and adolescents may have a decrease in quality of life due to a missed diagnosis of PANDAS/PANS and/or misdiagnosis of serious emotional disturbance. If appropriately diagnosed and treated immediately, we could reduce this estimated number, and substantially limit the burden on the State of Illinois.

Hospitalizations due to PANDAS/PANS are significantly more expensive for the Illinois health care system than community based services. Becker’s Hospital Review lists Illinois hospitals’ average daily rate for a nonprofit hospital at $2,049.\textsuperscript{35} Inpatient psychiatric care runs between $1,200 and $2,500 throughout the state.

If children with PANDAS/PANS are missed or misdiagnosed, the illness has the potential to become a chronic life-long condition, requiring extensive care. There can be no doubt that mental, behavioral and developmental disorders, such as PANDAS/PANS, and the associated conditions of Attention Deficit Hyperactivity Disorder, Obsessive Compulsive Disorder, Autism Spectrum Disorders, and Tourette Syndrome have a substantial impact on health care, families and communities.
STANDARD DIAGNOSTIC AND TREATMENT GUIDELINES

At present, the PANDAS/PANS diagnosis is based on subjective criteria and is considered a clinical diagnosis. However there are absolute, major, and minor criteria that can be met in various combinations.36

Absolute Criteria
- Sudden Onset. Sudden and precipitous development of symptoms over the course of hours or even a few days.
- Characteristic dynamic evolution of nature of symptoms and intensity of symptoms over a period of 2-6 weeks.

Major Criteria
- Presence of OCD symptoms
- Separation anxiety
  1. Daytime and Nighttime dependency on parent’s physical presence
  2. Psychological dependence on familiar physical environment with or without need for parents’ presence
- Anorexia
  1. Acute onset of food and/or liquid refusal
  2. Fear of choking
  3. Fear of vomiting
  4. Inability to swallow because of intolerable smell or texture
  5. Distorted body image (usually in children over 12, and can result from the other types of anorexia).

Minor Criteria Group 1
- Sleep disorders (insomnia, night terrors, refusal to sleep alone)
- Behavior regression (baby talk, temper tantrums, behaviors unbecoming of actual chronological age)
- Emotional Lability/Depression
- Hyperactivity, inattentiveness, inability to concentrate (ADHD/ADD diagnosis compatible)
- Learning disability (particularly mathematics) that was not there prior to symptom onset
- Hallucinations

Minor Criteria Group 2
- “Hyperalert” appearance and or “puppet-like” facial mannerisms
- Hypotonia
- Mydriasis (especially during acute phase of symptoms)
- Urinary frequency and/or enuresis and/or daytime incontinence
- Short-term memory loss
- Increased sensory responses (smells, sounds, light, touch)
- Fine motor skills deterioration
- Dysgraphia
- Tics and/or adventitious movements

Diagnostic Formulas
- In patients with the acute onset of symptoms, patients must meet the Absolute Criteria and TWO Major Criteria.
- If the acute onset in difficult to elucidate, patients must meet TWO Major Criteria and THREE Minor Criteria.
Additional Supporting Evidence

- Positive GAS titers
- Positive EBV IgM (VCA) (EBNA)
- Positive ANA titer (speckled)
- Elevated IgE levels
- Leukopenia
- Increased Circulating Immune Complexes (c1q,c3d, Raji cells)
- Sleep study abnormalities
- MRI abnormalities
- EEG abnormalities
- PET scan abnormalities
- Positive response to antibiotic trial
- Positive response to steroid “burst”
- Other positive specific autoimmune encephalopathic antibodies such as HSV, VZV, EV, HHV-6, AntiNMDAR, ALE, GAD-65
- Cunningham Panel (Moleculera Labs)
- “The best test is still taking a thorough history and listening to the parents.” Dr Sue Swedo, Chief of Developmental Pediatrics, Neuroscience Branch, NIMH

Based on peer-reviewed and published clinical evidence, there are three prongs of treatment modalities that are being regularly employed by physicians when treating cases of PANDAS/PANS:

1. Treating the SOURCE of infection with antibiotics and/or antivirals: the treatment with which is based on the clinical condition of the patient, the confirmed or suspected pathogen, and the patient’s response to treatment.
2. Resolving the SYMPTOMS using psychological or psychiatric therapies, such as Cognitive Behavior Therapy or Exposure Response Prevention;
3. Modulating the immune SYSTEM response to infections with steroids, IVIG or Plasmapheresis depending on severity.

Additionally, the PANDAS Physicians Network has created a diagnostic flowchart for physicians to aid in recognition and treatment. (See figures on next page.)
Quite often, children with PANDAS/PANS are also identified as having co-occurring conditions including, but not limited to, Autism Spectrum Disorders, Immune Deficiencies, or other Autoimmune illnesses or encephalopathies. In these cases, as in all cases of potential neuroimmune illness, it is very important that treatment decisions are made to ensure best possible clinical outcome. For example, if a child has both a moderate to severe PANDAS and a documented immune deficiency warranting immunomodulatory treatment, a “loading dose” of immunoglobulin may be required to halt the autoimmune attack before proceeding with the more typical monthly doses prescribed for the immune deficiency.

It is the recommendation of this Advisory Council that the diagnostic criteria, practice parameters and treatment protocol identified here shall be adopted as the standard of care for PANDAS/PANS in Illinois.

**INCREASING CLINICAL AWARENESS**

The Illinois Department of Public Health has created a PANDAS/PANS tab on their website to enable users of their site to learn more about PANDAS/PANS. The tab also provides direct links to the PANDAS Physicians Network flowchart to aid in ease of recognizing the disorder, and includes resources for physicians and families.

**OUTREACH**

The Advisory Council has developed a list of Medical Associations, Education Associations, and medical schools throughout Illinois that can be targeted to receive general information on the diagnosis and treatments of PANDAS/PANS. A PANDAS/PANS Summit has been scheduled for February 8, 2017. The goal of the Summit is to encourage necessary collaboration between the Advisory Council/Illinois Department of Public Health, the Department of Human Services, and the community to gather information on issues pertaining to educating medical providers, medical students, and the general public on the prompt diagnosis and treatment of PANDAS/PANS, to ensure health and maximum outreach, and to promote education related to the nature and extent, underlying causes, and prevention of PANDAS/PANS. Information attained at the Summit can be utilized to guide the Council’s goals and objectives for 2017.

**NETWORK OF EXPERTS**

Throughout the country there are many physicians practicing in the relevant clinical areas pertaining to the diagnostics and treatment of PANDAS/PANS. In addition, there are scientists continually researching the condition to improve upon the care of children. The PANDAS/PANS Collaborative Consortium members are listed here:

- Harvard (MGH) – Kyle Williams & Dan Geller (Child Psych), Mark Pasternack (Peds ID)
- Yale – James Leckman, Robert King (both Child Psych)
- Columbia – Dritan Agalli (basic science of blood-brain barrier), Mady Hornig (Neuroimmunology)
- Nemours/Delaware Children’s Hospital – Jo Elia (Child Psych), Harry Chugani (PET neuroimaging)
- NIMH – Susan Swedo (Pediatrics), Rebecca Hommer & Paul Grant (Child Psych)
- Georgetown – Beth Latimer (Peds Neuro), Earl Harley (ENT)
- UNC – Jim Crowley (Genetics)
• Univ South Florida – Tanya Murphy (Child Psych), Jolan Walter (Immunology)  
• Loyola Univ (Hinsdale IL) – Miro Kovacevic (Peds)  
• Univ Minnesota – Pat Cleary (basic science, microbiology of Group A strep)  
• Baylor University – Eyal Muscal (Peds Rheumatology)  
• Univ Oklahoma – Madeleine Cunningham (GAS microbiology; immune response to infection)  
• Univ Arizona – Sydney Rice (Dev/Behav Peds) & Michael Daines (Peds Immuno)  
• Stanford – Jenny Frankovich (Peds Rheumatology), Margo Thienemann & Kiki Chang (Child Psych)  
• Moleculara Labs - Craig Shimasaki (antibody testing)  

PANDAS Physicians Network – David Brick (Peds Cardiology)

Within the State of Illinois, the practicing members of this advisory council can be consulted for their expertise in the appropriate areas.  
• Diana Brown, School Psychology (dbrown@d45.org)  
• Kathleen M. Casey, RN, PEL-CSN (mandkcasey@gmail.com)  
• Dr. Pamela Campbell, MD, Child Psychiatry, Southern Illinois University (pcampbell@siumed.edu)  
• Dr. Natalie Drummond, MD, Whole Child Pediatrics (info@wholechildonline.com)  
• Jessica Gerdes, MS, RN, NCSN, Principal Consultant/School Health, Illinois State Board of Education (jgerdes@isbe.net)  
• Dr. Anette Mnabhi, DO, Synergy Healthcare (dranette@synergyhealthcare.org)  
• Wendy Nawara, MSW, Executive Director, PANDAS/PANS Advocacy and Support (wendy@pas.care)  
• Dr. Greg Sharon, MD, Immunologist, Asthma and Allergy Center (gesharon@aol.com)  
• Tiffany Tuminaro, LCSW, CADC, Life Care Counseling (ttuminaro.lifecare@gmail.com)  
• Dr. Anjum Usman, MD, True Health Medical Center (ausman@truehealthmedical.com)

RECOMMENDATIONS FOR THE FUTURE

In keeping with the original goals of Public Act 99-0320, while also expanding upon our goals for 2017, the PANDAS/PANS Advisory Council makes the following recommendations:

ENACT STANDARD PRACTICE GUIDELINES

Because the National Institute of Mental Health (one of the 27 differing institutes and centers under the National Institute of Health); the PANDAS/PANS Collaborative Consortium; and the PANDAS Physicians Network have established diagnostic and treatment guidelines that are now being employed by numerous experts and relevant practicing physicians throughout the country, the PANDAS/PANS Advisory Council of Illinois is recommending the standardization of care as reported here. We recognize that medicine is an ever changing and evolving field, and as such, we also recommend the members of this council stay up to date on any new science, research, and protocols to advise as needed.

DEVELOP MECHANISMS TO INCREASE PUBLIC AWARENESS

• With IDPH, DHHS and other pertinent government agencies, assist in the creation of awareness campaign materials appropriate for doctors’ offices and public health clinics.  
• Request assistance from Illinois State Medical Society, the Illinois American Academy of Pediatrics and other professional societies to disseminate educational materials.  
• Encourage any appropriate state agencies to provide an educational tab about PANDAS/PANS on their respective websites, or link to the IDPH tab, as well as local resources (treating physicians, support organizations).
• With PANDAS/PANS Advocacy and Support and assistance from the PANDAS/PANS Collaborative Consortium, participate in the development of continuing education (CEU/CME) online training for pediatricians, mental health providers, and first responders/Emergency Departments.
• Write “White paper” by our council’s physician experts.
• Investigate the possibility of bringing a PANDAS/PANS Center of Excellence to an Illinois teaching hospital to facilitate prompt recognition and treatment of PANDAS/PANS to ease the burden on the State.
• Collaborate with the Department of Insurance and insurers themselves to ensure appropriate and consistent access to care for families in need of treatment. Encourage the use of experts when conducting peer-to-peer reviews as other specialists may not yet have sufficient knowledge or experience to offer an informed opinion on physician recommended care.
• On February 8, 2017, the first PANDAS/PANS Summit will be held at the DuPage County Health Department. The meeting will pull together individuals from the various specialty areas involved in dealing with children and families impacted by PANDAS/PANS, and will continue to develop solutions for them. Breakout sessions will take place and workgroups will identify areas of action to meet the ongoing challenge of educating health care providers, educational professionals and families about PANDAS/PANS.

PROVIDE OUTREACH TO EDUCATORS AND PARENTS
• With IDPH, DHHS, ISBE and other pertinent government agencies, assist in the creation of awareness campaign materials appropriate for school nurses, school social workers and school psychologists, and school administrators.
• Continue to encourage the use of strep notices, and written explanations of school policies regarding the reporting of classroom illnesses and healthy practices to avoid the spreading of disease.
• Increase understanding of available support organizations for families through participation in state agencies’ special events, such as the IDPH’s School Health Days.

INCREASE UNDERSTANDING OF THE BURDEN ON ILLINOIS
• Gather data and surveillance of incidence statistics on PANDAS/PANS, and its co-occurring conditions such as Autism Spectrum Disorder, Immune Deficiencies or other autoimmune conditions in children.

The PANDAS/PANS Advisory Council will continue to work on its commission to make recommendations concerning standard practice guidelines for PANDAS/PANS; develop mechanisms to increase clinical awareness of PANDAS/PANS; provide outreach to educators and parents; and develop a network of volunteer experts who can serve as resources within the State.

Advisory Council meetings in 2017 will be held at Illinois Department of Public Health Springfield and West Chicago offices as follows (all times CT):
• January 13, 9-11AM
• Summit Meeting February 8, 12:30-4:30PM (DuPage County Health Department)
• May 9, 9-11PM
• August 2, 1-3PM
• November 2, 9-11PM
For more information, contact Laura Vaught at Laura.Vaught@illinois.gov.

In closing, PANDAS/PANS has long been a misunderstood condition. However, when it is estimated to effect approximately 1 in 200 children, its potential detriment cannot be ignored. The present available scientific evidence provides an excellent framework for the State of Illinois to impact the positive outcomes for these children and reduce the potential long-term physical and mental health consequences they may suffer.

CITATIONS


13. Prof Francesc Graus, Maarten J Titulaer, MD, Ramani Balu, MD, Susanne Benseler, MD, Prof Christian G Bien, MD, Tania Cellucci, MD, Irene Cortese, MD, Prof Russell C Dale, MD, Jeffrey M Gelfand, MD, Michael Geschwind, MD, Carol A Glaser, MD, Prof Jerome Honnorat, MD, Romana Höftberger, MD, Takahiro Iizuka, MD, Sarosh R Irani, MD, Eric Lancaster, MD, Frank Leyboldt, MD, Harald Prüss, MD, Alexander Rae-Grant, MD, Prof Markus Reindl, PhD, Prof Myrna R Rosenfeld, MD, Kevin Rostásy, MD, Albert Saiz, MD, Arun Venkatesan, MD, Prof Angela Vincent, FRS, Prof Klaus-Peter Wandinger, MD, Patrick Waters, PhD, Prof Josep Dalmau. A clinical approach to diagnosis of autoimmune encephalitis. The Lancet Neurology. Volume 15, No. 4, p391–404, April 2016.


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