RESEARCH PRIORITIES: PANDAS/PANS ROADMAP TO A CURE

PANDAS Network is dedicated to improving the diagnosis and treatment of children with PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) and PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) which can be described as forms of post-infectious basal ganglia encephalitis (BGE). This document provides a roadmap that will: a) identify research priorities; b) define better disease stages; and c) outline the areas of diagnosis and treatment with needs yet to be met. We believe this roadmap will help to build improved collaborative efforts at a global level as we work to accelerate the basic and clinical science that leads to improvement of diagnosis and development of treatments for those living with PANDAS/PANS.

PANDAS Network's Scientific Advisory Board (SAB) will work closely with the Board of Directors to incorporate how individual research studies may fit within the priorities of our non-profit organization. We encourage you to reach out to our SAB chair, Dr. Dritan Agalliu, with any questions about the roadmap.

OVERVIEW

The roadmap is divided into three main goals - each with targets that we hope to achieve through research, education and advocacy. The individual targets include a list of: a) what we know; b) what we don't know; c) what we need; and d) what we will do to meet these targets.

Goal 1: Stop Pathway - Detection

Target 1: Early Detection: Reduce or eliminate the impact before accumulated neurological changes/alterations occur.

Target 2: Precision Medicine: Develop personalized approaches to diagnose and treat the disease.

Goal 2: Restore Pathway - Treatment

Target 1: Develop/Improve Treatments/Outcomes (Acute Phase): Develop or improve treatment management and support to stop symptom progression during the acute phase of the disease.

Target 2: Implement Treatments (Chronic Phase): Advance implementation of rehabilitation and treatment management strategies for the chronic phase of the disease.

Goal 3: End Pathway - Prevention

Target 1: Primary Prevention: Educate clinicians about the nature of the disease.

Target 2: Secondary Prevention: Reduce or eliminate impact by identifying and educating high risk populations.

GOAL 1: STOP PATHWAY – DETECTION

Understanding disease heterogeneity across diverse populations over time is important to create diagnostic tests to aid clinicians in early diagnosis of the disease.

TARGET #1: EARLY DETECTION

TARGET 1: Early Detection

Reduce or eliminate the impact before accumulated neurological changes occur

WHAT WE KNOW

- Disease presentation can increase over time when interventions are not given.
- Early intervention leads to improved outcomes.
- MRI studies show basal ganglia inflammation during acute onset of PANDAS and PANS.
- Group A Strep infections generate immune responses that target the brain and the blood brain barrier.
- Repeated infections with Group A Strep lead to immune responses targeting the brain.

WHAT WE DON'T KNOW

- Which biomarkers (blood/CFS/Imaging) identify individuals in the acute or chronic phase of disease?
- What are the pathophysiological events leading to the initiation of PANDAS/PANS?
- Which strains of Group A Strep cause or promote PANDAS?
- What genetic risk factors predispose for disease development?
- How do antibodies that target the basal ganglia affect brain function?

WHAT WE NEED

- Diagnostic tests (blood, CSF, or MRI) for early detection and diagnosis of the disease.
- An understanding of the biological processes driving early vs. late stages of PANDAS/PANS.
- Interventions that target early disease pathways and determine if PANDAS/PANS will respond to treatment.
- To understand how environment, immunity and genetic risk factors impact disease.
- Improve and expand on animal models to explain diverse outcomes and healing processes.
- Develop reliable repositories of patient registries, data, and biospecimens from disease.

WHAT WE WILL DO

- Advance basic and clinical research of immune, genetic, and neurological mechanisms that affect disease initiation, progression and outcomes.
- Conduct clinical studies with biospecimens to understand disease heterogeneity and correlate it with basic science studies.
- Create and share registries, data, and biospecimen repositories from PANDAS/PANS patients.
- Track the incidence of Group A Strep infections in PANDAS/PANS families.
- Define PANS in a way that allows clinicians to give an accurate diagnosis.

TARGET #2: PRECISION MEDICINE

TARGET 2: Precision Medicine

Develop personalized approaches to diagnose and treat the disease

WHAT WE KNOW

- PANDAS/PANS/AE is likely heterogeneous (pathologically and clinically).
- Autoantibodies against a group of neuronal antigens have been identified in animal models and human disease in blood, cerebrospinal fluid, and on basal ganglia neurons, and interneurons.
- Specific inflammatory cytokine/chemokines have been identified in sera of PANDAS/PANS children that directly impair BBB integrity.
- Dopamine receptor autoantibodies are present in Sydenham chorea and PANDAS/PANS children.
- Lifestyle and psychiatric support influence disease course.

WHAT WE DON'T KNOW

- Are there subgroups of cases - stable, relapsing-remitting, chronic?
- Which biomarkers, immune or genetic factors identify who will respond to a particular therapy and when a therapy is no longer effective?
- Which therapies pose an increased risk to an individual?
- The relationship between inflammation, BBB damage and chronic disease.
- How can transition from stable, relapsing-remitting to chronic PANDAS/PANS be measured?

WHAT WE NEED

- Identify biomarkers of stable, relapsing-remitting, and chronic phases of disease
- Improved utilization of resources (sample biorepositories; genetic testing) to enable improved understanding of diseases outcomes and pathogenesis as well as therapeutic efficacies.

WHAT WE WILL DO

- Promote research to investigate clinical validation of biomarkers (autoantibodies, cytokines, chemokines, genetics) together with response to treatment outcomes (IVIG, naproxen, antibiotics, etc)
- Encourage investigation in therapeutic strategies for relapsing-remitting & chronic cases.

GOAL 2: RESTORE PATHWAY - TREATMENT

Translation of knowledge from basic mechanisms to treatment options is needed to optimize treatment, manage symptoms, and restore quality of life to patients and families.

TARGET #1

TARGET 1: Develop/Improve Treatments/Out-comes (Acute Phase)

Develop or improve treatment management and support to stop symptom progression during the acute phase of the disease

WHAT WE KNOW

- Immunomodulation treatments improve disease outcomes in some people.
- The identification of autoantibodies, T cells, & imaging data suggest that inflammatory processes present in the brain require treatment interventions to stop processes cause CNS alterations.
- Dopamine receptors are targeted by autoantibodies in some forms of the disease state.

WHAT WE DON'T KNOW

- Key pathways/targets to stop disease advancement from relapsing-remitting to chronic.
- How to limit blood-brain barrier alterations and maintain its stability in the disease?
- How age, sex, ethnicity, race, and genetics impact repair/improve outcomes and identify pathogenic mechanisms?

WHAT WE NEED

- Treatment plan(s) for stable, relapsing-remitting, and chronic cases.
- Treatments that are not off-label and are supported by research and clinical outcomes.
- Clarify the factors involved in disease severity.
- A better understanding of longitudinal outcomes based on sex, ethnicity, race, and genetics.
- New targets for therapeutics that promote prevention and cure of the disease.
- Accurate assessment of immune and neurological dysregulation in disease.
- Better imaging, biomarkers, and psychological profiles of patients and their outcomes.

WHAT WE WILL DO

- Encourage further study of psychological mechanisms involved in immunomodulation therapies.
- Develop outcome measures to detect successful psychological & immunomodulation therapies.
- Foster immunological, neurological, psychological testing methodologies that improve outcomes.
- Create a professional community to speed the development and use of treatment and testing methodologies.

TARGET #2

TARGET 2: Implement Treatments (Chronic Phase)

Advance implementation of rehabilitation and treatment management strategies for the chronic phase of the disease

WHAT WE KNOW

- Comorbidities affect symptoms, behaviors, and potentially progression.
- Patients with PANDAS/PANS have complex symptoms that impede their quality of life.
- Some immune modifying therapies do improve symptoms.
- Disease progression impacts care of self, family structure, employment status.
- Forms of OCD and other psychological issues are not well understood by the medical community.
- Poor access to psychological care and support prohibits the healing of the family and patient.

WHAT WE DON'T KNOW

- How to enhance proper treatment dosing of interventions to facilitate optimal recovery.
- How to achieve the best outcomes by tracking symptoms, monitoring progress, and tailoring appropriate interventions (into adulthood).
- Mechanisms to improve psychological, neurological and immune function.

WHAT WE NEED

- Better treatments, outcome measures, quantitative and qualitative.
- Sensitive, valid, and clinically meaningful measures of impairment.
- Large clinical and treatment and outcome trials that are sufficiently powered.
- Expanded access to treatment therapies for all by expanding fellowship opportunities and general education of clinicians and other health care professionals.
- Individually tailored treatment plans and interventions.

WHAT WE WILL DO

- Advance guidance and guidelines in trial design for clinical treatment trials - including immunological, neurological, psychological factors.
- Promote expanded access to psychological and immunological therapies and testing.
- Support the research and development of psychological interventions that target recovery, lifestyle and wellness strategies, and symptom management during the course of healing.
- Promote the use of outcomes with emerging technologies such as AI applications.

GOAL 3: END PATHWAY - PREVENTION

Ending PANDAS/PANS/AE is defined as no new cases. Preventing new cases will require population-based public health initiatives and individual -based interventions.

TARGET #1

TARGET 1: Primary Prevention

Educate clinicians about the nature of the disease

WHAT WE KNOW

- Some of the infectious risk factors; strep infections, Lyme disease, influenzae, mycoplasma, other infections for PANDAS/PANS.
- Risk incidence due to age factors (onset 4 to 12 years).
- Risk incidence increase with family history of Rheumatic Fever, familial history of chronic strep and severe autoimmune disease in first and second generations of family history.
- Sydenham chorea has similar onset with clear treatment outcomes in plasmapheresis.

WHAT WE DON'T KNOW

- The critical time frame for best treatment outcomes.
- The complete genetic contribution to etiology and how genes interact with infectious risk factors to cause PANDAS/PANS.
- Which public health interventions (e.g. schools) will reduce the risk for PANDAS/PANS?
- What are developing countries with higher incidence of Sydenham chorea doing to improve treatment outcomes?

WHAT WE NEED

- A better knowledge of all relevant strep-related risk factors for PANDAS/PANS (e.g. correlation of strep titers- positive only in 30-35% with disease or false negative tests for the group A strep bacteria that is positive later).
- A full understanding of the potential genetic contribution to sudden onset psychiatric symptoms in a child and the need for medical training to follow up with the family.
- Interventions that prevent the onset of PANDAS/PANS and its progression.

WHAT WE WILL DO

- Promote a better understanding of the genetic and infectious risk factors for PANDAS/PANS.
- Support the research and development of interventions that target PANDAS/PANS prevention in the general population.
- Advance research of best medical practices that reduce the risk of PANDAS/PANS and promote policies that support implementation of these behaviors in doctors

TARGET #2

TARGET 2: Secondary Prevention

Reduce or eliminate impact by identifying and educating high risk populations

WHAT WE KNOW

- Emerging knowledge of imaging/biomarkers that identify PANDAS/PANS.
- Early evidence of detailed family medical history and neurological and immunological testing can contribute to identification of high risk individuals for acute PANDAS/PANS.
- Ongoing immune modulation studies (including IVIG study cohorts US & Italy) show slowing and prevention of acute symptoms in PANDAS/PANS.
- Genetic, immune, and autoantibody pathways are involved in the initiation of PANDAS/PANS.

WHAT WE DON'T KNOW

- Precisely which biomarkers identify risk for developing PANDAS/PANS, when they become detectable, and what thresholds identify an individual as being at risk.
- Which interventions are going to stop further development of PANDAS/PANS?
- What aspects of a medical history and/or neurological test will contribute significantly to identifying people at high risk for PANDAS/PANS?
- A full understanding of the early pathways/events that lead to the initiation of PANDAS/PANS.
- Whether interventions targeted at the very earliest stages of PANDAS/PANS will slow down or stop disease progression.

WHAT WE NEED

- Screening tools to identify stable, relapsing-remitting, or chronic PANDAS/PANS coupled with confidence that these tools will modify disease course.
- Discovery of biomarkers that detect the course of the disease.
- A better understanding of the differences between inflammatory pathways in typical Tourette's, OCD and subclinical PANDAS/PANS.

WHAT WE WILL DO

- Promote the development of biomarkers and screening tools that identify people at high risk for PANDAS/PANS and subsequent implementation into clinical practice.
- Advocate & inform the research community on best practices in biomarker development.
- Accelerate discoveries that increase our knowledge of stable, relapse-remit, chronic pathologies.
- Support the development of therapeutic approaches targeting early pathological events in disease.
- Hold an annual meeting to expand current knowledge of PANDAS/PANS.
- Provide educational materials for clinicians, schools, and the general public.