Towards precision measures in neuronal synuclein disease (NSD):
A framework to identify and track progression in individuals prior to symptoms.

Parkinson's Progression Markers Initiative

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Disclosures

Consultant for the Michael J Fox Foundation, Mitro, Roche, BMS, GAIN, Calico, Sanofi, Teva, Biohaven, Merck, GEHC, Lilly, ABLi, and Prothena.

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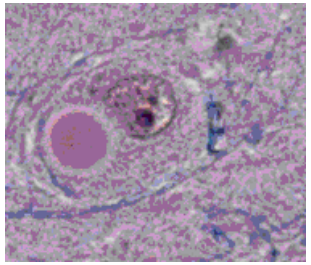
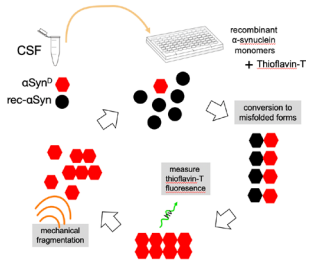
Changing the Paradigm in Parkinson Disease

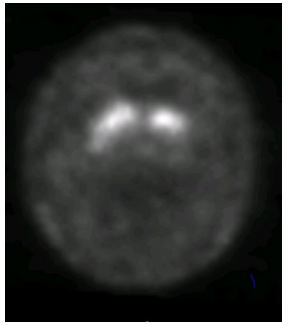
- Parkinson Disease Biologic Definition
- New terminology - Neuronal Synuclein Disease (NSD) - encompasses all neuronal synucleinopathies including PD and DLB
- Integrated Biologic and Clinical Staging for NSD (NSD-ISS)

Biologic Definition of NSD

Neuronal Synuclein disease (NSD) is defined by presence of disease specific neuronal a-synuclein pathology followed by dopaminergic neuronal degeneration







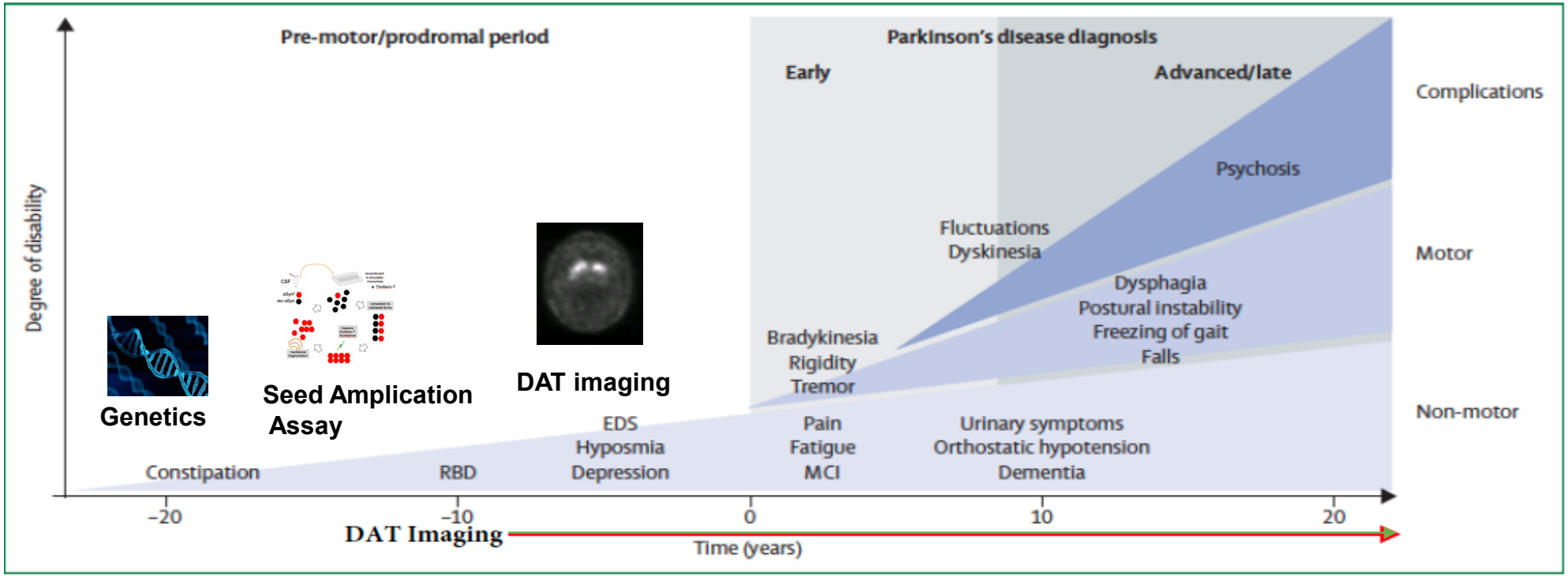
Synuclein Seed amplification Assay (SAA)

Dopamine transporter (DAT) imaging

Understanding biology has broad consequences for disease onset, progression, and therapeutics

Clinical Outcomes

Biologic Outcomes



Future Biologic Outcomes

Immune Function

Mitochondrial Function

Lysosomal Markers

Synaptic Density Markers

Protein Aggregation Markers

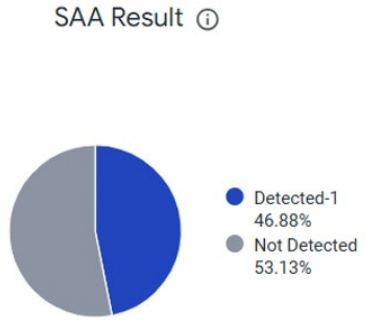
How to find study participants with disease biology, but without symptoms who are likely to develop symptoms

We can utilize early disease features (olfaction and RBD) to identify a large biomarker defined cohort for NSD stage 2.

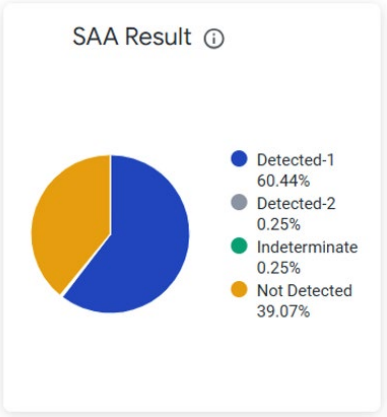
Olfactory dysfunction is highly associated with synuclein aggregation
99% of hyposmic symptomatic sporadic PD are asyn SAA Positive

Develop widespread screening UPSIT via with ST Direct – testing at home via online portal - >100,000 UPSIT completed

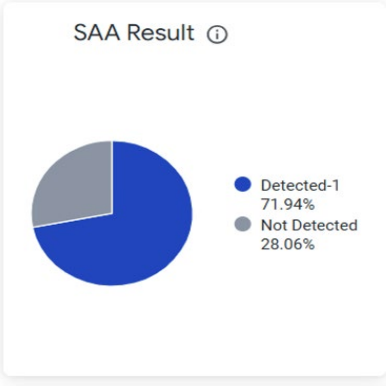
50-59 47% SAA pos



60-69 60% SAA pos



70-79 72% SAA pos



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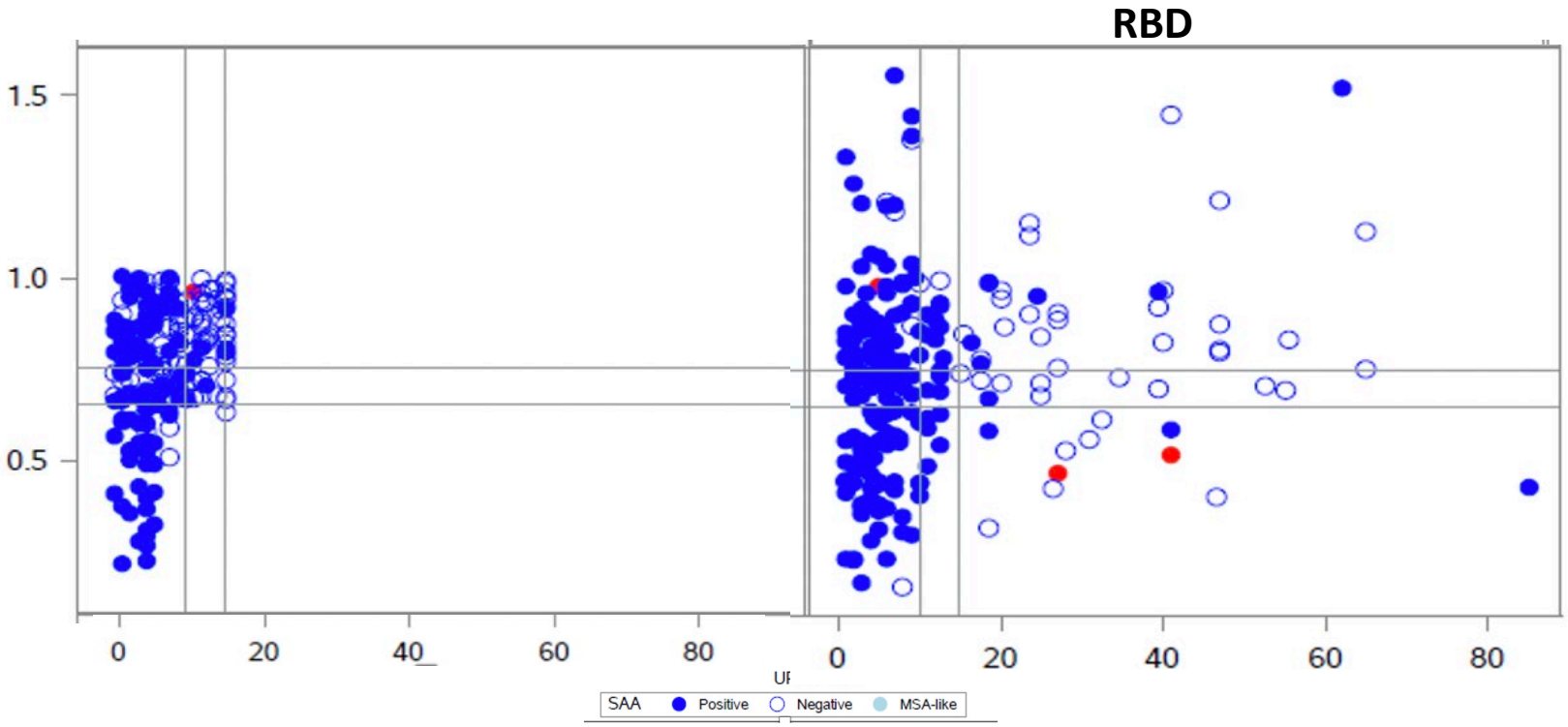
Majority of people with Hyposmia or RBD are asyn SAA+. Many show DAT deficit



- RBD are about 80% asyn SAA pos and Hyposmia are about 50% asyn SAA pos

- DAT deficit is present in about half of asyn SAA pos

Siderowf A, Concha-Marambio L, Lafontant D-E, et al. Assessment of heterogeneity and disease onset in the Parkinson's Progression Markers Initiative (PPMI) cohort using the α-synuclein seed amplification assay: a cross-sectional study. *Lancet Neurol* 2023; **22**(5): 407-17.

How to define timing for DAT dysfunction - Developing a DAT clock

Logistic decay function

The biomarker trajectory is modeled as

$$\boxed{g(s) = L + \frac{U - L}{1 + \exp(k(s - s_0))}}$$

Definition of parameters

Symbol	Meaning	Constraints	Interpretation
L	Lower asymptote	$L \geq 0$	End-stage (late disease) biomarker level
U	Upper asymptote	$U > L$	Pre-disease (healthy) biomarker level
k	Slope parameter	$k > 0$	Rate of disease progression
s_0	Inflection point	$s_0 \in \mathrm{R}$	Disease time at which decline is fastest

DAT for all asyn SAA pos PPMI participants
Putamen (average)

Model for DAT trajectory throughout PD natural history - approx. 40 years

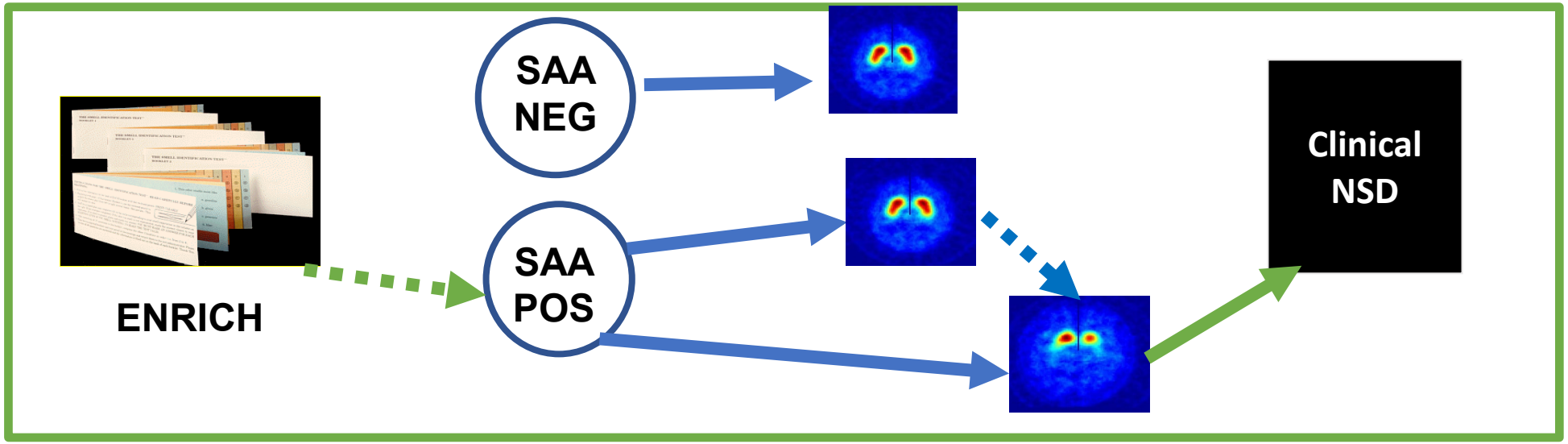
DAT Biological Staging derived from equal 20% cuts of SBR in the Putamen

Stage	0	I	II	III	IV

Age of Disease Onset is defined as when DAT drops below 20% of SBR value at T = -Inf

Stage	NSD Status	Age of Onset	UPDR3	UPDRS Total	H & Y
0					
I					
II					
III					
IV					

Proposed Temporal Pattern of Biomarkers leading to symptoms



Research questions:

- **Can we identify the start of synucleinopathy**
- **What are molecular drivers for synuclein**
- **What are the triggers for DAT Dysfunction/degeneration**
- **What are the trigger for clinical symptoms – motor, cognitive, sleep**

Baseline NSD Status–
PPMI Biomarker Derived Subgroups

PSG pos

Hyposmic
+/- DEB

	RBD/hyp (N = 260)	Hyp/DEB (N = 670)	Hyp (N = 995)
NSD-Asyn SAA	213 (94%)	537 (86%)	610 (66%)
DAT progression (% change in 2 yrs)	12% (9.3) N=103	8.3 (13.4) N=276	3.6 (13.9) N=360

RBD vs hyposmic – different biology vs disease timing

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What's next

- Investigate quantitative biomarkers to establish biology defined disease subsets
    - Asyn blood markers/Asyn imaging

- Remote data and sample collection to broaden and to target key biology defined subsets
    - myPPMI established worldwide with >50000 participants

- Therapeutic trials based on biology defined cohorts
    - Path to Prevention – an NSD platform trial

PPMI

PPMI STUDY TEAMS/CORES/COLLABORATORS FOR PUBLICATIONS

Executive Steering Committee:
Kenneth Marek, MD[1] (Principal Investigator); Caroline Tanner, MD, PhD[9]; Tanya Simuni, MD[3]; Andrew Siderowf, MD, MSCE[12]; Douglas Galasko, MD[27]; Lana Chahine, MD[41]; Christopher Coffey, PhD[4]; Kalpana Merchant, PhD[61]; Kathleen Poston, MD[40]; Roseanne Dobkin, PhD[43]; Tatiana Foroud, PhD[15]; Brit Mollenhauer, MD[8]; Dan Weintraub, MD[12]; Ethan Brown, MD[9]; Karl Kieburtz, MD, MPH[23]

Steering Committee:
Duygu Tosun-Turgut, PhD[9]; Werner Poewe, MD[7]; Susan Bressman, MD[14]; Jan Hammer[11]; Raymond James, RN[22]; Ekemini Riley, PhD[42]; John Seibyl, MD[1]; Leslie Shaw, PhD[12]; David Standaert, MD, PhD[18]; Sneha Mantri, MD, MS[62]; Nabila Dahodwala, MD[12]; Michael Schwarzschild[47]; Connie Marras[45]; Hubert Fernandez, MD[25]; Ira Shoulson, MD[23]; Helen Rowbotham[2]; Lucy Norcliffe-Kaufmann[2]; Claudia Trenkwalder, MD[8]

Michael J. Fox Foundation (Sponsor): Todd Sherer, PhD; Sohini Chowdhury; Mark Frasier, PhD; Jamie Eberling, PhD; Katie Kopil, PhD; Alyssa O'Grady; Maggie McGuire Kuhl; Leslie Kirsch, EdD

Study Cores, Committees and Related Studies: ***(Include as applicable to the paper)***
Project Management Core: Emily Flagg[1]
Site Management Core: Tanya Simuni, MD[3]; Bridget McMahon[1]
Strategy and Technical Operations: Craig Stanley[1]; Kim Fabrizio[1]
Data Management Core: Dixie Ecklund, MBA, MSN[4]; Trevis Huff[4]; Richard Peters[4]; Janel Fedler[4]
Screening Core: Tatiana Foroud, PhD[15]; Laura Heathers[15]; Christopher Hobbick[15]; Gena Antonopoulos[15]
Imaging Core: John Seibyl, MD[1]; Kathleen Poston, MD[40]
Statistics Core: Christopher Coffey, PhD[4]; Chelsea Caspell[4]; Michael Brumm, MS[4]
Bioinformatics Core: Arthur Toga, PhD[10]; Karen Crawford[10]
Biorepository Core: Tatiana Foroud, PhD[15]; Jan Hammer[11]
Biologics Review Committee: Brit Mollenhauer[8]; Doug Galasko[27]; Kalpana Merchant[61]
Genetics Core: Andrew Singleton, PhD[13]
Pathology Core: Tatiana Foroud, PhD[15]; Thomas Montine, MD, PhD[40]
Found: Caroline Tanner, MD PhD[9]
PPMI Online: Carlie Tanner, MD PhD[9]; Ethan Brown[9]; Lana Chahine[41]; Roseann Dobkin[43]; Monica Korell[9]

Site Investigators:
Ruth Schneider, MD[23]; Kelvin Chou, MD[44]; David Russell, MD, PhD[1]; Stewart Factor, DO[16]; Penelope Hogarth, MD[17]; Robert Hauser, MD, MBA[19]; Nabila Dahodwala, MD, MSc[12]; Marie H Saint-Hilaire, MD, FRCPC, FAAN[22]; David Shprecher, DO[24]; Hubert Fernandez, MD[25]; Kathrin Brockmann, MD[26]; Yen Tai, MD, PhD[29]; Paolo Barone, MD, PhD[30]; Stuart Isaacson, MD[31]; Alberto Espay, MD, MSc, FAAN, FANA[32]; Maria Jose Martí, MD, PhD[34]; Eduardo Tolosa MD, PhD[34]; Shu-Ching Hu, MD, PhD[21]; Douglas Galasko, MD[27]; Emile Moukheiber, MD[28]; Jean-Christophe Corvol, MD[39]; Nir Giladi, MD[36]; Javier Ruiz Martinez, MD, PhD[35]; Jan O. Aasly, MD[37]; Leonidas Stefanis, MD, PhD[38]; Karen Marder, MD MPH[39] ; Arjun Tarakad, MD[20]; Connie Marras, MD, PhD, FRCP(C)[45]; Tiago Mestre, MD, PhD[46]; Aleksandar Videnovic, MD, MSc[47]; Rajesh Pahwa, MD[48]; Mark Lew, MD[49]; Holly Shill, MD[50]; Amy Amara, MD, PhD[18]; Charles Adler, MD, PhD[51]; Caroline Tanner, MD, PhD[9]; Susan Bressman, MD[14]; Tanya Simuni, MD[3]; Maureen Leehey, MD[52]; Giulietta Riboldi, MD[53]; Nikolaus McFarland, MD, PhD, FAAN[54]; Lana Chahine, MD[41]; Ron Postuma, MD, FRCPC[55]; Brit Mollenhauer, MD[8]; Werner Poewe, MD[7]; Zoltan Mari, MD[56]; Nicola Pavese, MD, PhD[57]; Michele Hu, MD, PhD[58]; Norbert Brüggemann, MD[59]; Christine Klein, MD, FEAN[59]; Bastiaan Bloem, MD, PhD[60]

Coordinators:
Anisha Singh, BS[23]; Angela Stovall, BS[44]; Julie Festa, BA[1]; Lianne Ramia, BS[1]; Katrina Wakeman, BS[17]; Karen Williams, BA, CCRP[3]; Courtney Blair, MA[18]; Krista Specketer, BS[21]; Diana Willeke[8]; Jennifer Mule, BS[25]; Ella Hilt[26]; Shawnees Peacock, BS[27]; Kori Ribb, RN, BSN, CNRN[28]; Susan Ainscough, BA[30]; Lisbeth Pennente, BA[31]; Julia Brown, BS[32]; Christina Gruenwald, BS, CCRP[32]; Barbara Sommerfeld MSN, RN, CNRN[16]; Farah Kausar, PhD[9]; Alicia Garrido, MD[34]; Deborah Raymond, MS, CGC[14]; Ioana Croitoru[35]; Anne Grete Kristiansen[37]; Helen Mejia Santana, MA[39]; Anjana Singh, BS[20]; Danica Nogo, BS[45]; Shawna Reddie, BA[46]; Samantha Murphy, BS[47]; Lauren O'Brien[48]; Ashwini Ramachandran, MSc[12]; Fnu Madhuri, MS[19]; Daniel Freire, MS[49]; Farah Ismail, MBChB[50]; Raymond James, BS, RN[22]; Tom Osgood, BA, CCRP[51]; Heidi Friedeck, BS[3]; Jenny Frisendahl, BS[52]; Ying Liu, MD[52]; Caitlin Romano, BA[53]; Kelly Clark[24]; Kyle Rizer, BA[54]; Stephanie Carvalho[39]; Sherri Mosovsky, MPH[41]; Farah Sulaiman, MPH[55]; Dora Valent, MS[7]; Raquel Lopes, BSN, MS[29]; Michelle Torreliza, AS[56]; Shira Paz, BS[36]; Victoria Kate Foster[57]; Madita Grümmer[59]; Myrthe Burgler, MA[60]; Sabine van Zundert, MS[60]; Christos Koros, MD, PhD[38]; Jamil Razzaque, MS[58]

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