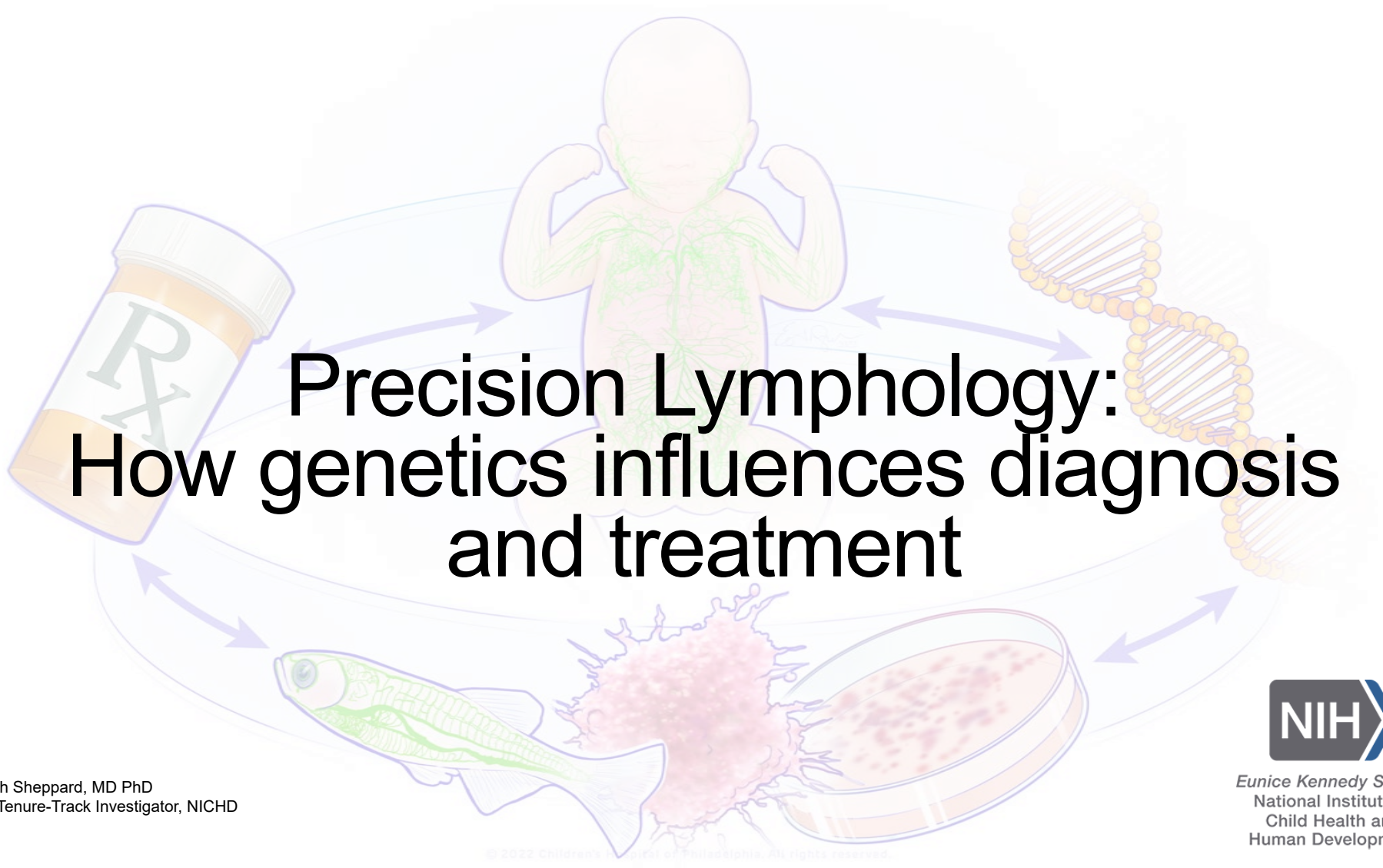
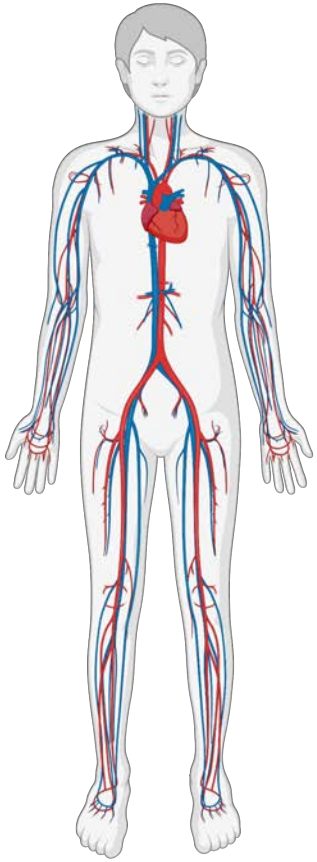


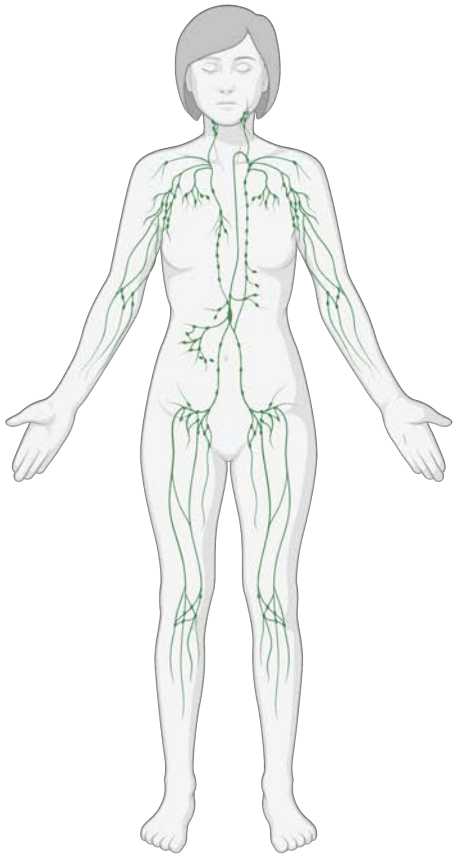
Precision Lymphology: How genetics influences diagnosis and treatment

Dr. Sarah Sheppard, MD PhD
Clinical Tenure-Track Investigator, NICHD

NIH
Eunice Kennedy Shriver
National Institute of
Child Health and
Human Development

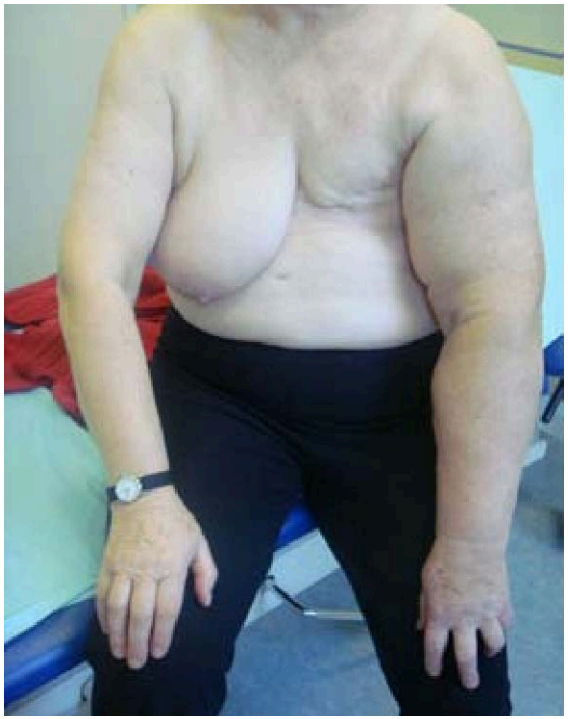
Circulatory and lymphatic systems



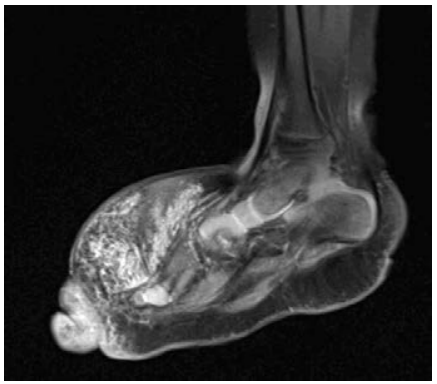


Created with BioRender.com

Lymphatic dysfunction is costly for Americans

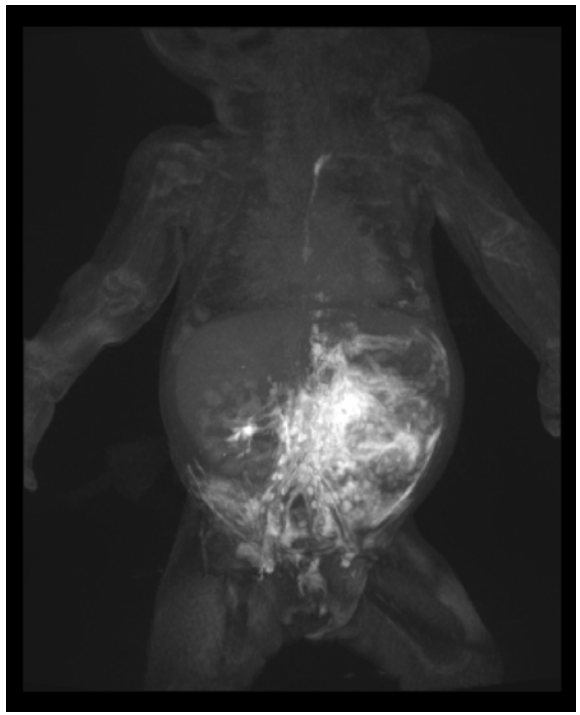


Acquired lymphedema
1:1000





Lymphatic malformations



Central conducting lymphatic anomaly
1:5000



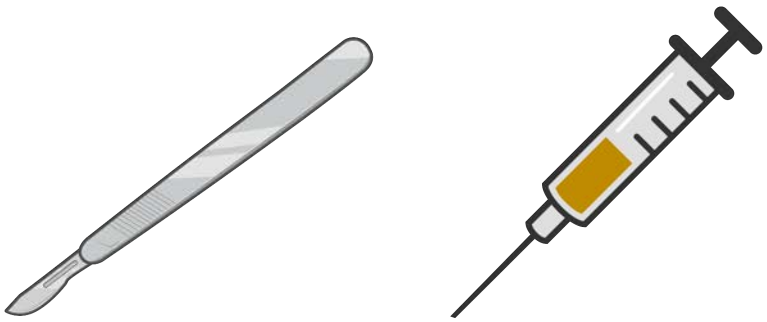
Primary lymphedema
1:100,000

Estimated cost: > $40 B/year

Financial impact courtesy of Dr. Steele/ARPA-H; Rucigai et al, *Acta Derm Croa* 2015; Nriagu…Sheppard, *AJMG Part A* 2024

Limited treatments are mostly symptomatic

Interventional



Medical



Created with BioRender.com

Current limitations to diagnosis and treatment



- **Natural history**

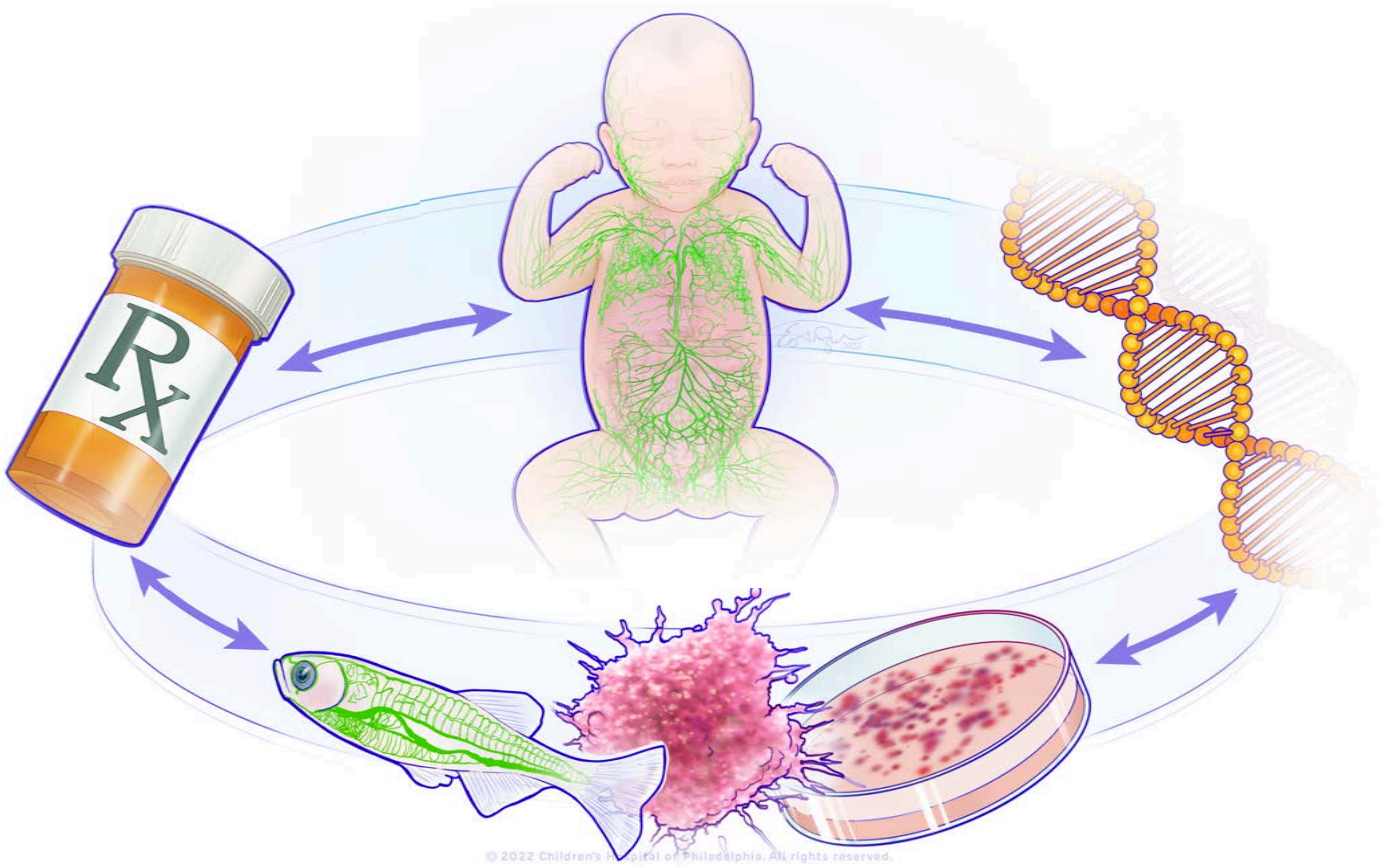


- **Molecular pathogenesis**



- **Treatments targeting the underlying cause**

Bedside to bench and back program for lymphatic anomalies



Intra-institute collaborations facilitates discovery

NIH Clinical Center

NIH NATIONAL CANCER INSTITUTE



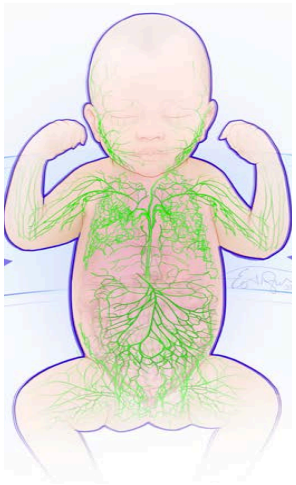


NIH National Institute of Allergy and Infectious Diseases



Photos courtesy of participant family, Burgess lab website

Natural history study improves diagnosis



Phenotypes



Genotypes

- Definition of the disease?
- Evolution over time?
- Monitoring disease progression and therapy response?

NCT:05731141
IRB: 001084

Lymphatic disease presents and causes disability throughout the lifespan







Non-immune hydrops fetalis



Chylothorax



Generalized lymphatic dysplasia



Primary lymphedema

https://fetus.ucsf.edu/hydrops-fetalis/; Li*, Sheppard* et al, *Nature Medicine* 2023; Sheppard lab, unpublished, biorender.com

NCT:05731141; NIH PI Sheppard

NICHD_LymphaticAnoma@mail.nih.gov

Natural history study facilitates discovery of novel phenotypes and genotypes











Andrea Bowling, DNP

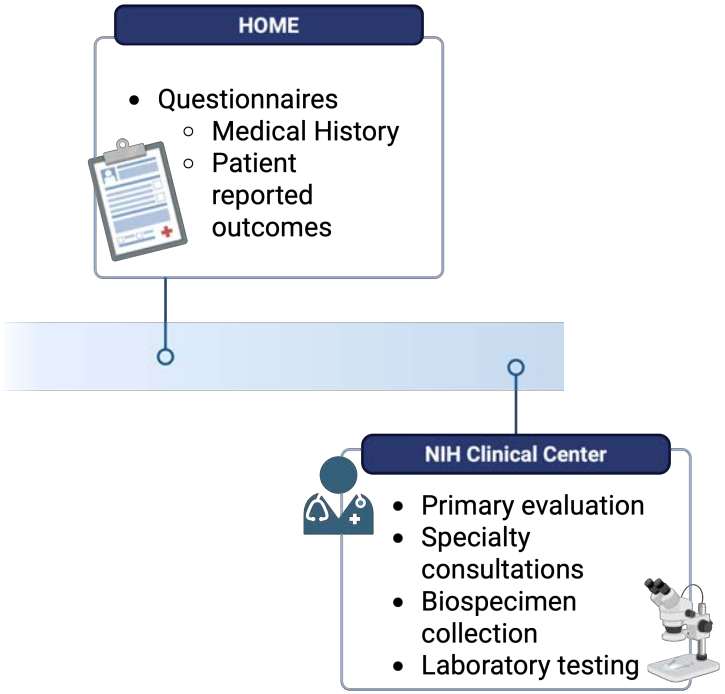


Deena Zeltser, MD

NCT:05731141; NIH PI Sheppard
NICHD_LymphaticAnoma@mail.nih.gov
Biorender.com

Natural history study facilitates discovery of novel phenotypes and genotypes





NCT:05731141

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Joan Elliott DPT
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Leslie Bardin

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NIDCR
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Iris Hartley, M.D.

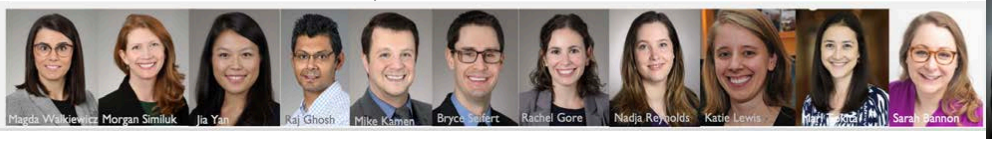
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Kelli Karacki, PA-C

NIAID Centralized Sequencing Program
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Karen Baker CRNP



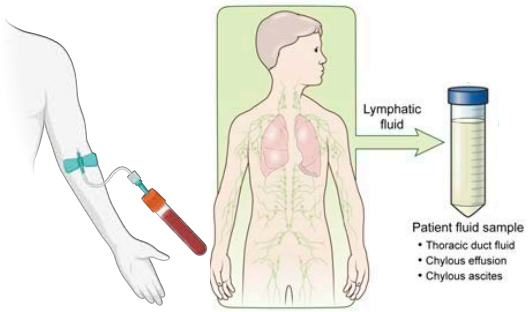




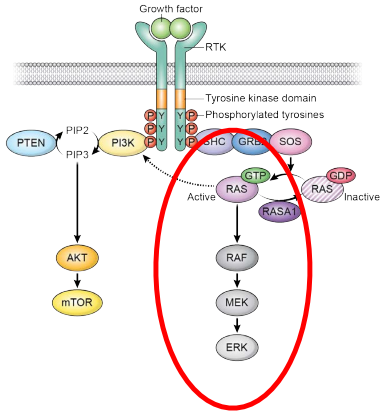


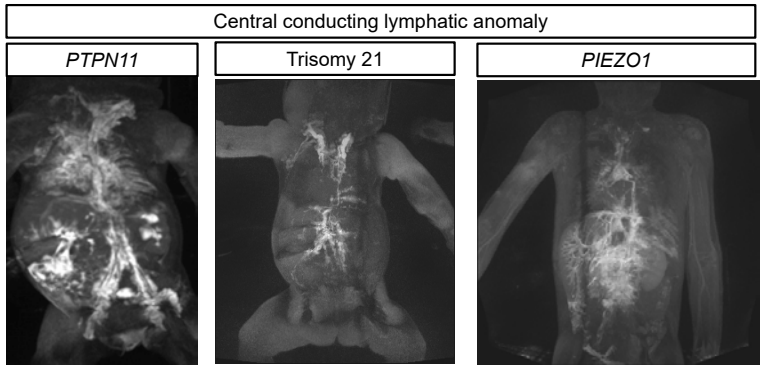


Improved Genetic Diagnosis



Cell free DNA





- Developed non-invasive diagnostics
- 22 new genetic causes
- Distinct central lymphatics

Foster…**Sheppard**…et al, *EMBO Mol Med* 2020, Li*,**Sheppard*** et al, *Clin Genet* 2021; Byrne…**Sheppard**…Harvey et al, *Sci Trans Med* 2022; Liu…**Sheppard**, *EJHG* 2022; **Sheppard** et al *JCI Insight* 2023; Li*,**Sheppard*** et al, *Nat Med* 2023

Families want more resources!

1. Lack of literature about prenatal vascular malformations
2. Support groups that exist do not fit everyone

Shukla…Sheppard, *AJMG Part A* 2024, Bowling et al, submitted

A prenatal support guide for parents











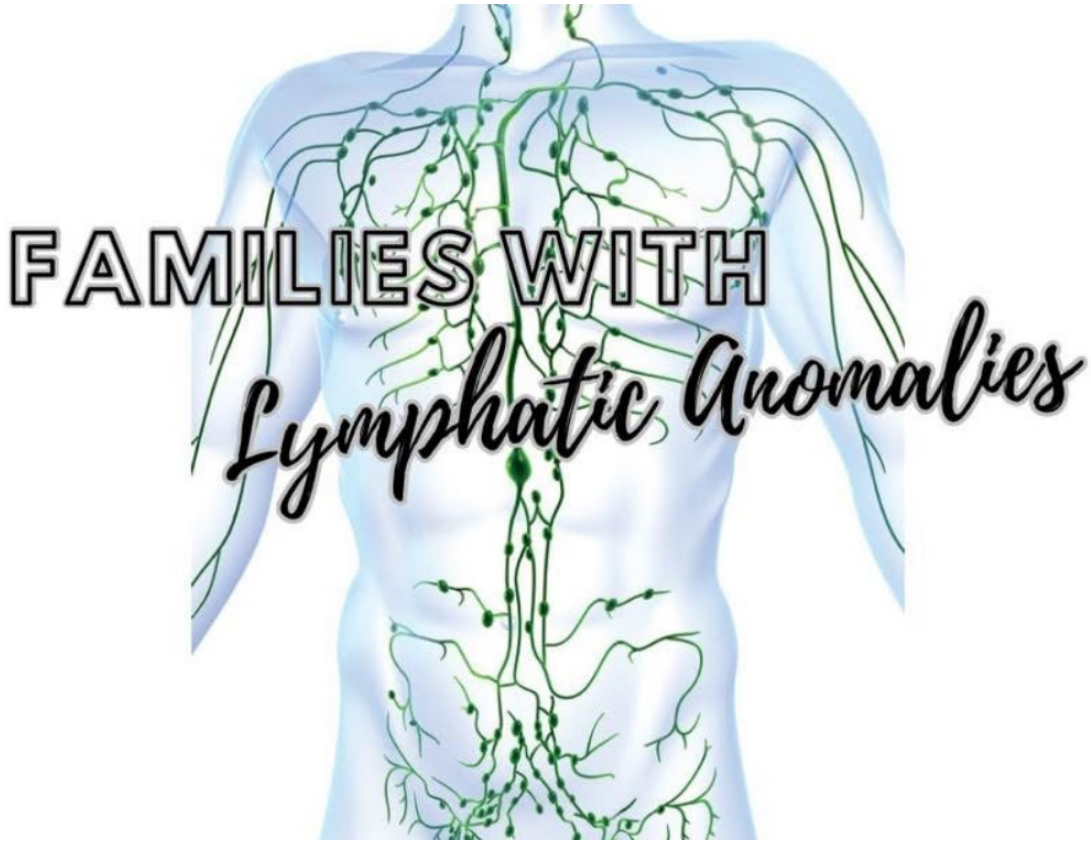






Shukla…Sheppard, *AJMG Part A* 2024; In collaboration with CMTC-OVM

A virtual support group inspires mothers to start their own

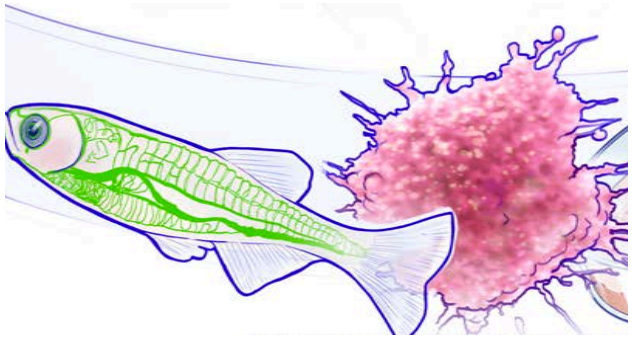




Andrea Bowling, DNP

Bowling…Sheppard, *submitted; Graphic courtesy of SK*

Zebrafish models improve understanding of molecular pathogenesis and facilitate therapy identification

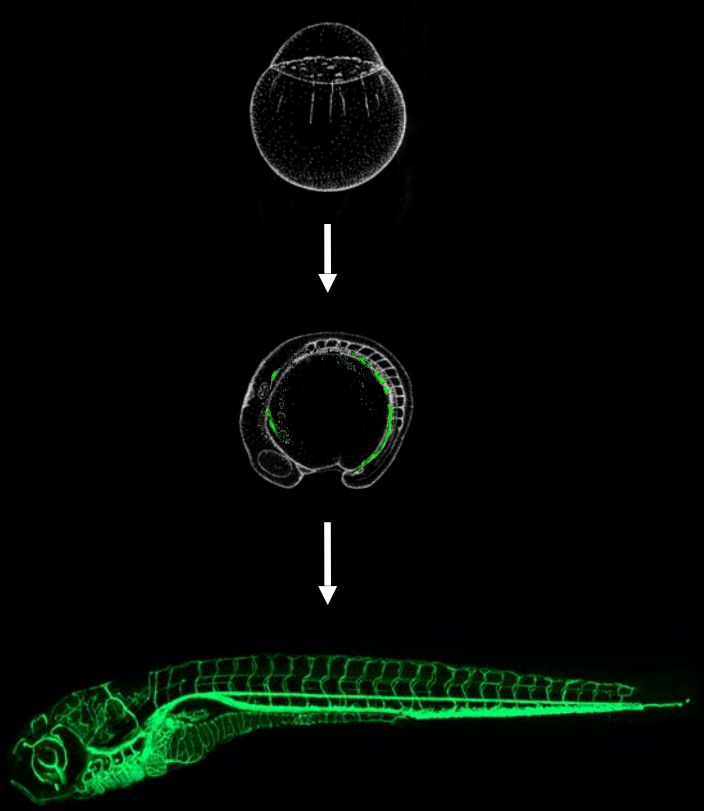


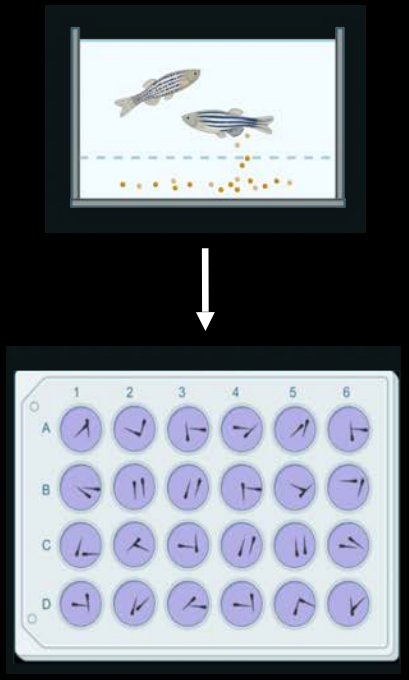
Models & Mechanisms



Drug Development

Benefits of the zebrafish model

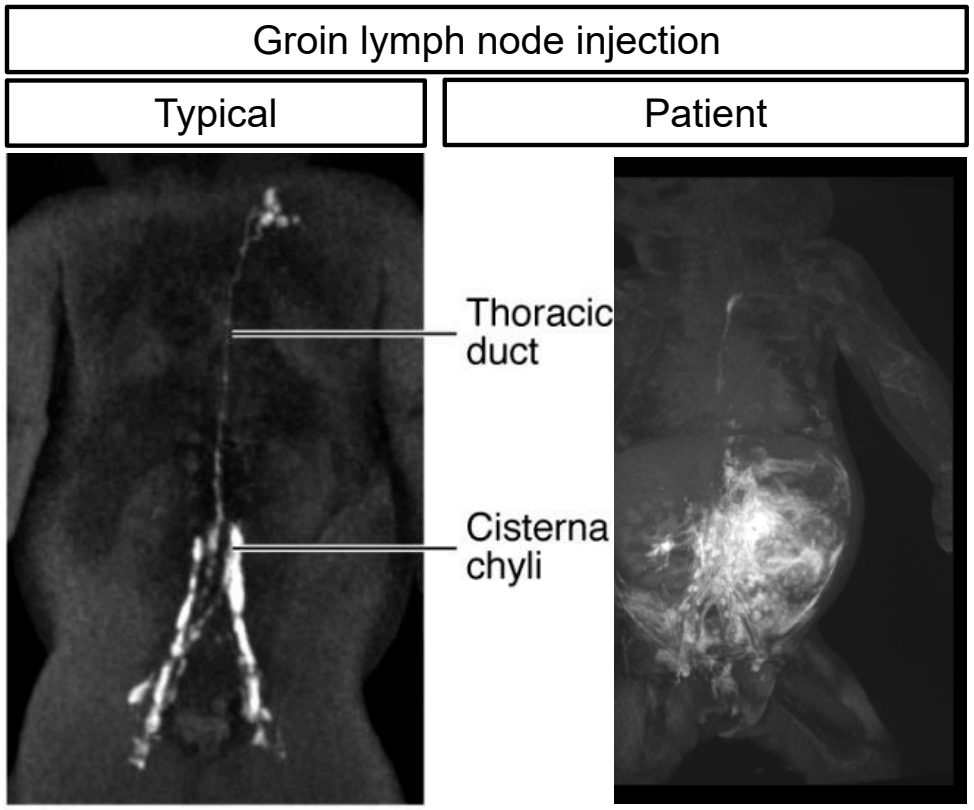




Slide modified from Nathan Lawson

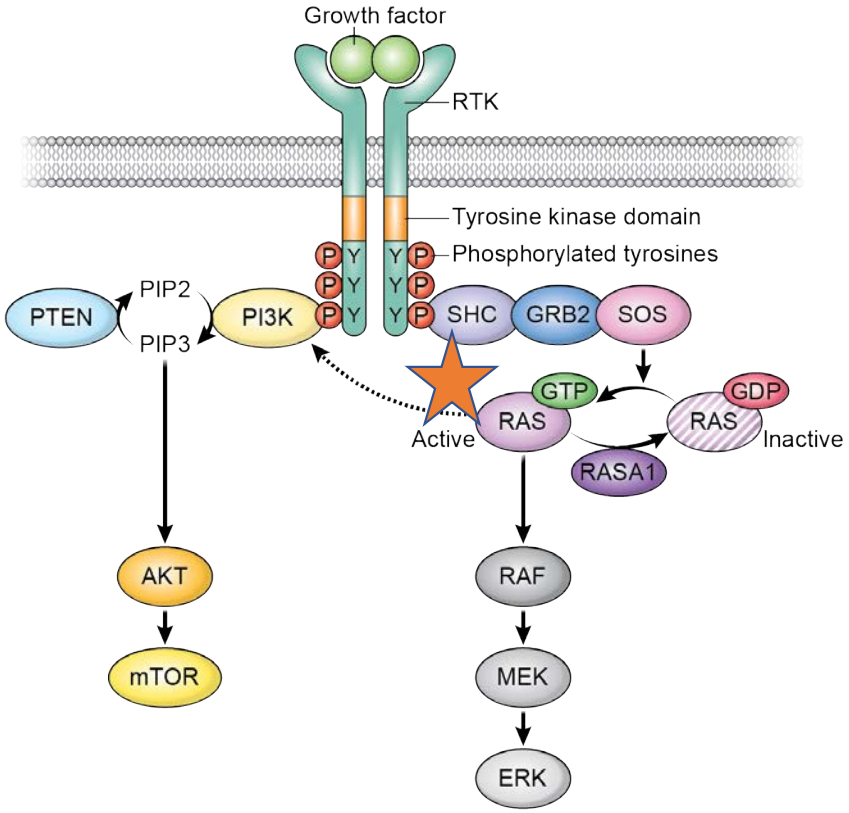
KRAS causes central conducting lymphatic anomaly





Sheppard et al, *JCI Insight* 2023; Garlisi Torales…Sheppard *JCI* 2024

Mosaic *KRAS* pathogenic variant identified

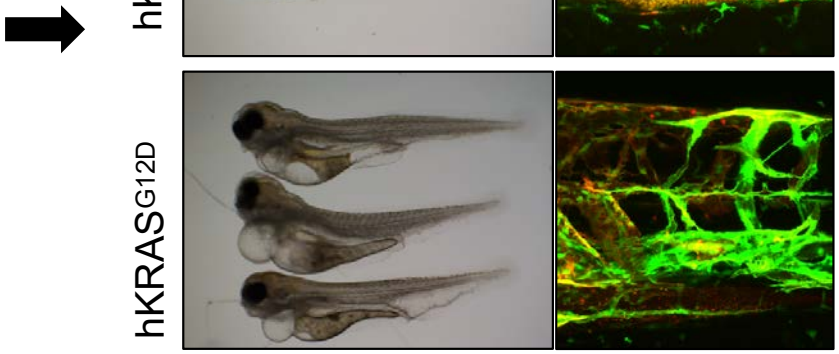


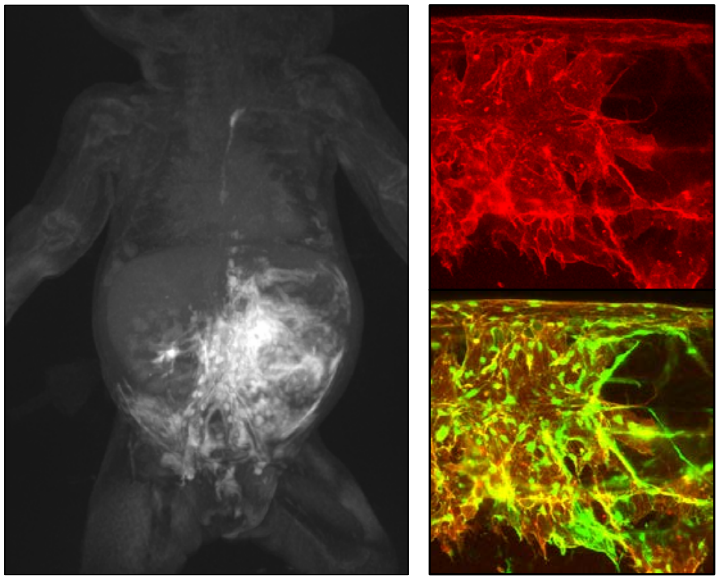
Zebrafish model for *KRAS*-related CCLA

mrc1a:wt-hKRAS
mrc1a:hKRAS p.G12D



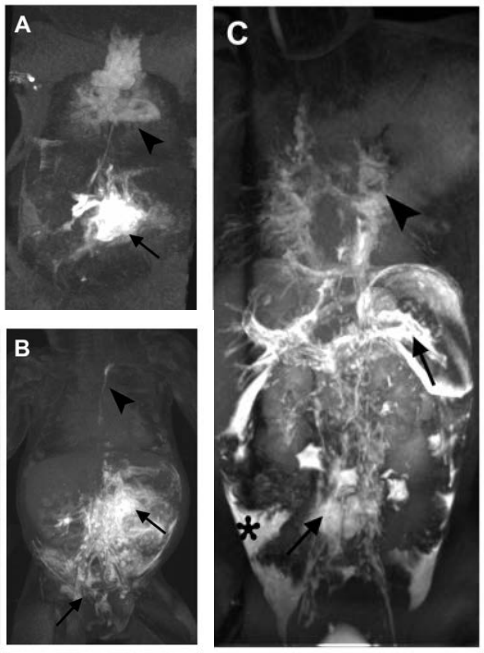
mrc1a-GFP

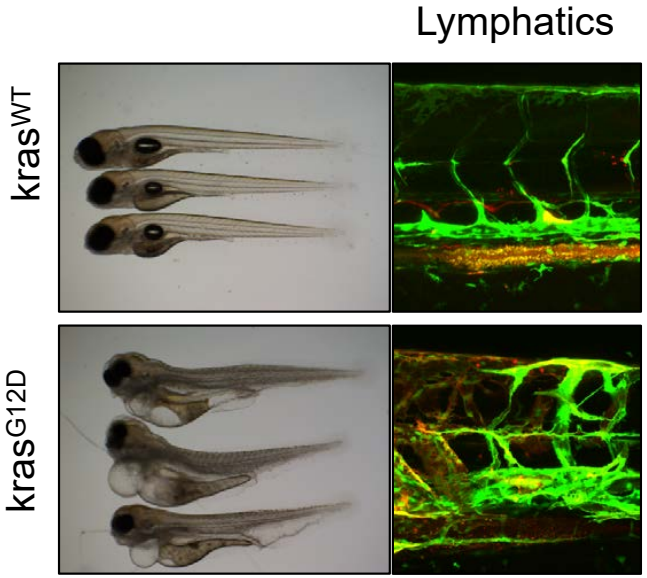


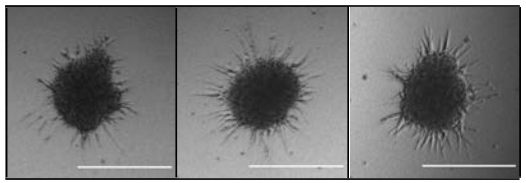


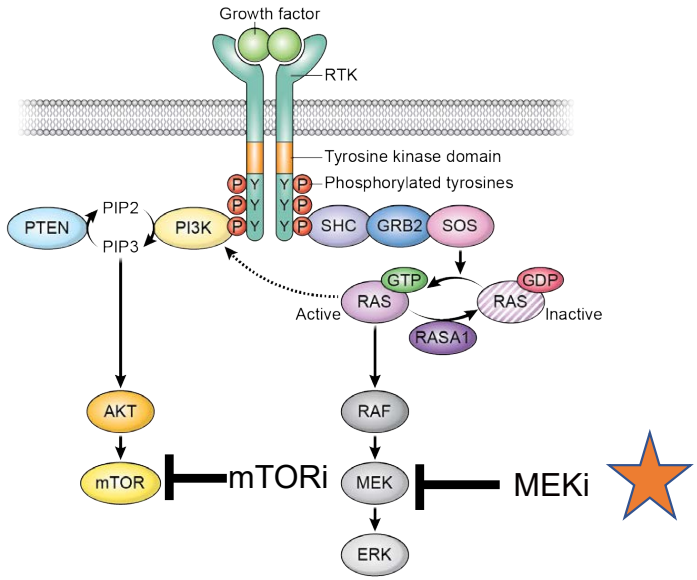
Sheppard SE et al, *JCI Insight* 2023

MEK inhibitors are efficacious for *KRAS*-related lymphatic anomalies



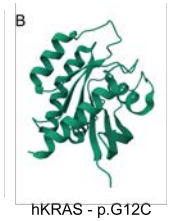


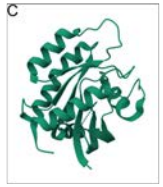




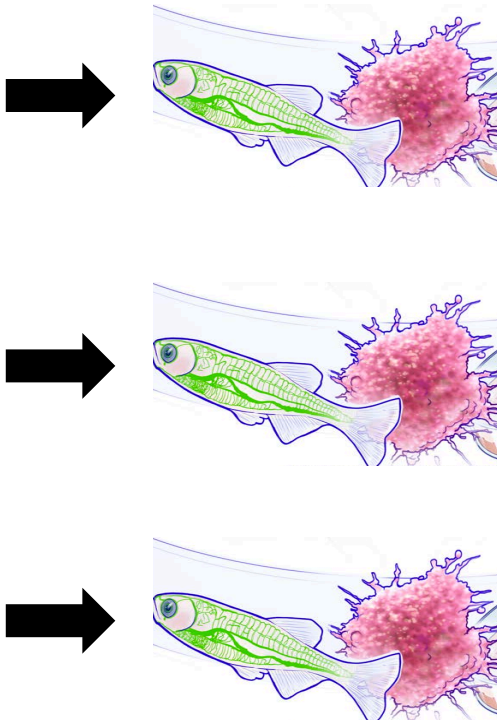
Sheppard SE et al, *JCI Insight* 2023

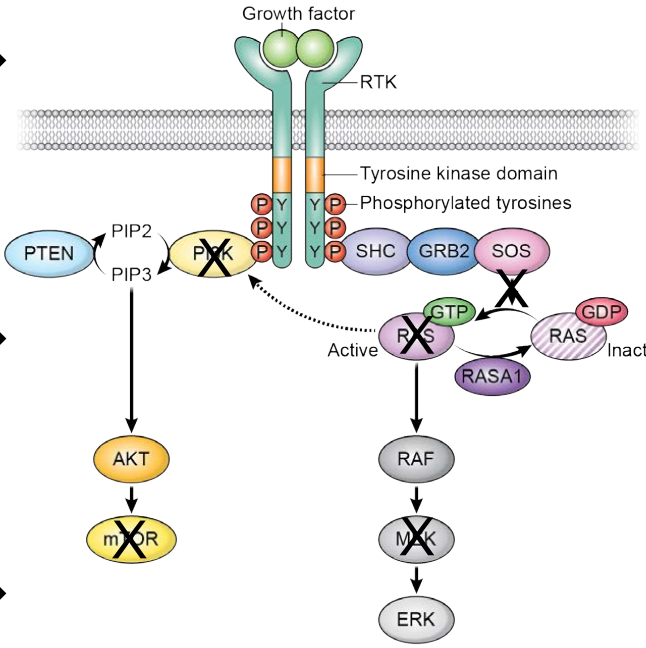
Do individuals with different *KRAS* variants need different treatments?



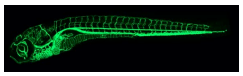








Cellular mechanisms?



Molecular mechanisms?

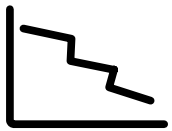


Crystal Structures from UniProt

Indications for off label therapy



Failure of conventional therapies



Diminished performance status



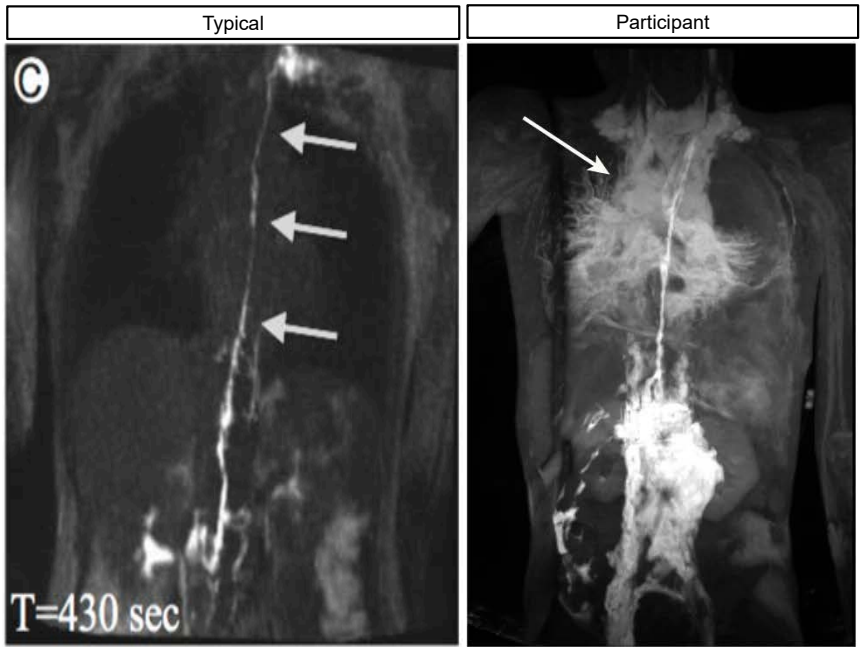
Poor quality of life

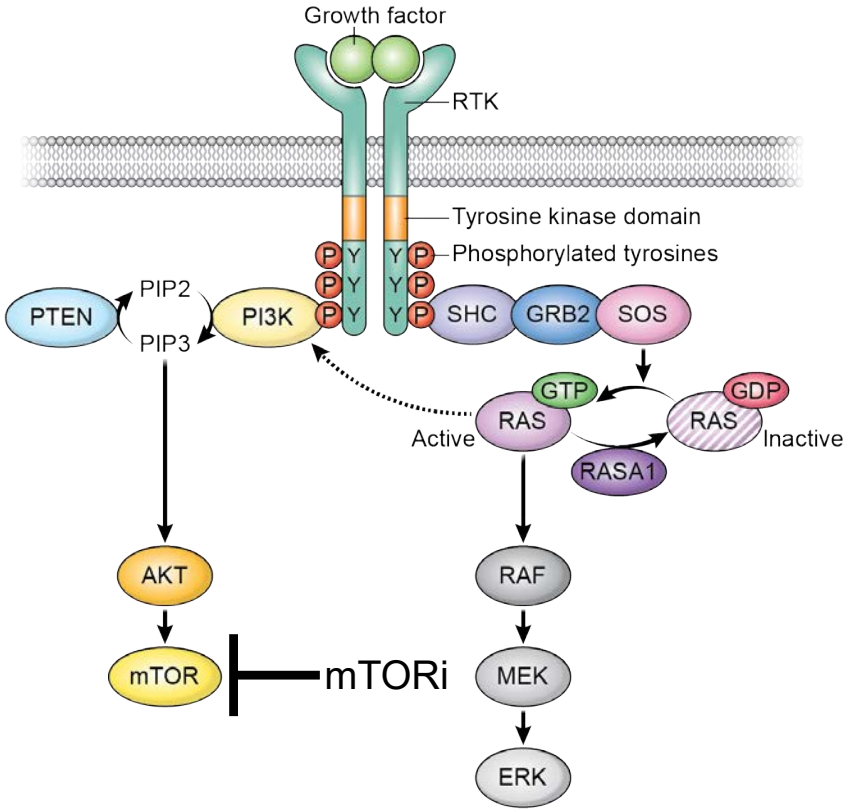
9 year old with chylothorax



Li*, Sheppard* et al *Nature Medicine* 2023

Kaposiform lymphangiomatosis





Dori. *Tech Vasc Interventional Rad* 2016;Li*, Sheppard* et al *Nature Medicine* 2023

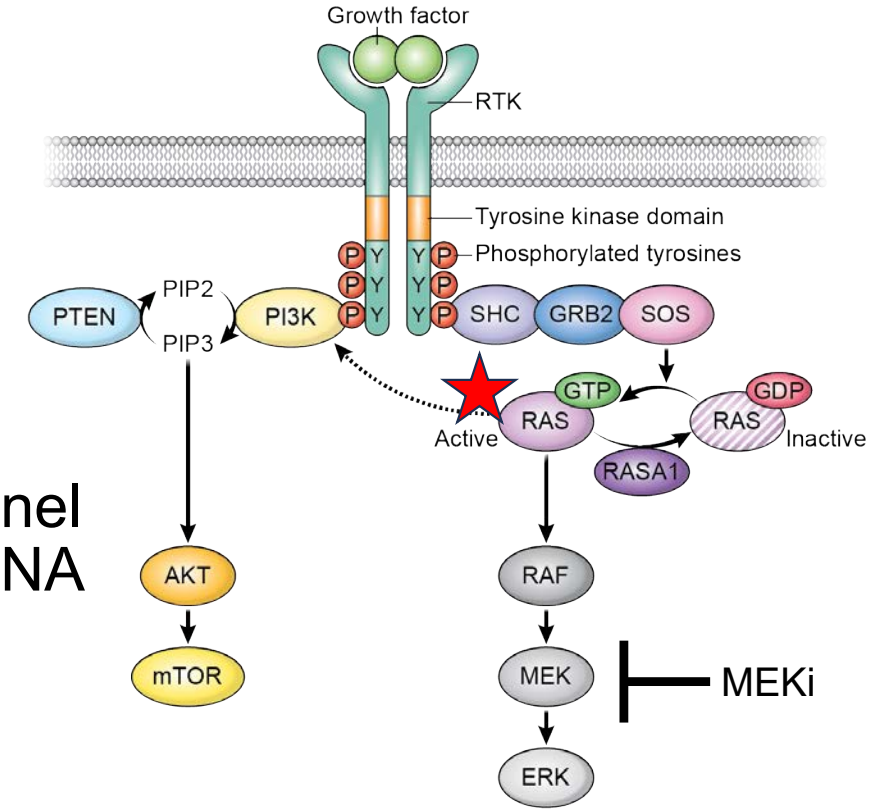
Kaposiform lymphangiomatosis



Mosaic

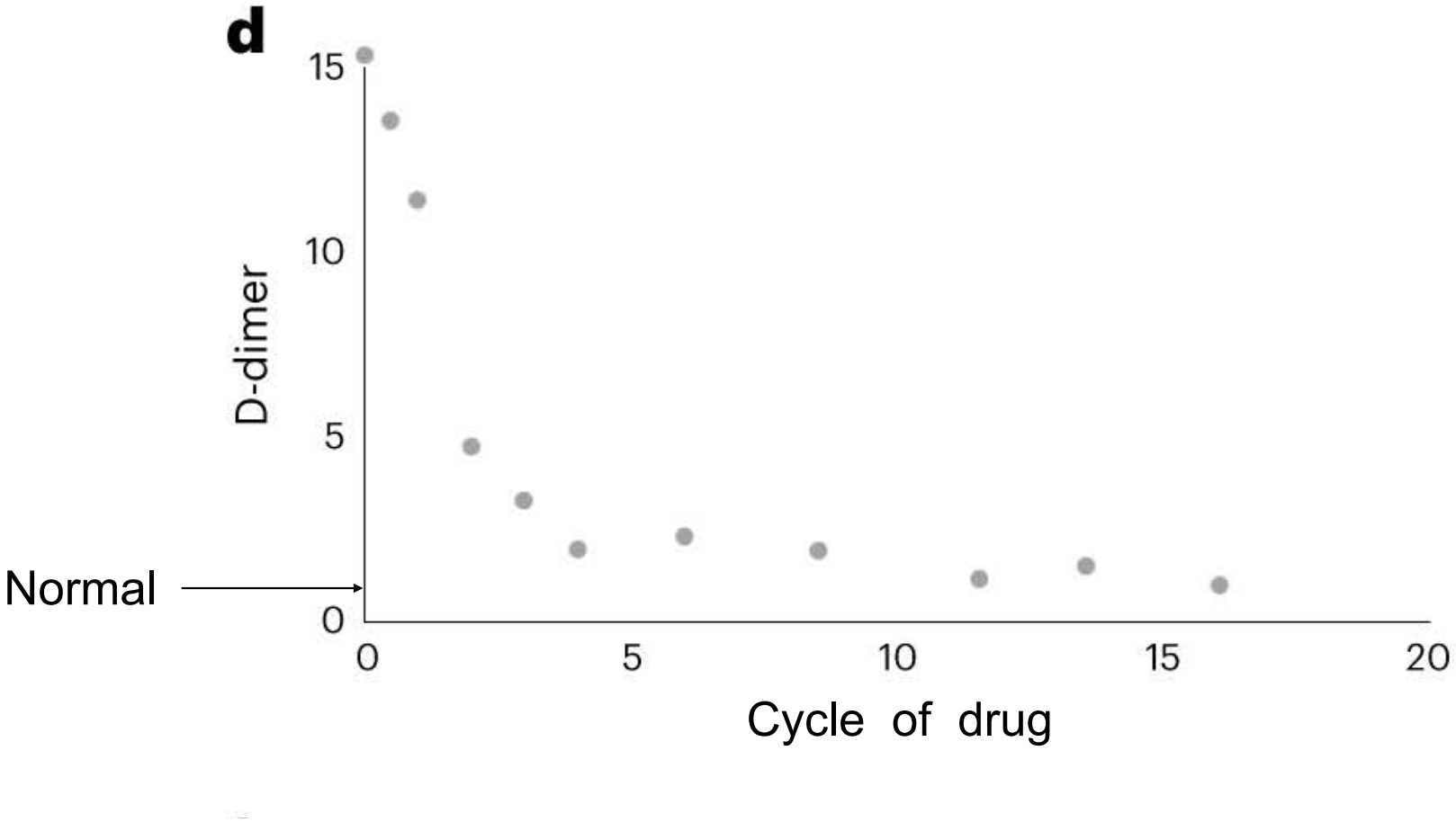
- *NRAS*

- Deep panel from cfDNA from plasma



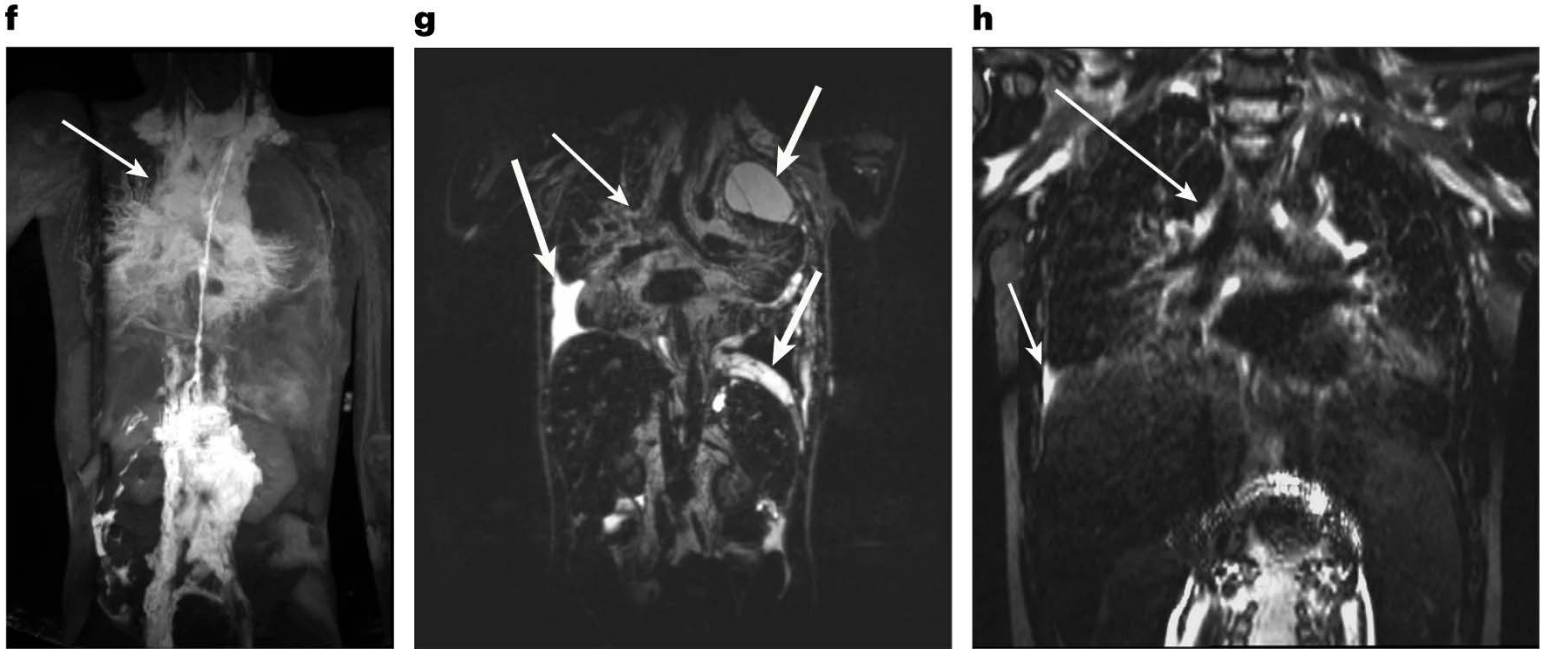
Li*, Sheppard* et al *Nature Medicine* 2023

Targeted therapy normalizes D-dimer



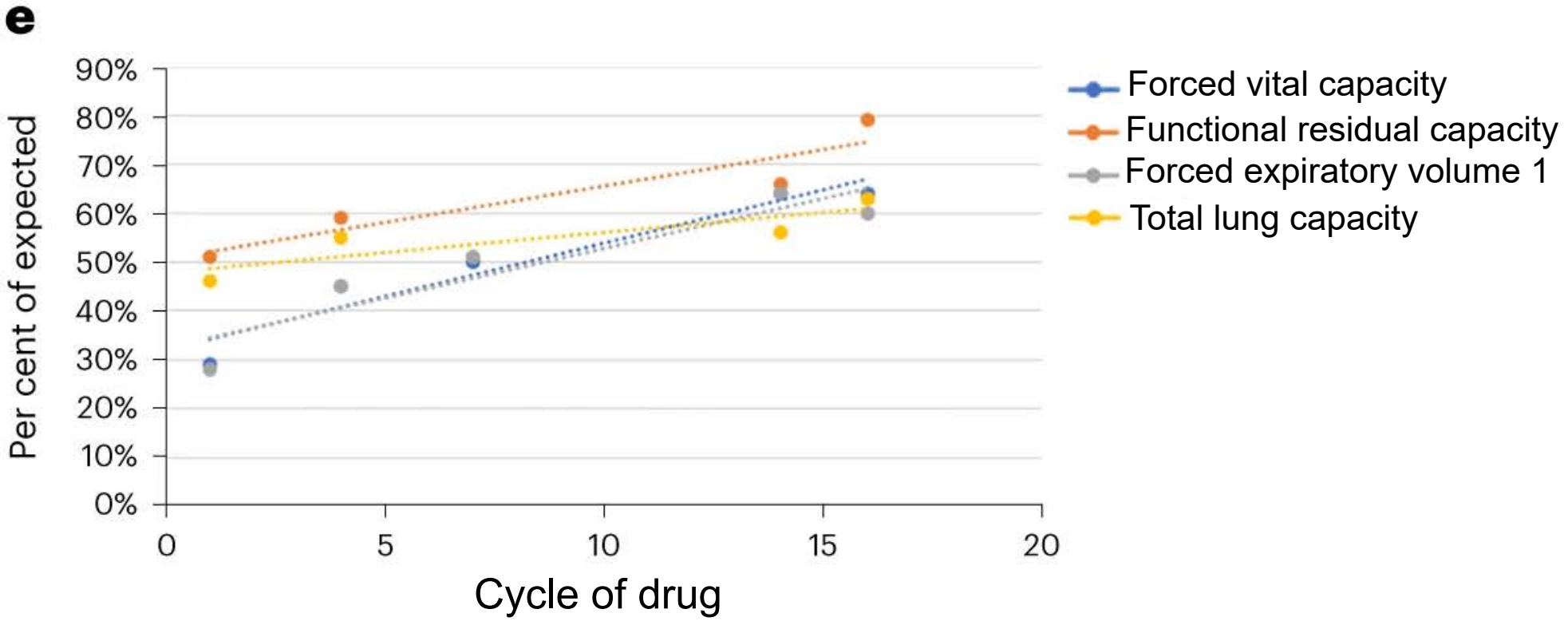
Li*, Sheppard* et al *Nature Medicine* 2023

Targeted therapy reduces pleural effusions in *NRAS*-Kaposiform lymphangiomatosis



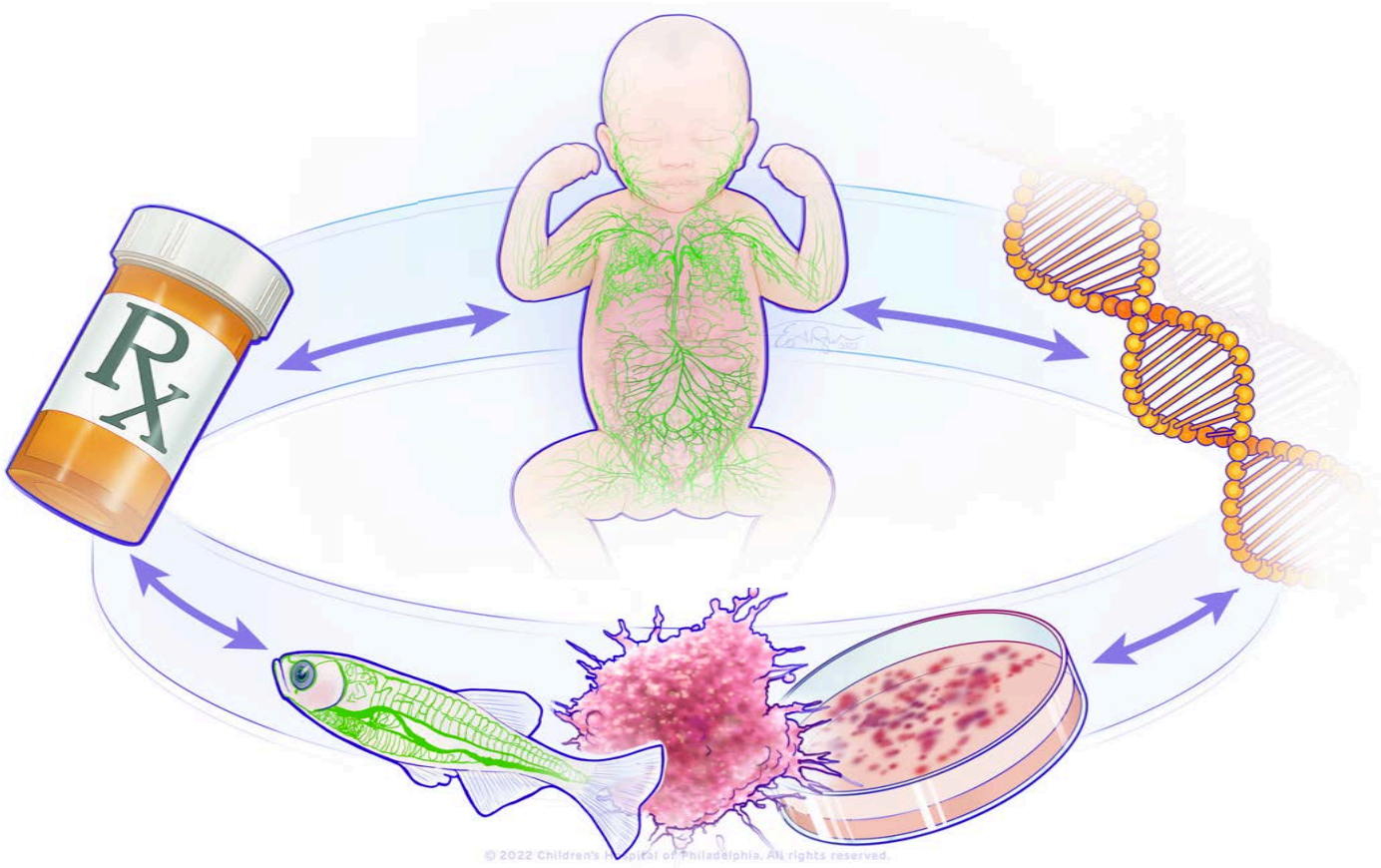
Li*, Sheppard* et al *Nature Medicine* 2023

Targeted therapy improves pulmonary function



Li*, Sheppard* et al *Nature Medicine* 2023

Bedside to bench and back program for lymphatic anomalies



Insights reach farther than lymphatic anomalies



Sheppard et al, *JCI Insight* 2023; Nriagu…**Sheppard**, *AJMG Part A* 2024; Britt…**Sheppard**, *JOVA* 2025; Li*__Sheppard__ et al *Nature Medicine* 2023; Rucigai et al, *Acta Derm Croa* 2015; Mukhopadhyay et al *Nature Cancer* 2021

Acknowledgements






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Laila Lawson
Pari Nautiyal
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Brylan's Feat Foundation
Brittany Williams
Betty Westbrook

Veteran's Fighting Lymphedema
Kelly Bell
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NICHD (ZIA-HD009003)
NIH Distinguished Scholars Program

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Kelly King Au.D., Ph.D.

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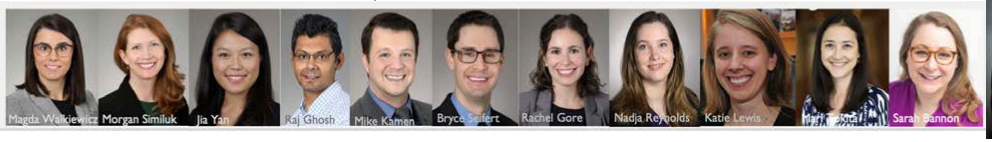
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