The SDS Registry: A Partnership Between Patients, Families, and Researchers

Akiko Shimamura, MD PhD
Kas Myers, MD

SDS Camp Sunshine
July 10, 2023

SDSR
Shwachman-Diamond Syndrome Registry

Boston Children's Hospital
Until every child is well™

Cincinnati Children's™
changing the outcome together

What is the SDS Registry?

- A partnership between researchers and the SDS community, working together to find cures for SDS.

Why is an SDS Registry needed?

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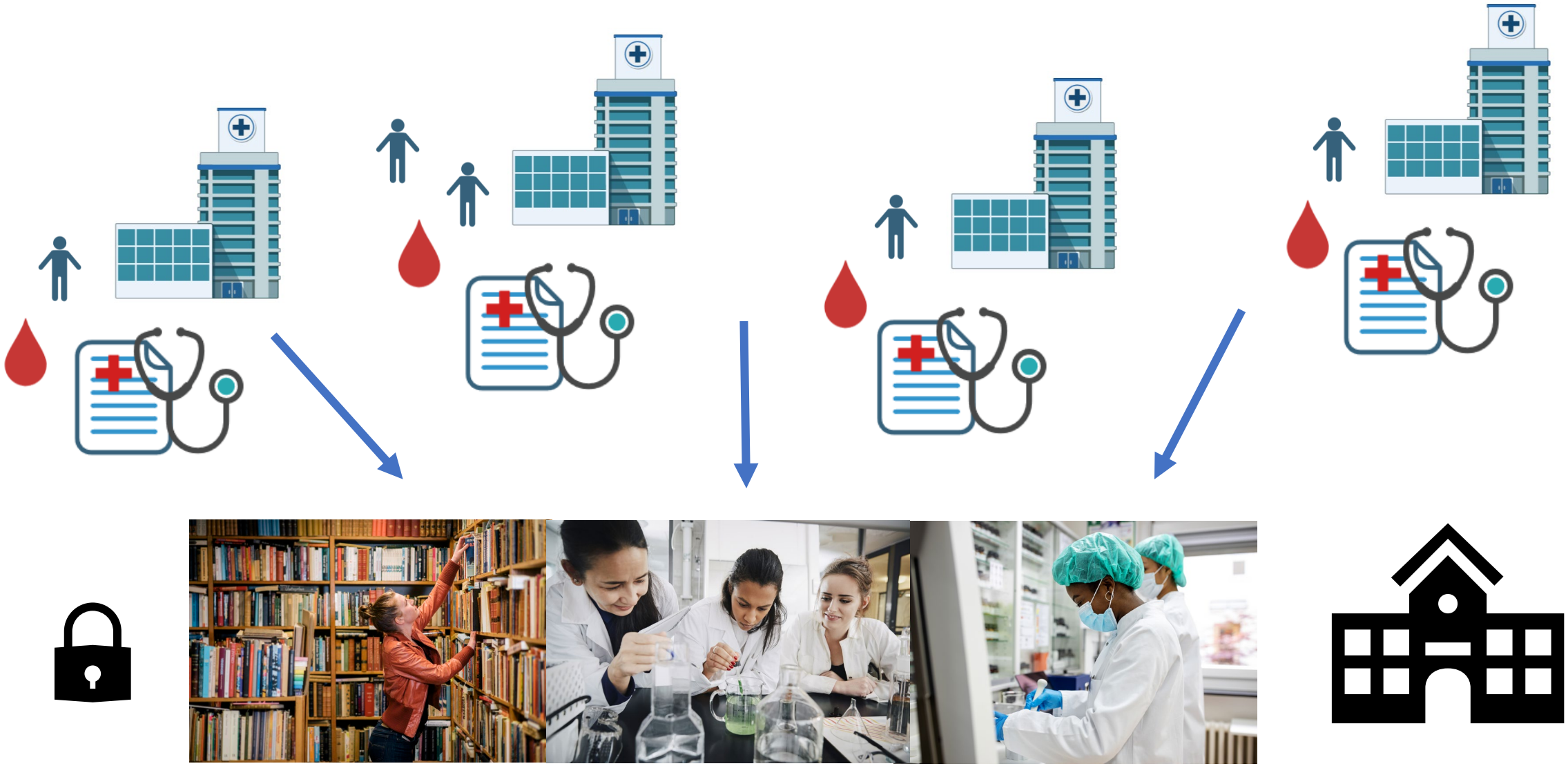

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SDSR Enrollment (Patients Only) 2010 – July 2023

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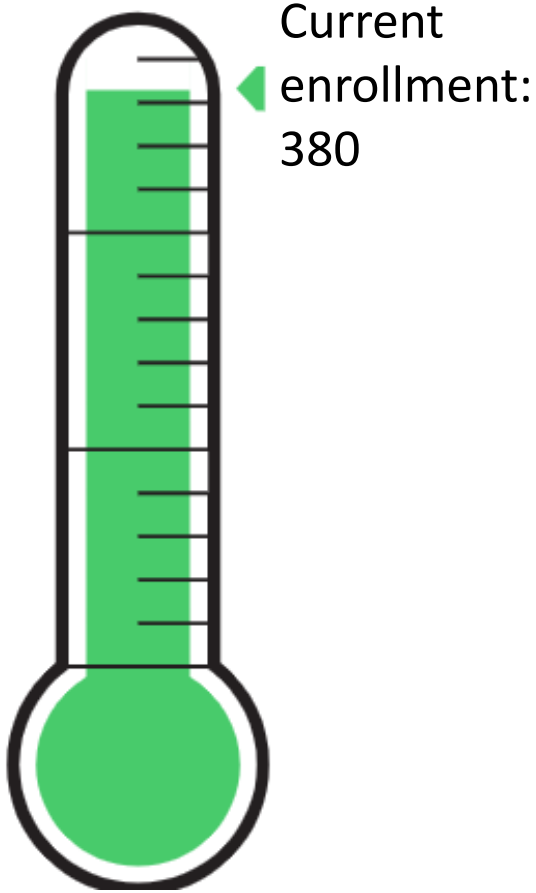
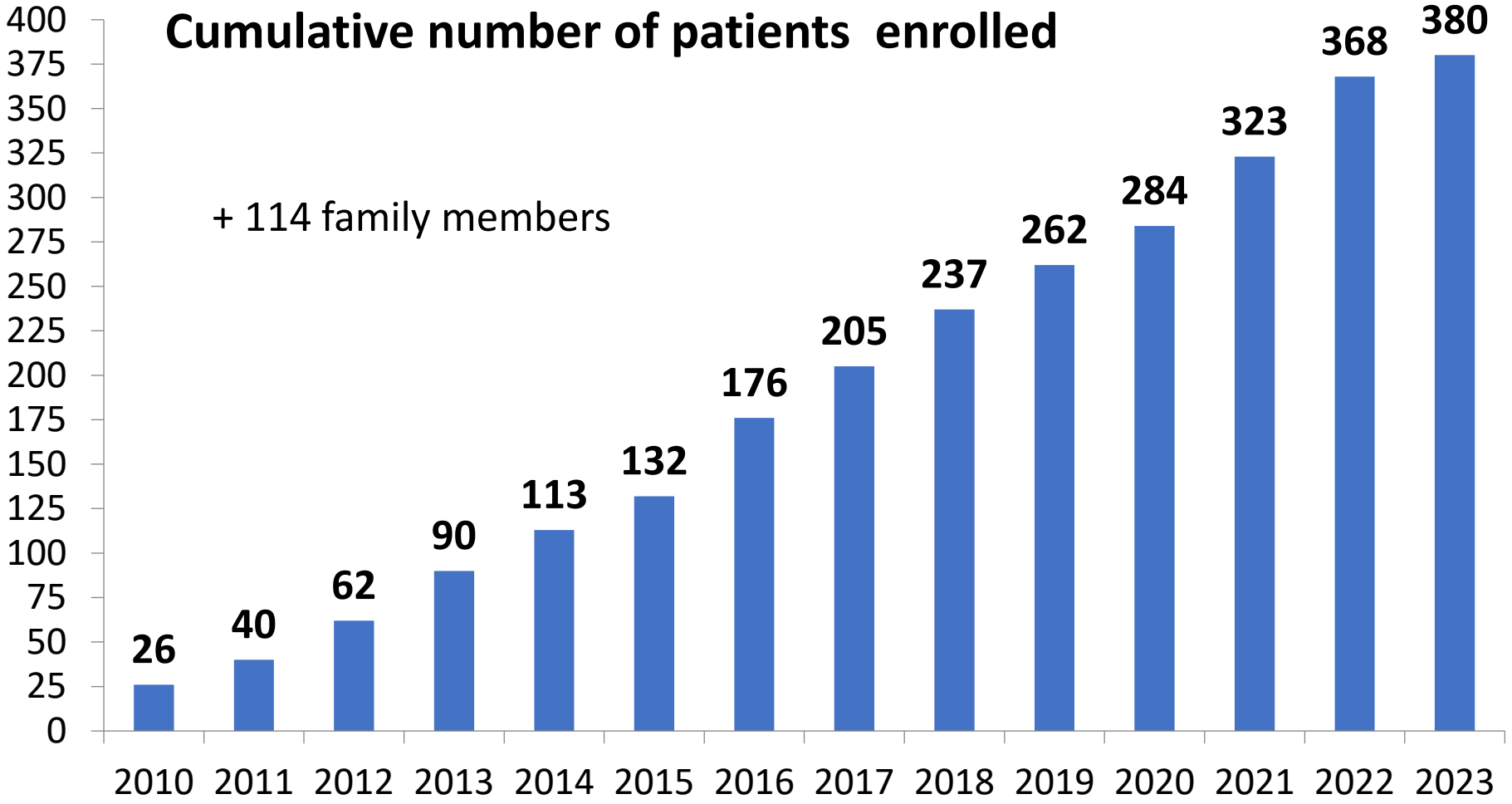
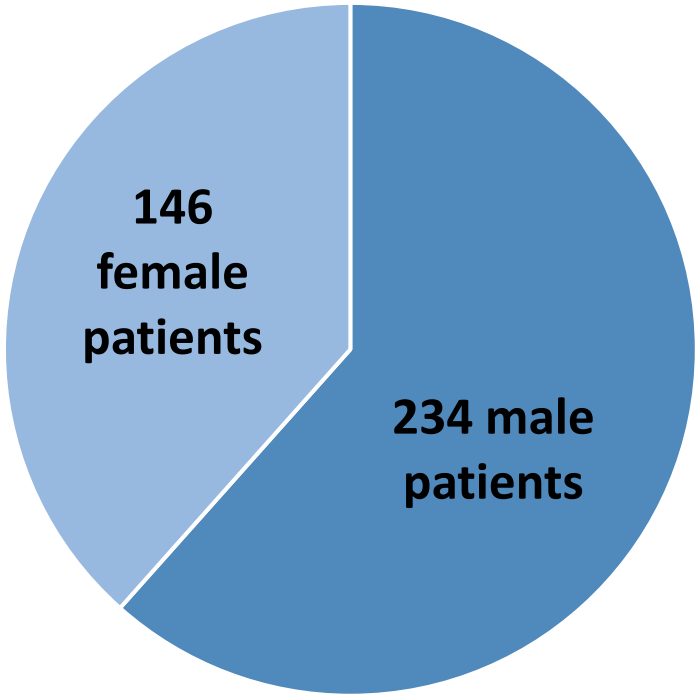
Goal enrollment: 400

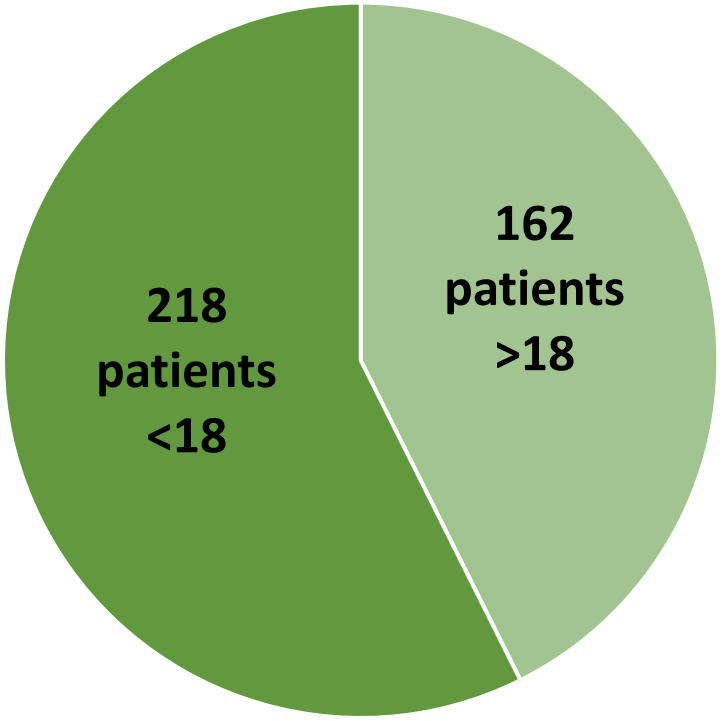


Current enrollment: 380



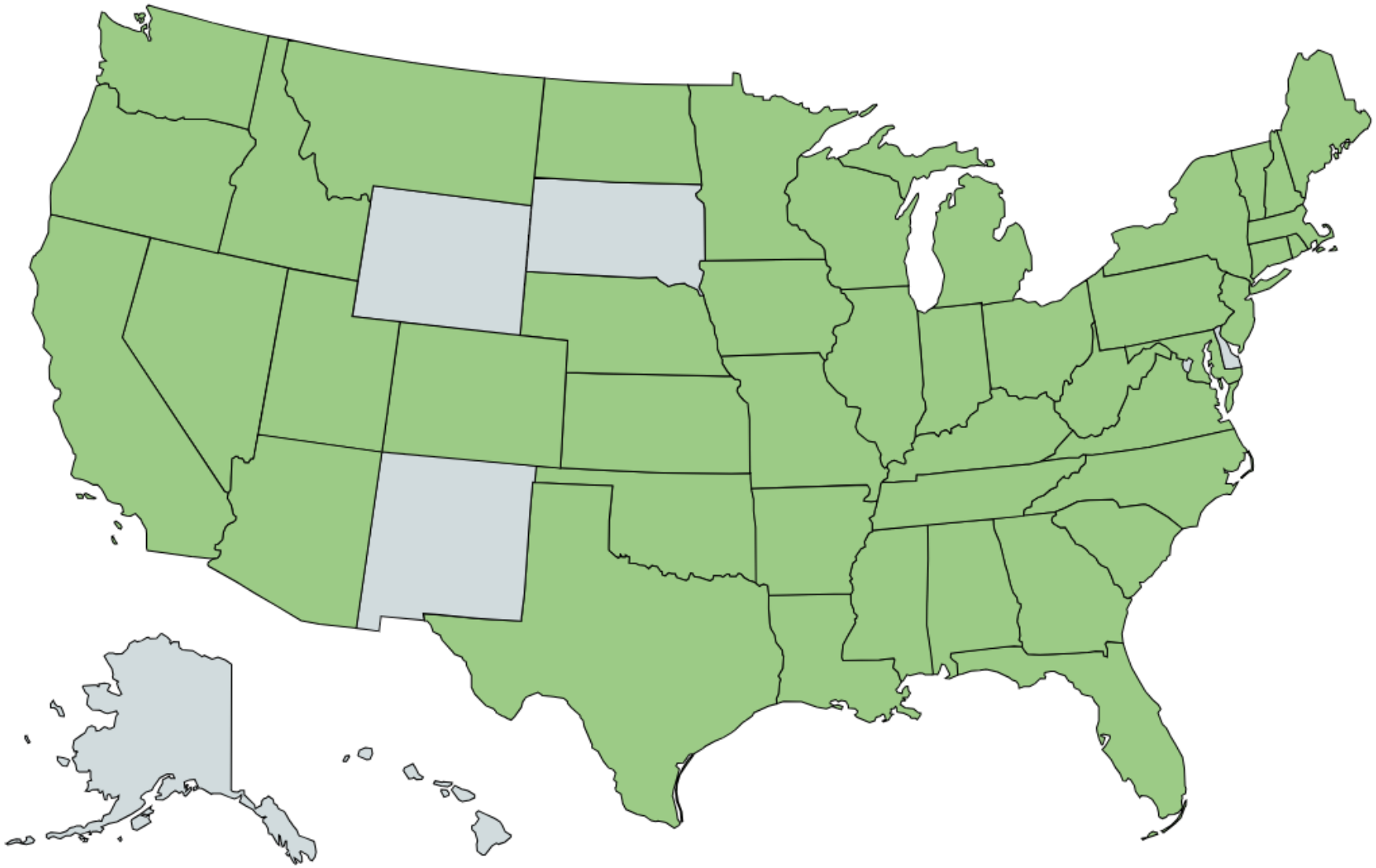
SDSR Enrollment Demographics



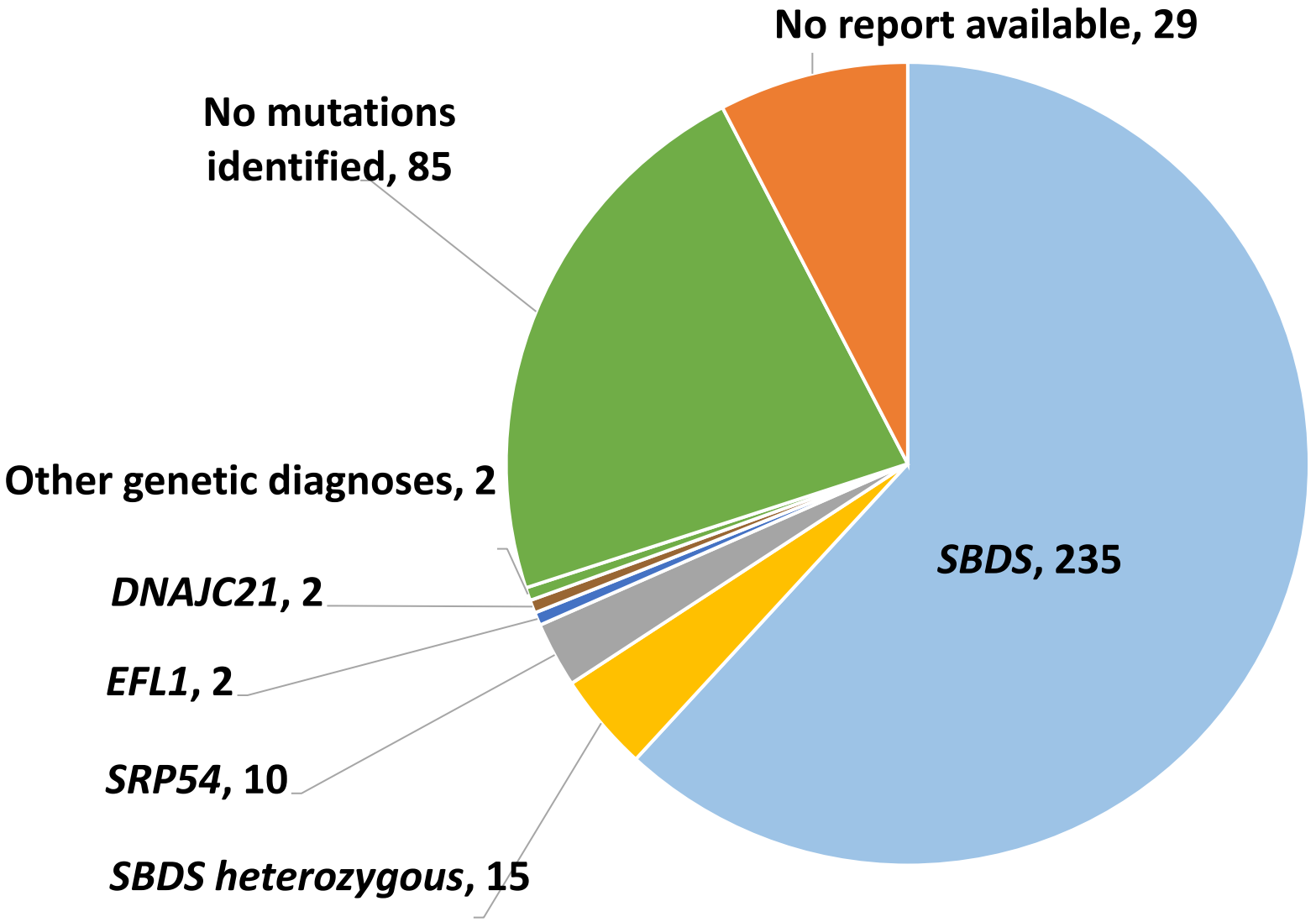


Oldest patient with *SBDS* mutations:	**52**
Youngest patient with *SBDS* mutations:	**0**
Oldest genetically-undefined patient:	**73**
Youngest genetically-undefined patient:	**2**

States represented in the SDSR



SDSR Genetics



SDS Registry Impact: Publications (partial list)

THE LANCET Haematology

nature communications

nature biomedical engineering

The JOURNAL of PEDIATRICS

SDS Registry

JCI The Journal of Clinical Investigation

Pediatric Blood & Cancer

Leukemia

blood

blood advances

JCI insight

Biology of Blood and Marrow Transplantation

Molecular Cytogenetics

Pancreas
JOURNAL OF NEUROENDOCRINE TUMORS AND PANCREATIC DISEASES AND SCIENCES

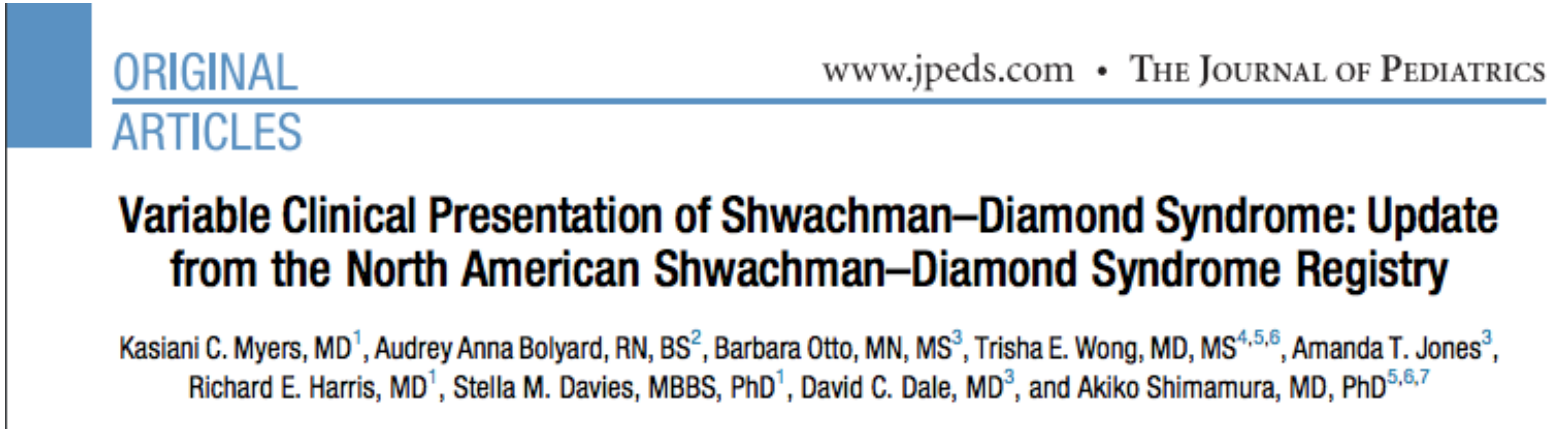
AJMG AMERICAN JOURNAL OF medical genetics

Questions that require a Registry

- What are the major health complications over the life of someone with SDS? How many people stay healthy?
- What are the chances that someone with SDS will develop severely low blood counts, MDS or AML? Do most patients eventually develop these?
- Can we predict who will develop bone marrow failure, MDS or AML?
- Can we prevent medical complications of SDS?
- Can we develop better treatments?

SDS Registry: What have we learned so far?
How does SDS present?

- Patients with SDS often lack typical symptoms of low blood counts or digestive problems
  - Why is this important?
    - Doctors willing to test more patients.
    - Patients had been unable to get insurance coverage for SDS testing if they did not fit the clinical stereotype for SDS



ORIGINAL ARTICLES

www.jpeds.com • The Journal of Pediatrics

Variable Clinical Presentation of Shwachman–Diamond Syndrome: Update from the North American Shwachman–Diamond Syndrome Registry

Kasiani C. Myers, MD[1], Audrey Anna Bolyard, RN, BS[2], Barbara Otto, MN, MS[3], Trisha E. Wong, MD, MS[4,5,6], Amanda T. Jones[3], Richard E. Harris, MD[1], Stella M. Davies, MBBS, PhD[1], David C. Dale, MD[3], and Akiko Shimamura, MD, PhD[5,6,7]

SDS Registry: What have we learned so far?
Gene Discovery

- Collaboration with Dr. Bahram
- Identified *SRP54* mutations as a cause of an SDS-Like disorder
  - Why is this important?
    - Provides diagnosis for patients who present with features of SDS and advances our understanding of these diseases.

JCI The Journal of Clinical Investigation

Mutations in signal recognition particle *SRP54* cause syndromic neutropenia with Shwachman-Diamond–like features

Raphael Carapito,[1,2,3] Martina Konantz,[4] Catherine Paillard,[1,2,5] Zhichao Miao,[6] Angélique Pichot,[1,2] Magalie S. Leduc,[7,8] Yaping Yang,[7] Katie L. Bergstrom,[9] Donald H. Mahoney,[9] Deborah L. Shardy,[9] Ghada Alsaleh,[1,2] Lydie Naegely,[1,2] Aline Kolmer,[1,2] Nicodème Paul,[1,2] Antoine Hanauer,[1,2] Véronique Rolli,[1,2,3] Joëlle S. Müller,[4] Elisa Alghisi,[4] Loïc Sauteur,[4] Cécile Macquin,[1,2] Aurore Morlon,[10] Consuelo Sebastia Sancho,[11] Patrizia Amati-Bonneau,[12,13] Vincent Procaccio,[12,13] Anne-Laure Mosca-Boidron,[14] Nathalie Marle,[14] Naël Osmani,[1] Olivier Lefebvre,[1] Jacky G. Goetz,[1] Sule Unal,[15] Nurten A. Akarsu,[16] Mirjana Radosavljevic,[1,2,3] Marie-Pierre Chenard,[17] Fanny Rialland,[18] Audrey Grain,[18] Marie-Christine Béné,[19] Marion Eveillard,[19] Marie Vincent,[20] Julien Guy,[21] Laurence Faivre,[22] Christel Thauvin-Robinet,[22] Julien Thevenon,[22] Kasiani Myers,[23] Mark D. Fleming,[24] Akiko Shimamura,[25] Elodie Bottollier-Lemallaz,[26] Eric Westhof,[6] Claudia Lengerke,[4,27] Bertrand Isidor,[20,28] and Seiamak Bahram[1,2,3]

SDS Registry: What have we learned so far?
Biology of Bone Marrow Problems

- Collaboration with Dr. Carl Novina:
- Discovered that the TGFbeta pathway is hyperactivated in the bone marrow of individuals with SDS.
  - Why is this important?
    - Drugs to inhibit the TGFbeta pathway might improve blood counts.

JCI The Journal of Clinical Investigation

TGF-β signaling underlies hematopoietic dysfunction and bone marrow failure in Shwachman-Diamond syndrome

Cailin E. Joyce,[1,2] Assieh Saadatpour,[3,4] Melisa Ruiz-Gutierrez,[5] Ozge Vargel Bolukbasi,[5] Lan Jiang,[3,4] Dolly D. Thomas,[1,2] Sarah Young,[6] Inga Hofmann,[5] Colin A. Sieff,[5] Kasiani C. Myers,[7] Jennifer Whangbo,[5] Towia A. Libermann,[2,8] Chad Nusbaum,[6] Guo-Cheng Yuan,[3,4] Akiko Shimamura,[5] and Carl D. Novina[1,2,5]

SDS Registry: What have we learned so far?
New Models of SDS to Develop Treatments

- Modeling MDS in SDS using induced pluripotent stem cells (iPS cells)
- TGFbeta pathway is increased in SDS but decreased with deletion of chromosome 7q
  - Why is this important?
    - This study identified a potential strategy to improve blood counts without promoting MDS/AML

Therapeutic discovery for marrow failure with MDS predisposition using pluripotent stem cells

Melisa Ruiz-Gutierrez,[1,2] Özge Vargel Bölükbaşı,[1] Gabriela Alexe,[1,3,4] Adriana G. Kotini,[5,6] Kaitlyn Ballotti,[1] Cailin E. Joyce,[7] David W. Russell,[8] Kimberly Stegmaier,[1,2,3] Kasiani Myers,[9] Carl D. Novina,[3,7] Eirini P. Papapetrou,[5,6,10] and Akiko Shimamura[1,2]

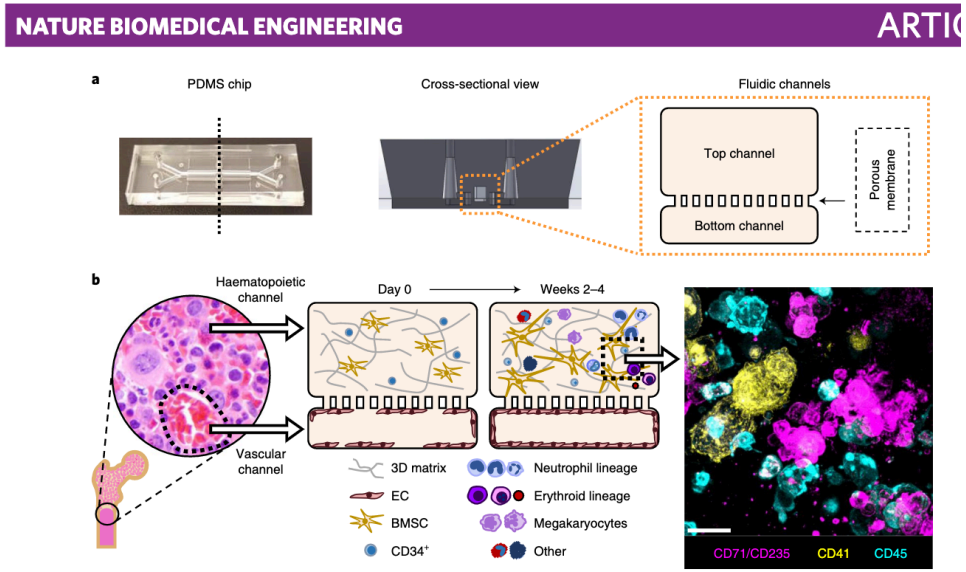
SDS Registry: What have we learned so far?
New Models of SDS to Develop Treatments

- Collaboration with Dr. Don Ingber
- Developed a “marrow on a chip” organoid model for SDS
- Why is this important:
  - Study bone marrow abnormalities in SDS
  - Preclinical model to test potential drugs to treat SDS

ARTICLES
https://doi.org/10.1038/s41551-019-0495-z
nature biomedical engineering
There are amendments to this paper

On-chip recapitulation of clinical bone marrow toxicities and patient-specific pathophysiology

David B. Chou[1,2,17], Viktoras Frismantas[1,17], Yuka Milton[1], Rhiannon David[3], Petar Pop-Damkov[4], Douglas Ferguson[4], Alexander MacDonald[5], Özge Vargel Bölükbaşı[6], Cailin E. Joyce[7,8], Liliana S. Moreira Teixeira[1], Arianna Rech[1,9], Amanda Jiang[10], Elizabeth Calamari[1], Sasan Jalili-Firoozinezhad[1,11], Brooke A. Furlong[1], Lucy R. O'Sullivan[1], Carlos F. Ng[1], Youngjae Choe[1], Susan Marquez[1], Kasiani C. Myers[12,13], Olga K. Weinberg[14], Robert P. Hasserjian[2], Richard Novak[1], Oren Levy[1], Rachelle Prantil-Baun[1], Carl D. Novina[7,8,15], Akiko Shimamura[6], Lorna Ewart[3] and Donald E. Ingber[1,10,16]*



SDS Registry: What have we learned so far?
Understanding Blood complications

- Severe bone marrow failure requiring transplant generally develops in younger patients with SDS
- Patients with SDS are at risk for developing blood cancer: MDS/AML
- Risk of MDS/AML increases with age but young children can develop MDS/AML
- Standard treatments for leukemia either don't work or are too toxic for patients with SDS
- MDS/AML is leading cause of mortality (80%) in SDS

blood advances

SDSR Shwachman-Diamond Syndrome Registry

Hematologic complications with age in Shwachman-Diamond syndrome

Elissa Furutani,[1] Shanshan Liu,[2] Ashley Galvin,[3] Sarah Steltz,[2] Maggie M. Malsch,[3] Sara K. Loveless,[4,5] Leann Mount,[4,5] Jordan H. Larson,[3] Kelan Queenan,[3] Alison A. Bertuch,[6] Mark D. Fleming,[7] John M. Gansner,[8] Amy E. Geddis,[9] Rabi Hanna,[10] Sioban B. Keel,[11] Bonnie W. Lau,[12] Jeffrey M. Lipton,[13] Robert Lorsbach,[4,5] Taizo A. Nakano,[14] Adrianna Vlachos,[13] Winfred C. Wang,[15] Stella M. Davies,[4,5] Edie Weller,[2] Kasiani C. Myers,[4,5,*] and Akiko Shimamura[1,*]

THE LANCET Haematology

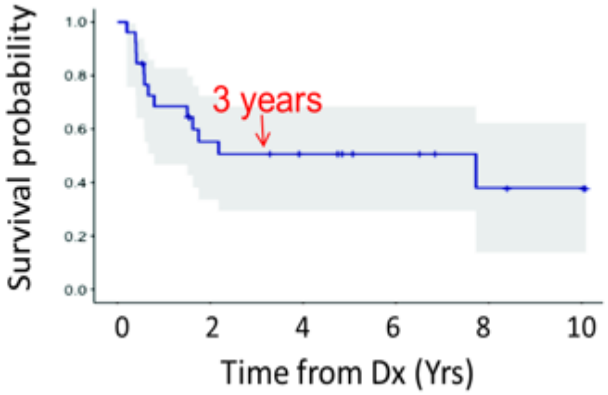
Clinical features and outcomes of patients with Shwachman-Diamond syndrome and myelodysplastic syndrome or acute myeloid leukaemia: a multicentre, retrospective, cohort study

Kasiani C Myers, Elissa Furutani*, Edie Weller, Bradford Siegele, Ashley Galvin, Valerie Arsenault, Blanche P Alter, Farid Boulad, Carlos Bueso-Ramos, Lauri Burroughs, Paul Castillo, James Connelly, Stella M Davies, Courtney D DiNardo, Iftikhar Hanif, Richard H Ho, Nicole Karras, Michelle Manalang, Lisa J McReynolds, Taizo A Nakano, Grzegorz Nalepa, Maxim Norkin, Matthew J Oberley, Etan Orgel, Yves D Pastore, Joseph Rosenthal, Kelly Walkovich, Jordan Larson, Maggie Malsch, M Tarek Elghetany, Mark D Fleming, Akiko Shimamura*

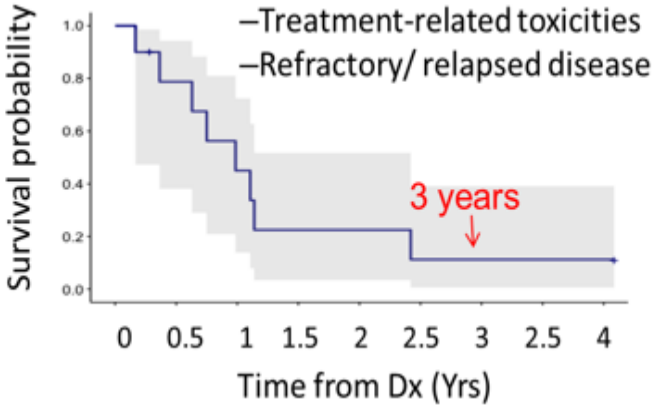
SDS Registry led International Collaboration: What have we learned so far?

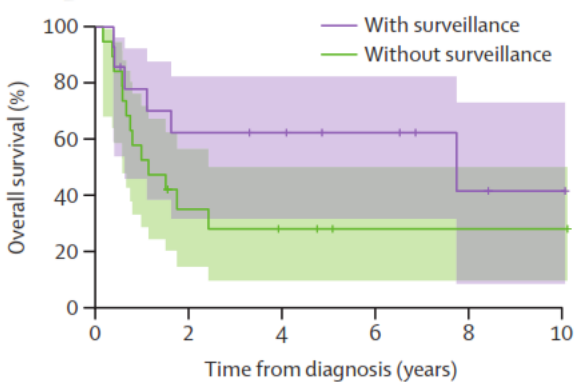
Understanding outcomes of MDS/AML

MDS



AML





MDS:
Median survival 7.7 years
3 years OS: 51% n=26

AML:
Median survival 0.99 years
3 years OS: 11% n=10

3 year overall survival 28% vs 62% in those with surveillance compared to those without

Clinical features and outcomes of patients with Shwachman-Diamond syndrome and myelodysplastic syndrome or acute myeloid leukaemia: a multicentre, retrospective, cohort study

THE LANCET Haematology

Kasiani C Myers*, Elissa Furutani*, Edie Weller, Bradford Siegele, Ashley Galvin, Valerie Arsenault, Blanche P Alter, Farid Boulad, Carlos Bueso-Ramos, Lauri Burroughs, Paul Castillo, James Connelly, Stella M Davies, Courtney D DiNardo, Iftikhar Hanif, Richard H Ho, Nicole Karras, Michelle Manalang, Lisa J McReynolds, Taizo A Nakano, Grzegorz Nalepa, Maxim Norkin, Matthew J Oberley, Etan Orgel, Yves D Pastore, Joseph Rosenthal, Kelly Walkovich, Jordan Larson, Maggie Malsch, M Tarek Elghetany, Mark D Fleming, Akiko Shimamura

SDSR
Shwachman-Diamond Syndrome Registry

SDS Registry: What have we learned so far?
Understanding the Development of MDS/AML

- Collaboration with Dr. Daniel Link
- Discovered that *TP53* mutations frequently developed in individuals with SDS at an early age
  - Why is this important?
    - This study was the beginning of efforts to understand why people with SDS are at increased risk to develop bone marrow failure and leukemia.
    - But: unknown significance of *TP53* mutations

blood
Regular Article

HEMATOPOIESIS AND STEM CELLS

Somatic mutations and clonal hematopoiesis in congenital neutropenia

Jun Xia,[1] Christopher A. Miller,[1,2] Jack Baty,[3] Amrita Ramesh,[1] Matthew R. M. Jotte,[1] Robert S. Fulton,[2] Tiphanie P. Vogel,[4] Megan A. Cooper,[5] Kelly J. Walkovich,[6] Vahagn Makaryan,[7] Audrey A. Bolyard,[7] Mary C. Dinauer,[8] David B. Wilson,[8] Adrianna Vlachos,[9] Kasiani C. Myers,[10] Robert J. Rothbaum,[11] Alison A. Bertuch,[12] David C. Dale,[7] Akiko Shimamura,[13] Laurence A. Boxer,[6] and Daniel C. Link[1]

SDS Registry: What have we learned so far?
Understanding the Development of MDS/AML

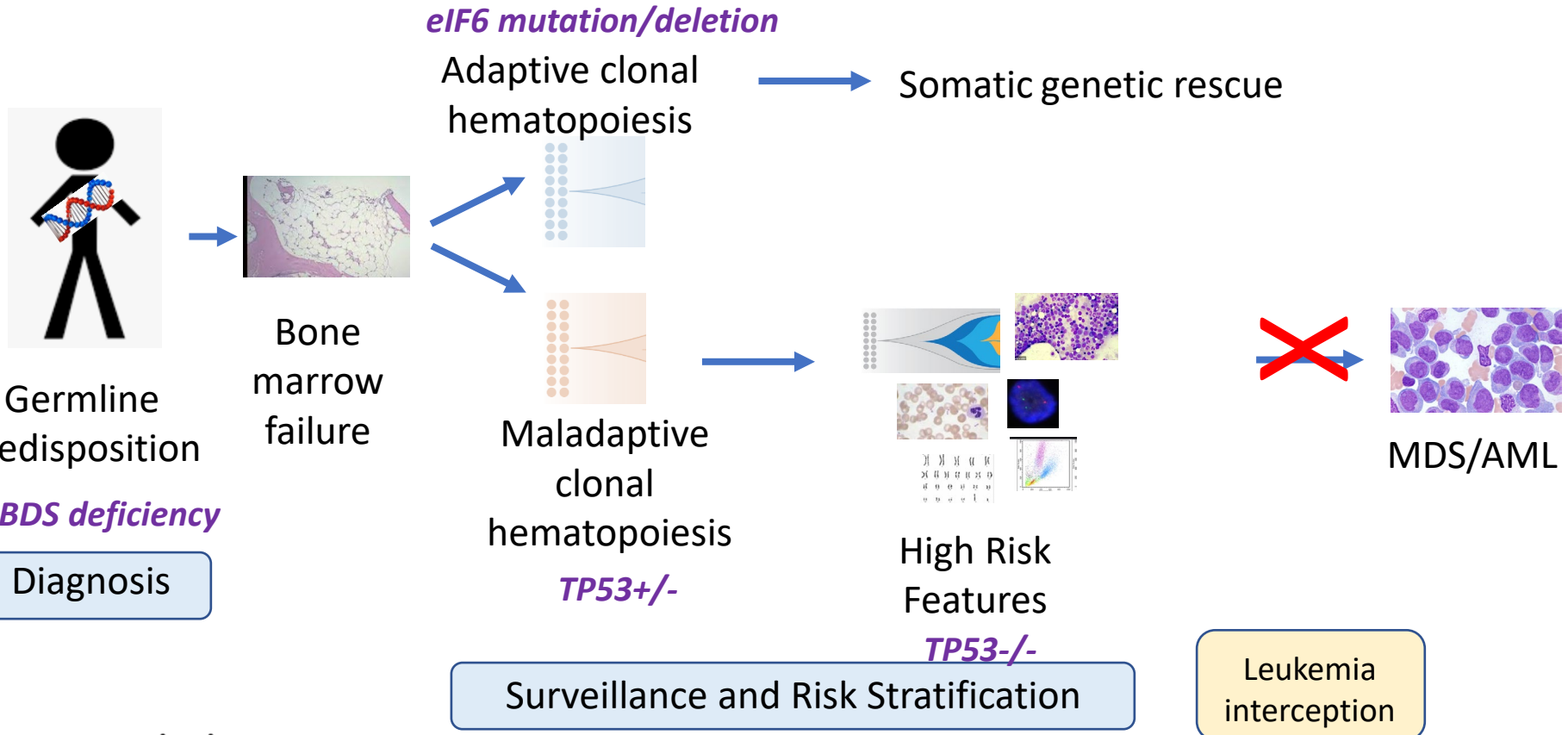
- Collaboration with Dr. Coleman Lindsley (with Dr. Alyssa Kennedy)
- Identified genomic signatures associated with MDS and leukemia using *single cell sequencing*
  - Why is this important?
    - Method to identify patients at high risk of MDS or AML to allow early transplant when survival is high
    - Lead to recommendation to add NGS and LOH microarray testing added to surveillance marrow

nature communications

Distinct genetic pathways define pre-leukemic and compensatory clonal hematopoiesis in Shwachman-Diamond syndrome

Alyssa L. Kennedy, Kasiani C. Myers, James Bowman, Christopher J. Gibson, Nicholas D. Camarda, Elissa Furutani, Gwen M. Muscato, Robert H. Klein, Kaitlyn Ballotti, Shanshan Liu, Chad E. Harris, Ashley Galvin, Maggie Malsch, David Dale, John M. Gansner, Taizo A. Nakano, Alison Bertuch, Adrianna Vlachos, Jeffrey M. Lipton, Paul Castillo, James Connelly, Jane Churpek, John R. Edward, Nobuko Hijiya, Richard H. Ho, Inga Hofmann, James N. Huang, Siobán Keel, Adam Lamble, Bonnie W. Lau, Maxim Norkin, Elliot Stieglitz, Wendy Stock, Kelly Walkovich, Steffen Boettcher, Christian Brendel, Mark D. Fleming, Stella M. Davies, Edie A. Weller, Christopher Bahl, Scott L. Carter, Akiko Shimamura, R. Coleman Lindsley

SDSR: Surveillance→High risk disease identification



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- Why is this important?
  - Method to identify patients at high risk of MDS or AML to allow early transplant when survival is high

SDS Registry: What have we learned so far?
Clinical problems in SDS

- Characterized heart abnormalities in SDS
  - Why is this important?
    - Many medical treatments (such as chemotherapy or bone marrow transplant) are associated with an increased risk of heart complications. This study found that a new method (cardiac strain) of looking at heart function identified abnormalities missed on standard testing.

Pediatric Blood & Cancer · 2015;62:1228–1231

Abnormal Circumferential Strain Measured by Echocardiography Is Present in Patients With Shwachman–Diamond Syndrome Despite Normal Shortening Fraction

Thomas D. Ryan, MD, PhD,[1]* John L. Jefferies, MD, MPH,[1] Clifford Chin, MD,[1] Joshua J. Sticka, MD,[1] Michael D. Taylor, MD, PhD,[1] Richard Harris, MD,[2] Joan Moore, RN,[2] Erica Goodridge, RN,[2] Leann Mount, RN,[2] Audrey A. Bolyard, RN,[3] Barbara Otto, MN, MS,[4] Amanda Jones, BA,[4] Akiko Shimamura, MD, PhD,[5,6,7,8] Stella Davies, MBBS, PhD,[2] and Kasiani Myers, MD[2]

SDS Registry: What have we learned so far?
New Clinical Problems in SDS

- With young investigator Dr. Elissa Furutani
- Identified inflammatory complications in SDS patients
- Why is this important:
  - Raise awareness of this complication and treatments
  - Insights into the biology of SDS, with potential implications for medical management

Received: 20 December 2019 | Revised: 20 March 2020 | Accepted: 24 March 2020
DOI: 10.1002/ajmg.a.61593

Check for updates

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A WILEY

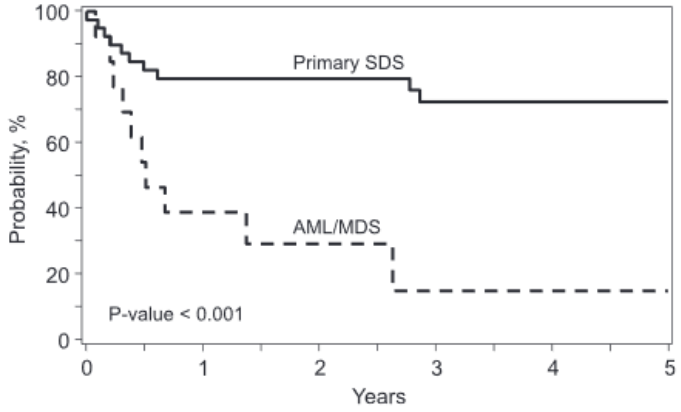
Inflammatory manifestations in patients with Shwachman–Diamond syndrome: A novel phenotype

Elissa Furutani[1] | Ankoor S. Shah[2] | Yongdong Zhao[3] | David Andorsky[4] | Fatma Dedeoglu[5] | Amy Geddis[6] | Yu Zhou[1] | Towia A. Libermann[7] | Kasiani C. Myers[8,9] | Akiko Shimamura[1]

SDS Registry: Additional Published Collaborations

- Cell polarity in SDS (Dr. Geiger) – *published initial studies demonstrating abnormal structure of stem cells in SDS*
- HSCT in SDS (Dr. Myers and the CIBMTR)

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH



- Transplant outcomes have improved for patients with SDS and BMF
- We have more work to do for our patients with MDS/AML

Biology of Blood and Marrow Transplantation
journal homepage: www.bbmt.org

Pediatric

Hematopoietic Stem Cell Transplantation for Shwachman-Diamond Syndrome

Kasiani Myers[1], Kyle Hebert[2], Joseph Antin[3], Farid Boulad[4], Lauri Burroughs[5], Inga Hofmann[6], Rammurti Kamble[7], Margaret L. MacMillan[8], Mary Eapen[2,*]

- Chromosomal changes in SDS (Dr. Valli &Italian registry)
- COVID19 in SDS (Dr. Galetta)

The SDS Registry recruits world-class experts to work together

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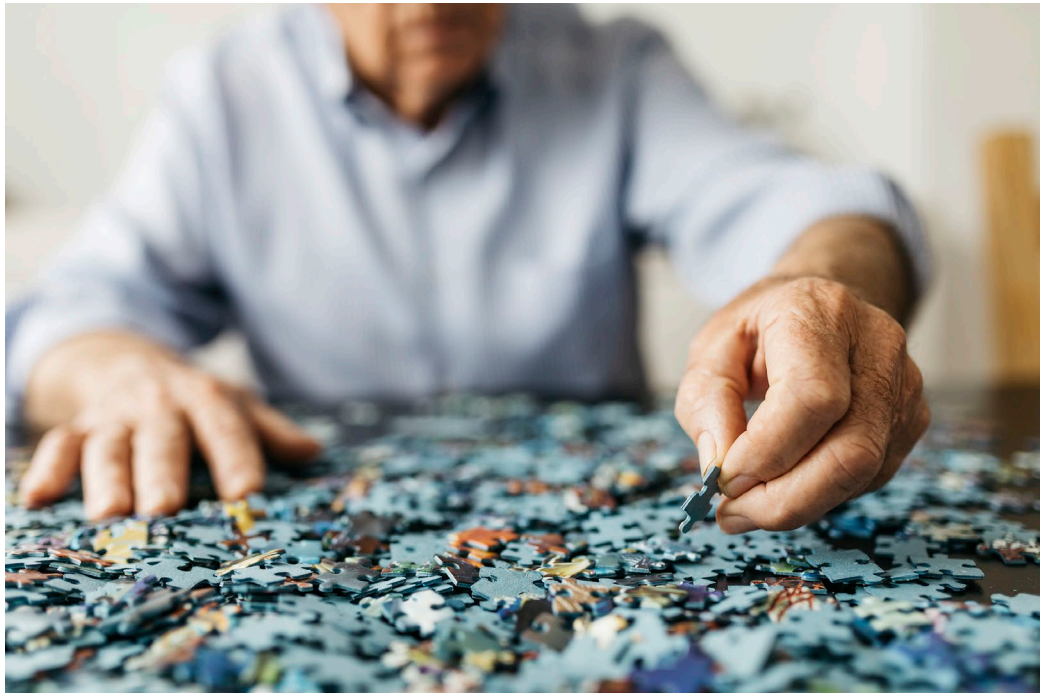
- Collaboration
- Innovation
- Success



Some SDS Registry Ongoing Projects/Collaborations

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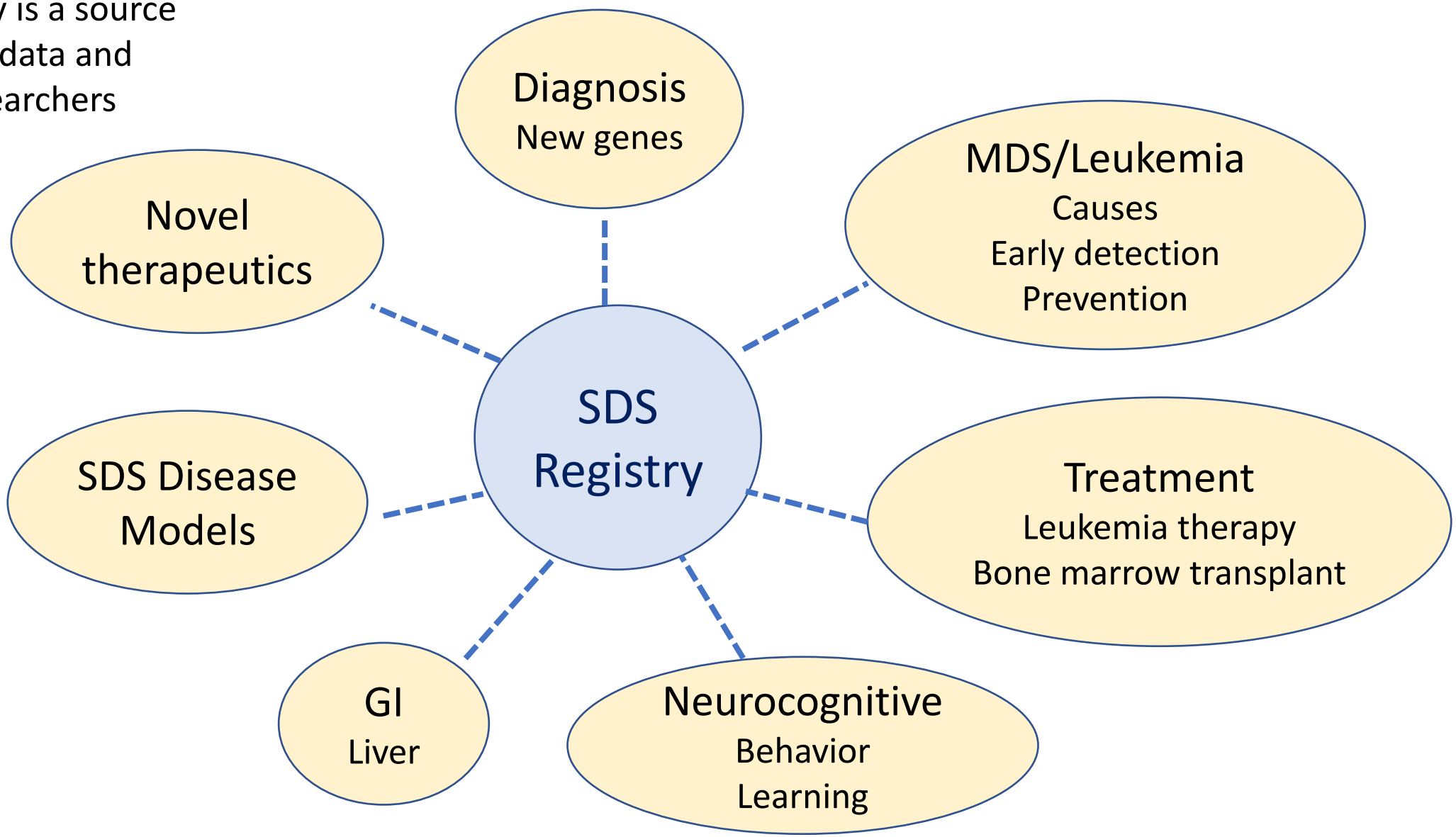
The SDS Registry is a source of de-identified data and samples for researchers internationally



SDS Registry Impact: Grant funding (partial list)

National Institute of Diabetes and Digestive and Kidney Diseases

National Heart, Lung, and Blood Institute

National Institute of Allergy and Infectious Diseases

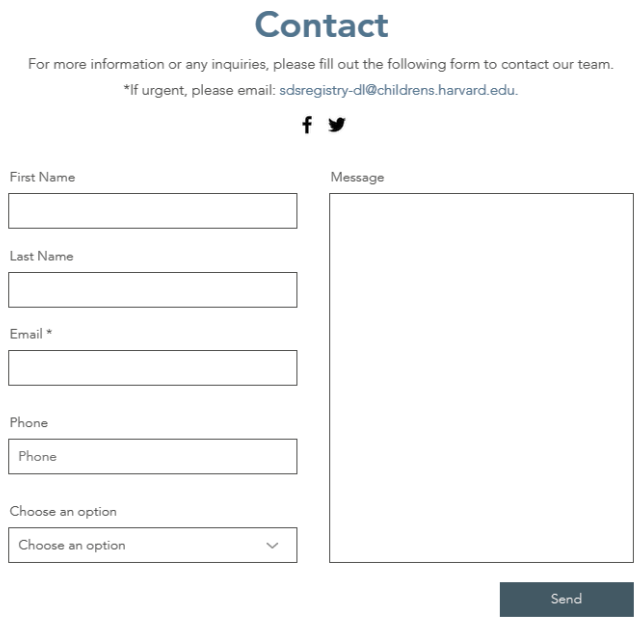
LEUKEMIA & LYMPHOMA SOCIETY®

St. Baldrick's FOUNDATION | CONQUER KIDS' CANCER

EvansMDS
A funding initiative of
The Edward P. Evans Foundation

The SDSR is a resource for patients/families/medical providers

website: sdsregistry.org



Twitter
@SDSregistry

Facebook
@SDSregistry

SDSR Family Day

Newsletters

Email
SDSRegistry-dl@childrens.harvard.edu

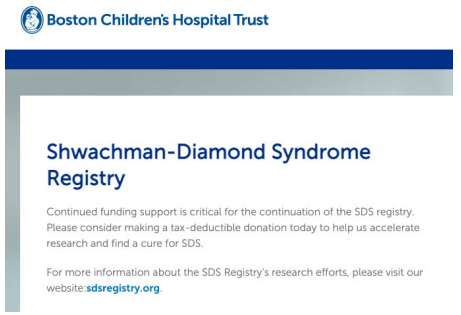
SDS Registry Board

zoom

SDS Registry Impact: Conference Presentations (partial list)

FAQ: “How can I help?”

- Participate in the SDS Registry
  - Send samples of blood and marrow every year
  - Share medical records (annually): clinic notes, marrow reports, blood counts
- Get the word out about the SDS Registry
  - The SDSR is a resource for questions from patients, families, and medical providers
- Donate to support SDS Registry research
  - sdsregistry.org



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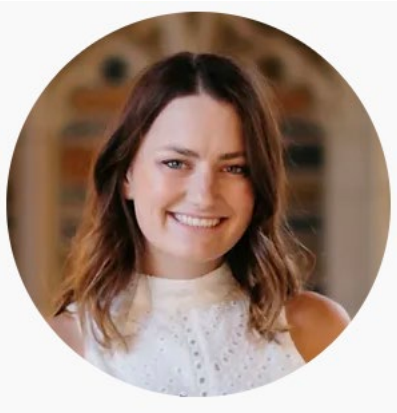
SDS Registry Study Team Camp Sunshine

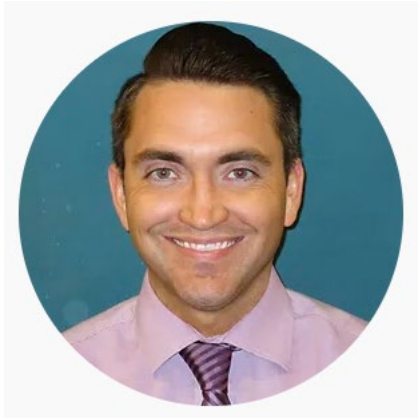
Karyn Brundige
Research nurse

Sara Loveless
Research nurse



Greta Joos
Research Assistant

Katie Coyne
Research Assistant



Dr. Chris Reilly
Adult Hematology/Oncology

Dr. Jane Koo
Pediatric Hematology/Oncology

Dr. Helen Reed
Pediatric Hematology/Oncology

Maggie Malsch
Research nurse manager

Patients
Families
Physicians
Researchers

Together we can find a cure for SDS

Donors

Special thanks to all participants who have contributed records and samples year after year!

The 11th International Congress on Shwachman Diamond Syndrome

Cincinnati, OH
June 5th-8th, 2025