NeuroNEXT

The NEXT Generation of Neurologic Treatments

NIH-Network for Excellence in Neuroscience Clinical Trials

NeuroNEXT:
Challenges and possibilities for exploratory trials in neurological diseases

International Rare Disease Research Consortium
Shenzen,China 8 November 2014

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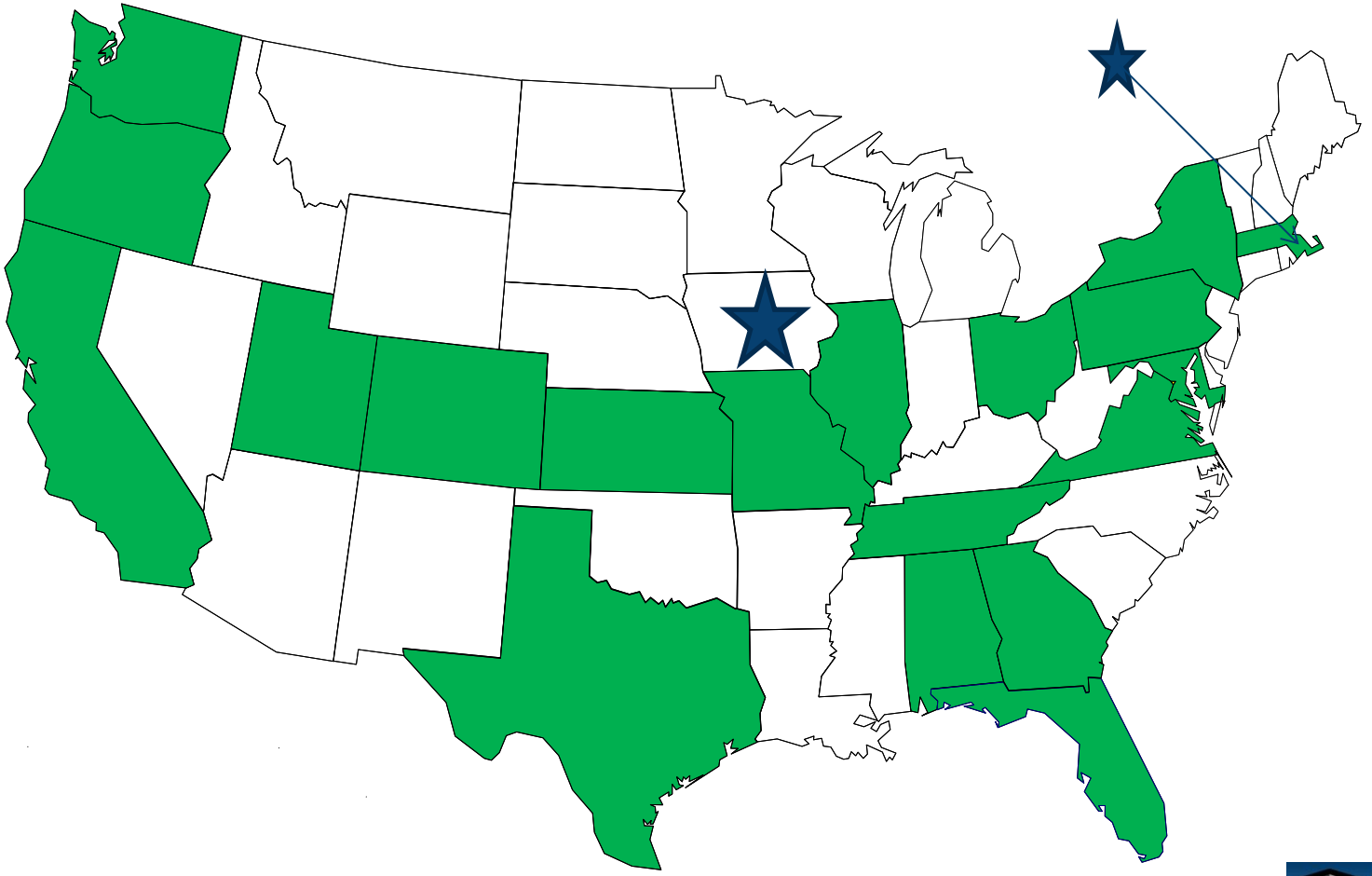
NeuroNEXT

- NeuroNEXT, a NIH-NINDS supported network, offers an innovative infrastructure for conduct of exploratory trials in neurological indications.
  - Adaptive, seamless Phase II/III designs for diseases with prevalence of <5,000 in US
- The NeuroNEXT Network consists of a Clinical Coordinating Center (Massachusetts General Hospital), a Data Coordinating Center (The University of Iowa) and 25 Clinical Study Sites geographically distributed across the USA.

NeuroNEXT



CCC-Mass General Hospital
DCC-University of Iowa

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- NeuroNEXT is designed to facilitate, from initial conception through final analysis, exploratory clinical trials for neurological disorders in adult and pediatric populations by creating infrastructure that provides expert methodological, organizational and logistical support.
- The proposals submitted thus far cover 19 categories of neurological disorders consisting of adult, pediatric, biomarker, drug, device and rare/orphan disease studies.

133 Proposals received as of 8/31/14

Indications (FY2012)	#
Stroke	11
Epilepsy	8
Multiple sclerosis	6
Traumatic brain injury	5
Duchenne Muscular Dystrophy	4
Parkinsons disease	4
Cerebral palsy	3
Diabetic Neuropathy	3
ALS/PLS	2
Myasthenia Gravis	2
SMA	2

2012 - Seven other indications had one proposal each (non-dystrophic myotonia, vascular cognitive impairment, craniopharyngioma, tardive dyskinesia, tuberous sclerosis, HSAN-1, neuromelitis optica)

Indications (FY2013)	#
Stroke	8
Autism	7
Parkinson's disease	5
ALS/PLS	3
Epilepsy	2
SMA	2

2013 - Twelve other indications had one proposal each (Rett, Fragile X, Post-op delirium, IBM, PML, Narcolepsy, NMO, SMA, Headache, TBI, CP, Tourettes)

Indications (FY2014)	#
Parkinson's Disease	4
Epilepsy	3
CMT	3
GBM	2
Migraine	2
Neuropathy	2
TBI	2

2014- nine other indications had 1 proposal each (ALS Pompe's, Low back pain, Autism, MSA, SCIHIE, Acute demyelinating disease, Neuropathy, West Nile Virus)

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Rare disease challenges

- Is there an animal model?
- What is the in vitro evidence?
- Is there known target engagement?
- Is the pathophysiology of the disease understood?
- What is known of the natural history?
- What is the geographic distribution of patients?

Challenges of rare disease studies

- Limited patient pool
- Narrow window for potential intervention
- Heterogeneity of disease
- Hard to randomize/blind
- Underpowered using conventional designs

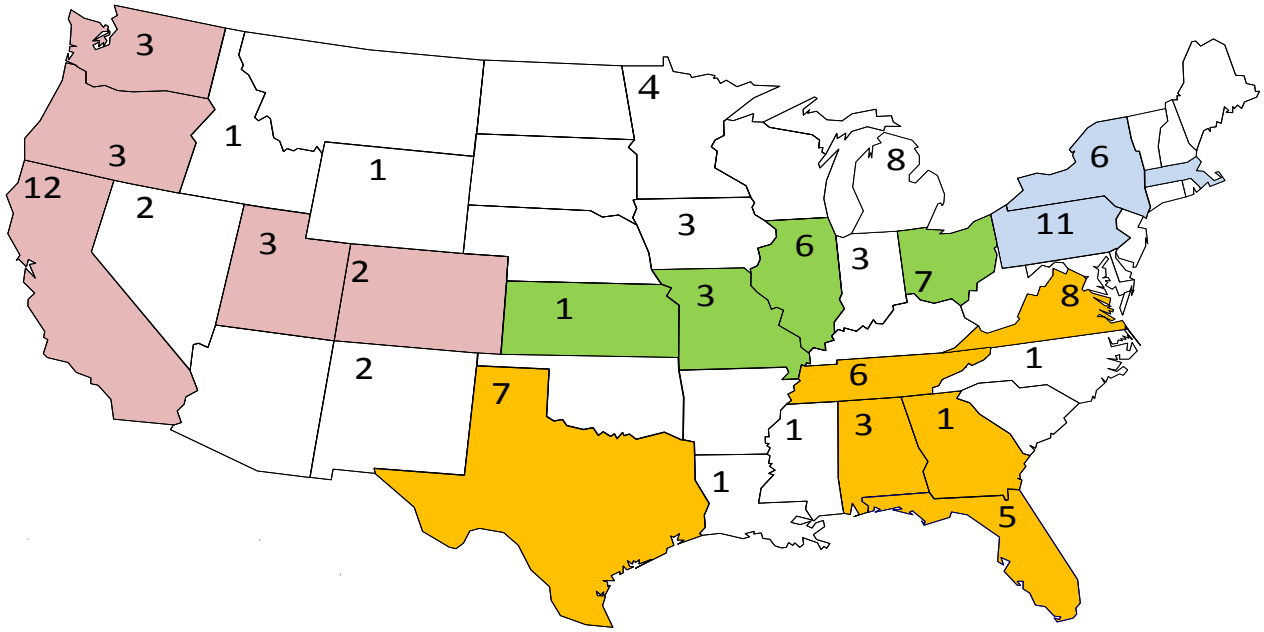
Opportunity to work with advocacy

- Niemann-Pick C disease
- 133 known patients in the USA
- Where are they?
- Can we feasibly use the infrastructure to conduct a trial in a population this small?

Location of 133 known living NPC patients

(sources-NIH and NNPDF)

CT-4
DE-1
MA-1
MD-3
NH-3
NJ-1
RI-1
VT-2
Unknown-3



Rare disease challenges

- Many neurodegenerative diseases are slowly progressive-how long should the study last?
- Many neurodegenerative diseases have notable symptom heterogeneity-how do you select endpoints?
- Imaging, electrophysilogical endpoints are often used in phase 2 studies-do these reliably predict clinically meaningful results?

Current NN Studies

- **NN 101** (Kolb) Spinal Muscular Atrophy (SMA) Biomarkers in the Immediate Postnatal Period of Development
- **NN102** (Fox) SPRINT-MS: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Activity of Ibudilast (MN-166) in Subjects with Progressive Multiple Sclerosis
- **NN 103** (Nowak): A Phase II Trial of Rituximab In Myasthenia Gravis
- **NN104** (Pryor/Lyden): ZZ-3K3A-201, a Phase 2 safety evaluation of 3K3A-APC in ischemic stroke

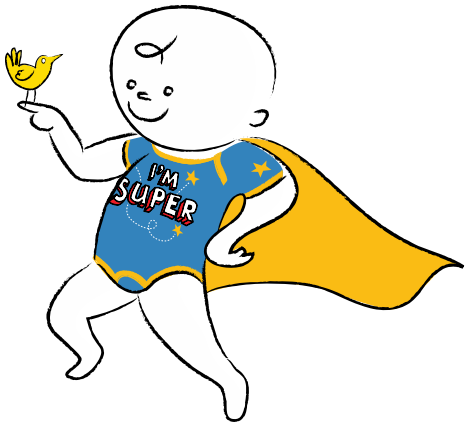
SMA Biomarkers in Infants NeuroNEXT Study

Stephen J. Kolb, M.D., Ph.D.

The Ohio State University

Wexner Medical Center

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠



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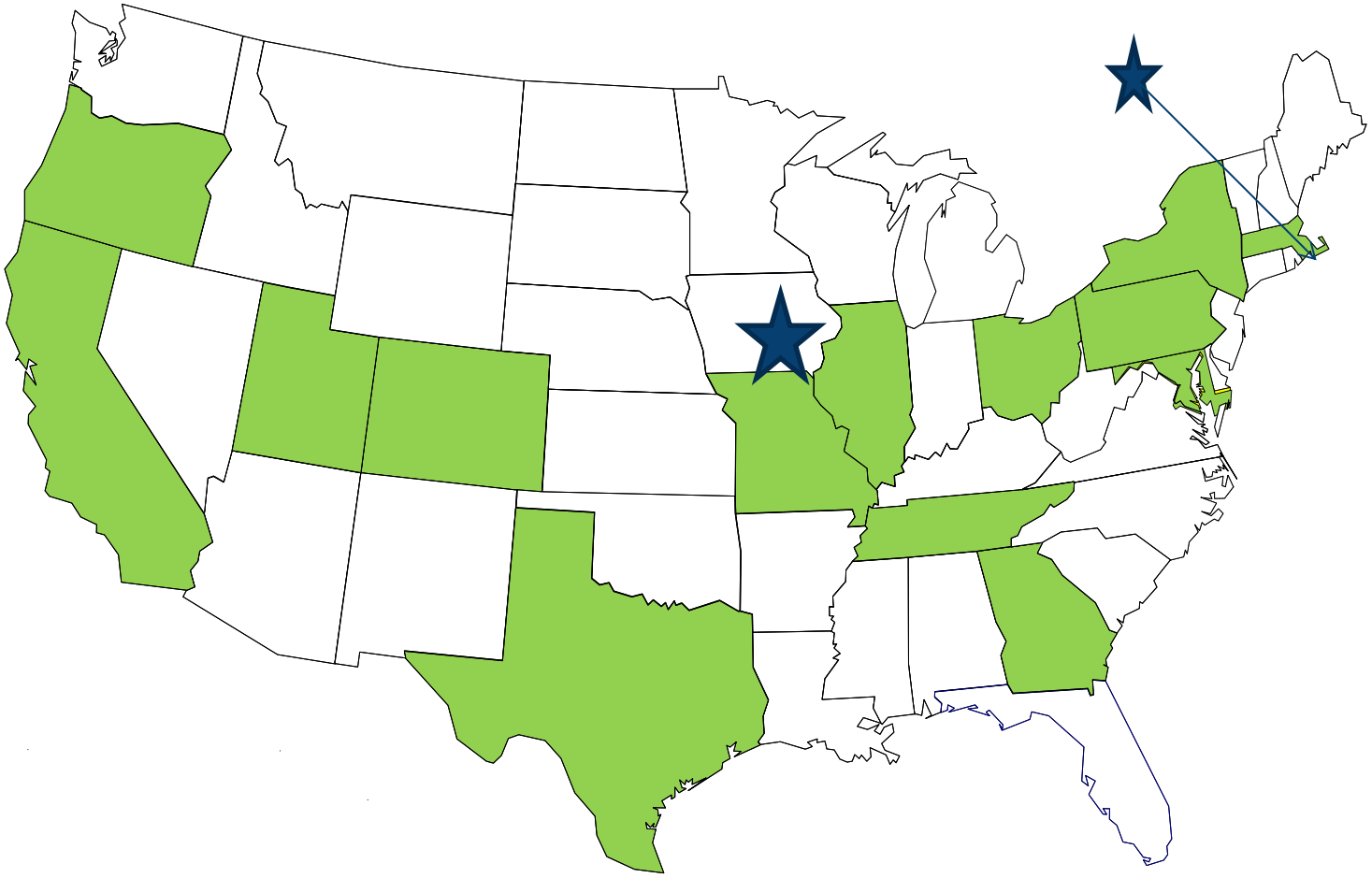
NeuroNEXT-SMA study sites



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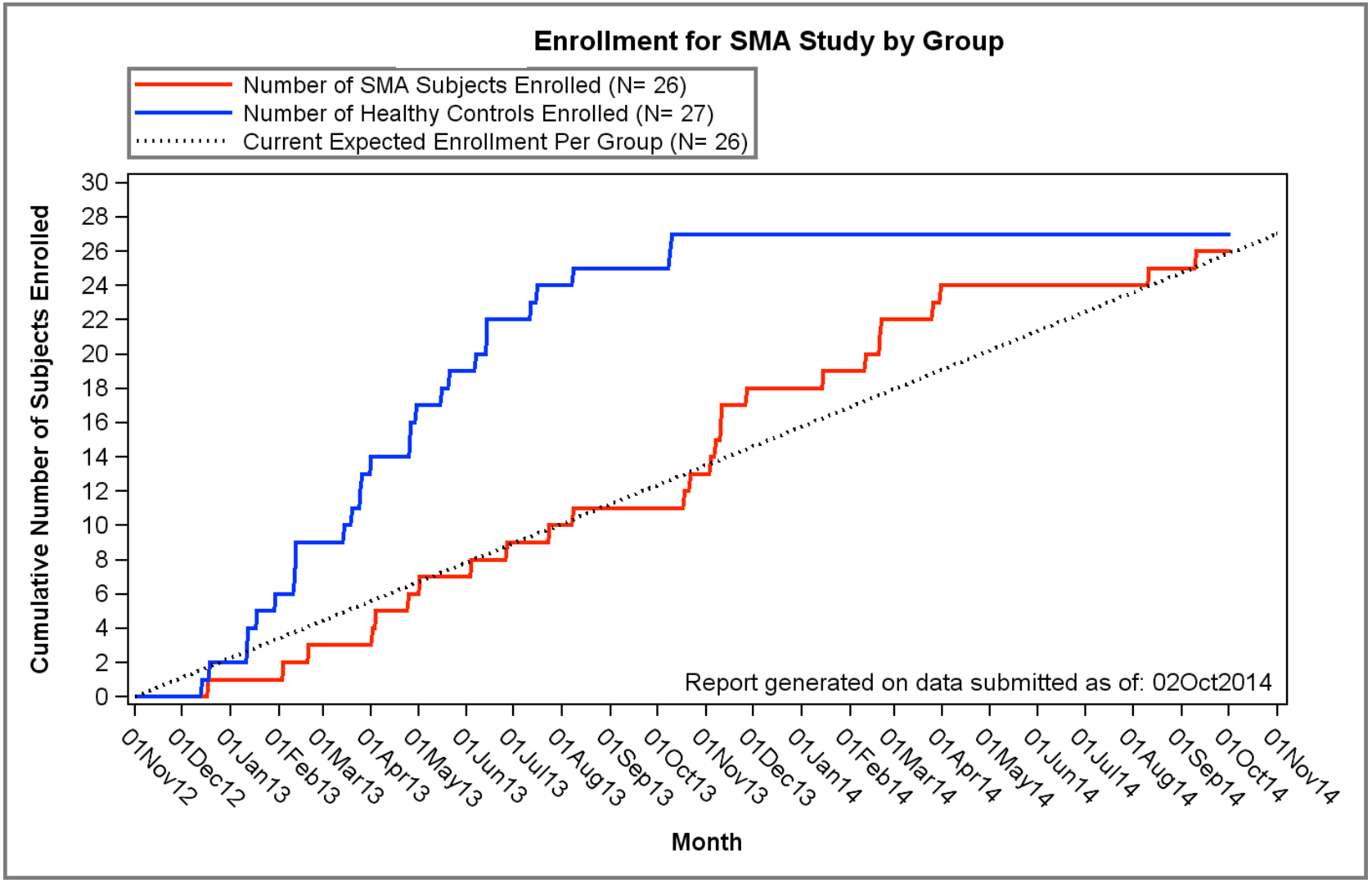
Opportunity to work with advocacy

- Patient advocate on the planning committee
- Advocate input changed the way study procedures were outlined
- Advocate input changed aspects that were key to patient recruitment/retention

Study Design

A longitudinal, natural history study to understand how potential SMA biomarkers and motor function change during the first two years of life.

Recruitment Complete



Wexner Medical Center

Unpublished data courtesy of Stephen J. Kolb, MD/PhD

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- While challenges exist, NINDS is particularly proud of the work done thus far in conjunction with advocacy groups, patients, and industry in rare diseases/disease variants such as spinal muscular atrophy, myasthenia gravis and progressive multiple sclerosis.

Website and contact information

www.neuronext.org

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