DATE: July 25, 2025

RE: Rebuttal to the American Academy of Pediatrics Clinical Report on PANS (12/16/24)

TO:

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Dear Drs. Kressly, Shaw, Szilagyi, and Sanders, Mr. Del Monte, and Secretary Kennedy:

We are compelled to respond to the **American Academy of Pediatrics'** ("AAP") Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Clinical Report ("Report") published on

December 16, 2024, which is now being misused by pediatric providers to diagnose and treat PANDAS/PANS, as well as by insurers to justify the denial of IVIG coverage.The AAP itself explicitly states that this document is not a clinical guideline and should not be used to dictate treatment decisions:

> *"Because they are limited by the present level of evidence on the topic, the findings are presented as a report rather than a clinical practice guideline."*

Despite this disclaimer, pediatric providers are **misapplying the report** by disregarding established clinical guidelines, leading to failures in properly diagnosing and treating PANDAS/PANS. At the same time, insurers are **misusing the report** as definitive evidence against IVIG, ignoring its limitations, lack of transparency, and omitted research. This **misrepresentation** threatens access to critical treatment and delays necessary medical care..

OUR IMMEDIATE REQUEST

Given the **serious flaws** in the AAP Report and the inappropriate ways in which it is being used,we call for the following immediate actions.:

- **The AAP must retract this report** until its flaws are corrected and its intended use is clarified. Its lack of transparency, omitted research, and misrepresentation of IVIG make it unreliable and misleading.
- **The imperative of medical rule-out in psychiatric diagnoses:** Under the DSM-5 guidelines, mental health practitioners and physicians must rule out any underlying medical cause before assigning a psychiatric diagnosis. However, much of this report relies heavily on psychiatric labeling. Failing to perform an "etiological medical rule-out" not only risks medical negligence but can also deny patients access to accurate, potentially life-saving diagnoses and treatments.
- **Insurers must stop using this report to deny care.** It is not a clinical guideline, and its misuse harms families and obstructs physician-led treatment.
- **All IVIG denials based on this report must be reconsidered immediately** in light of strong medical evidence supporting its use for moderate-severe PANS/PANDAS.

CONSEQUENCES OF A FAILURE TO ACT

The failure to act allows pediatricians and insurers to continue leveraging an incomplete document at the expense of patient care, forcing children into needless **suffering and irreversible harm**. Without treatment, these children may experience a panoply of consequences, including:

- **Severe neuropsychiatric decline**, leaving them unable to speak, eat, or attend school
- **Malnutrition and medical starvation**, requiring hospitalization and feeding tubes
- **Increase in autoimmune biomarkers** demonstrated in 54.2% of children in a 2024 cohort study by Ma *et al*
- **Psychiatric crises**, leading to emergency interventions and long-term disability
- **Permanent cognitive and developmental regression**, forcing families into financial hardship
- **Fatalities -** The POND brainbank was established in 2022 with the goal of understanding the pathogenesis and mechanisms associated with PANS/PANDAS. The 11 specimens within the brain bank were donated by the families of their deceased children.

When pediatric providers rely on a non-guideline document to guide diagnosis and treatment, it undermines evidence-based care and delays appropriate interventions, worsening outcomes and increasing long-term costs. Likewise, denying IVIG does not reduce costs—it **escalates them**, shifting the burden to **emergency hospitalizations, feeding interventions, and more expensive treatments like plasmapheresis**.Both examples fail to recognize established diagnostic and treatment guidelines published by subject experts having worked in the field of PANDAS/PANS for 30 years.

Why the AAP Report Fails as Pediatric Clinical Guidance and Justification for IVIG Denial

1. It Is Not a Clinical Guideline

The AAP explicitly states that this report does not provide official treatment recommendations. It lacks consensus-based standards and does not establish clear directives for insurers to follow. This may represent misuse of clinical reports in medical practice.

2. Impedes Access to Testing and Diagnosis

The **2024 AAP Report** on PANS/PANDAS restricts key diagnostic tools, advising against routine streptococcus testing (e.g., throat cultures, rapid antigen tests) unless classic symptoms like pharyngitis are present, and discouraging brain imaging (e.g., MRI) unless focal neurological signs suggest alternative diagnoses such as autoimmune encephalitis. The imposed limitations risk delaying or preventing accurate diagnosis, making it harder for families to access appropriate testing, specialist care, and insurance coverage—ultimately obstructing timely intervention for children with acute-onset neuropsychiatric symptoms while driving up longer term direct and indirect costs to families, employers and insurers.

3. Lack of Transparency and Expert Input

The AAP report **does not disclose its authors or the specialists consulted**, raising serious credibility concerns. There is no indication that experts in pediatric neuroimmunology, infectious disease, or immunology—fields essential to understanding PANS/PANDAS as well as IVIG's role—were involved.

The AAP **did not consult any of the major multidisciplinary university clinics that research and treat PANS/PANDAS**. These institutions represent thousands of cases of collective experience, yet their input was neither sought nor included.

By **failing to adequately disclose potential conflicts of interest**, the AAP **violated transparency standards**, calling the report's validity into question. According to **International Committee of Medical Journal Editors (ICMJE) standards**: *"Authors should disclose relationships and activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, their work. This includes, but is not limited to, relationships with for-profit and not-for-profit third parties whose interests may be affected by the content of the manuscript."*

4. Omits Key Studies and Is Already Outdated

The review period for the AAP report ended in 2023, meaning it **fails to incorporate newer research**—including **Melamed et al. (2024)**— which demonstrated statistically significant improvements in OCD-related symptoms following IVIG treatment. Additionally, the omission of studies on the use of steroids to shorten the duration of flares.

Even within its stated review period, the report **omitted clinical guidelines and studies that support the use of steroids and IVIG**, including:

- **Swedo, Cooperstock, Frankovich, Thienemann et al. (2017):** Consensus Guidelines explicitly include IVIG as a recommended treatment for severe cases. These expert-driven guidelines remain a valid and authoritative clinical framework.
- **Pavone (2020), Hajjari (2022), and Eremija (2023):** All demonstrated IVIG's effectiveness for severe or persistent cases.
- **Melamed et al. (2021):** A multi-site, open-label study of 21 patients over six months showed measurable improvements in psychological function with IVIG. Results were statistically significant.
- **Brown K, Farmer C, Farhadian B, Hernandez J, Thienemann M, Frankovich J. (2017)** Corticosteroids may be a helpful treatment intervention in patients with new-onset and relapsing/remitting PANS and PANDAS, hastening symptom improvement or resolution. When corticosteroids are given earlier in a disease flare, symptoms improve more quickly and patients achieve clinical remission sooner. Additionally, the AAP report **selectively dismisses positive IVIG studies** due to small sample sizes while accepting **weak or inconclusive evidence against IVIG** without applying the same scrutiny, introducing bias into its conclusions.

Further, standard prescribing and coverage policies routinely approve **off-label pediatric treatments** (Carmack et al., 2020; Allen et al., 2018; Shah et al., 2007) and **therapies for small patient populations** using similar evidence standards. PANS/PANDAS is widely accepted to be a rare disease, and thus large multi-arm randomized and double-blinded studies are methodologically impractical.

A 2025 randomized, placebo-controlled Phase III study (NCT04508530) of PANZYGA® in PANS patients demonstrated a clinically meaningful reduction in CY-BOCS scores (31.1% improvement vs. 12.1% in placebo), though the p-value narrowly missed statistical significance ($p = 0.072$). However, the secondary endpoint—the Clinical Global Impression scale (CGI-I)—achieved statistical significance ($p = 0.017$), validating PANZYGA®'s real-world clinical benefit across multiple domains of functioning. These findings directly contradict the AAP Report's implication that evidence for IVIG is weak or unreliable.

5. Denials Based on This Report Contradicts Cost-Saving Measures

Blocking access to IVIG is not only harmful—it is financially irresponsible. **Calaprice et al. (2023)** found that unrestricted access to care for PANS results in more symptom-free days, significantly reducing the need for **costly hospitalizations, psychiatric admissions, emergency interventions**, and **lost wages** for caregiving parents.

When IVIG is denied, families face greater financial and medical burdens, including:

- **Severe psychiatric hospitalizations**
- **Feeding tube interventions** due to OCD-driven food refusal
- **Plasmapheresis**, a far more expensive treatment that could have been avoided with IVIG

Families who are denied access based on the AAP Report have been forced to pay out of pocket, which serves to further widen the disparities associated outcomes along socioeconomic lines. Access problems caused by sequential denials may only be ameliorated with access to legal counsel, which again is generally not widely available to many families.

PEDIATRIC PROVIDERS ARE FAILING TO PROPERLY DIAGNOSE AND TREAT PANDAS/PANS — AND INSURERS ARE MISUSING THE AAP REPORT TO JUSTIFY DENIALS

Many pediatric providers are citing the AAP Report to justify treating PANS/PANDAS solely as a psychiatric condition—directly contradicting **peer-reviewed, evidence-based guidelines** developed by the PANS Research Consortium. These guidelines were published in *JCAP* in 2017 and 2019, authored by leading experts from institutions including Stanford, Columbia, and the NIMH. Yet due to the AAP's institutional weight, its flawed report is often prioritized over these more specialized clinical standards.

This widespread clinical misapplication is not occurring in isolation—insurers are seizing on it to justify treatment denials and further restrict access to care.

A review of over 100 denied PANS/PANDAS-related cases shows an accelerating pattern since early 2025: insurers are increasingly invoking the 2024 AAP Report in ways that distort its intent. Although the report explicitly states it is not a clinical guideline, it is being treated as one—used to justify denials and restrict access to care, often without appropriate clinical justification or specialty input.

For example, **Wellmark** justified a denial by stating:

> *"A recent AAP review article-position published recently indicates essentially nothing has changed regarding the utilization of IVIG in the treatment of presumed PANS-PANDAS."*

Here, Wellmark conflates the AAP Report and the outdated AAP Red Book, using both to assert a lack of evidence while disregarding more current, supportive data.

Premera Blue Cross similarly cited the AAP to dismiss IVIG, asserting:

> *" In 2024, the American Academy of Pediatrics (AAP) published a clinical report in which their expert panel concluded… there are no well-designed trials that provide evidence-based guidance on treatment for PANS' symptoms…"*

Premera's framing misrepresents the evidence base, and the denial falsely implies that psychiatric and antibiotic care alone is sufficient—despite acknowledging that PANS is likely a valid diagnosis.

These examples demonstrate a dangerous pattern: insurers are using a non-guideline report to undermine medical judgment, deny treatment access, and sidestep robust clinical evidence.

CONCLUSION

The AAP report is not a clinical guideline and should not be used to dismiss diagnosis or treatment of PANS/PANDAS by pediatric providers, nor to justify IVIG denials. Coverage decisions must be based on clinical needs and strong medical evidence supporting IVIG for PANS/PANDAS.

We urge the following immediate actions:

- Pediatricians **must stop using** the flawed AAP report in place of well-established, evidence-based clinical guidelines that are essential for the proper diagnosis and treatment of PANS/PANDAS.
- The AAP should **retract the report** until its flaws are addressed and its intended use clarified.
- Insurers must **stop using the report for utilization management to deny care.**
- Insurers must **reconsider all IVIG denials based on this report.**
- Employer **fiduciaries of self-funded plans** must ensure the AAP report is not used to restrict care.
- State Departments of Insurance should **sanction insurers for misusing unsound evidence** in unsound coverage determinations.

The continued misuse of this non-guideline report to dismiss diagnosis and deny treatment is an unacceptable violation of the principles of non-maleficence (do no harm) and beneficence (act in the patient's best interest). Denying IVIG based on this flawed report is medically unsound, financially reckless, and ethically indefensible—contradicting clinical guidelines, increasing long-term costs, and undermining clinician authority.

Sincerely,

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COMPARISON OF AAP REPORT CLAIM VS. LITERATURE EVIDENCE

AAP REPORT CLAIM	EVIDENCE-BASED RESPONSE
IVIG lacks a robust evidence base for efficacy in treating PANS.	Two randomized, placebo-controlled trials show significant improvements with IVIG. At least seven additional studies demonstrate benefits in neuropsychiatric outcomes and immune markers. Animal models also show abnormal behavior reversed after IVIG, supporting its mechanism of action.
IVIG carries significant risks	In every trial to date, IVIG was well tolerated in PANS. The most common adverse events are headache, nausea, and vomiting, which are typically mild or moderate and self-limiting (e.g. Melamed 2021)
The pathophysiology of PANS is unclear	PANS is an immune mediated neuroinflammatory disorder as is evidenced by a) animal model demonstrating Th17 mediated blood brain barrier breakdown, b) elevations in inflammatory monocytes and immune activation markers during flares, c) abnormal cytokine levels in patients, d) extremely high rate of family history of autoimmunity and known association with genetic variants affecting immune system, e) microbiome alterations in patients, f) association with immunoglobulin deficiencies, g) elevated markers of neuronal damage, h) autopsy data, h) polysomnography abnormalities similar to other basal ganglia disorders, i)neuroimaging studies showing basal ganglia edema during flares, j) elevated anti dopamine receptor antibodies, k) clinical similarities including treatment response to Sydenham Chorea, a well recognized post-infectious neuroimmune disorder.
RCT and Systematic Reviews Are Inconclusive	Two randomized controlled trials (Perlmutter 1998 and Daines 2025—publication pending, data available online) have demonstrated the benefit of IVIG. The most authoritative review (Frankovich 2017) reflects consensus from experts in psychiatry, pediatrics, infectious disease, neurology, immunology, and related fields across NIH, major academic centers, and large practices. These RCTs and expert guidelines support IVIG for severe or refractory PANS and PANDAS. The PANDAS Physicians Network, an international consortium of researchers and clinicians, maintains updated treatment guidelines that continue to recommend IVIG as safe and effective in such cases.
Should Not Be Used Outside Clinical Trials or Specialty Centers	Currently, there is no clinical trial of IVIG in PANS in progress. Specialty centers lack capacity to manage the volume of cases in the community. Stanford's Immune Behavioral Health Clinic, for instance, can accept only 10% of referrals. Waiting lists for all PANS specialty centers are months to years. For this reason, PPN provides guidelines for community physicians such as "Seeing Your First Child with PANDAS/PANS," since delaying care to wait for a trial or tertiary appointment is associated with worse neurological outcomes and more persistent disease.

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