Community

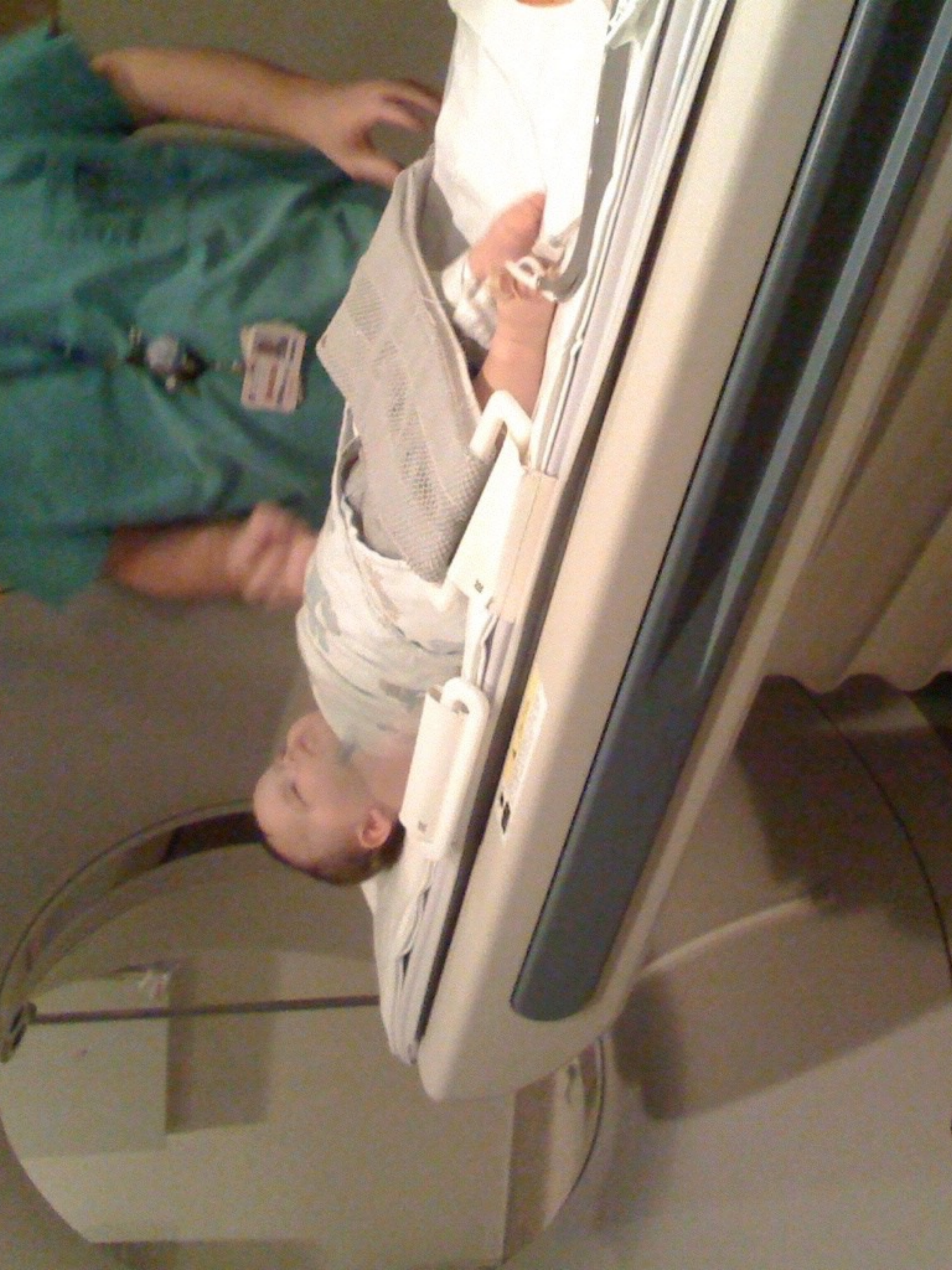
What do you do when you're the first?

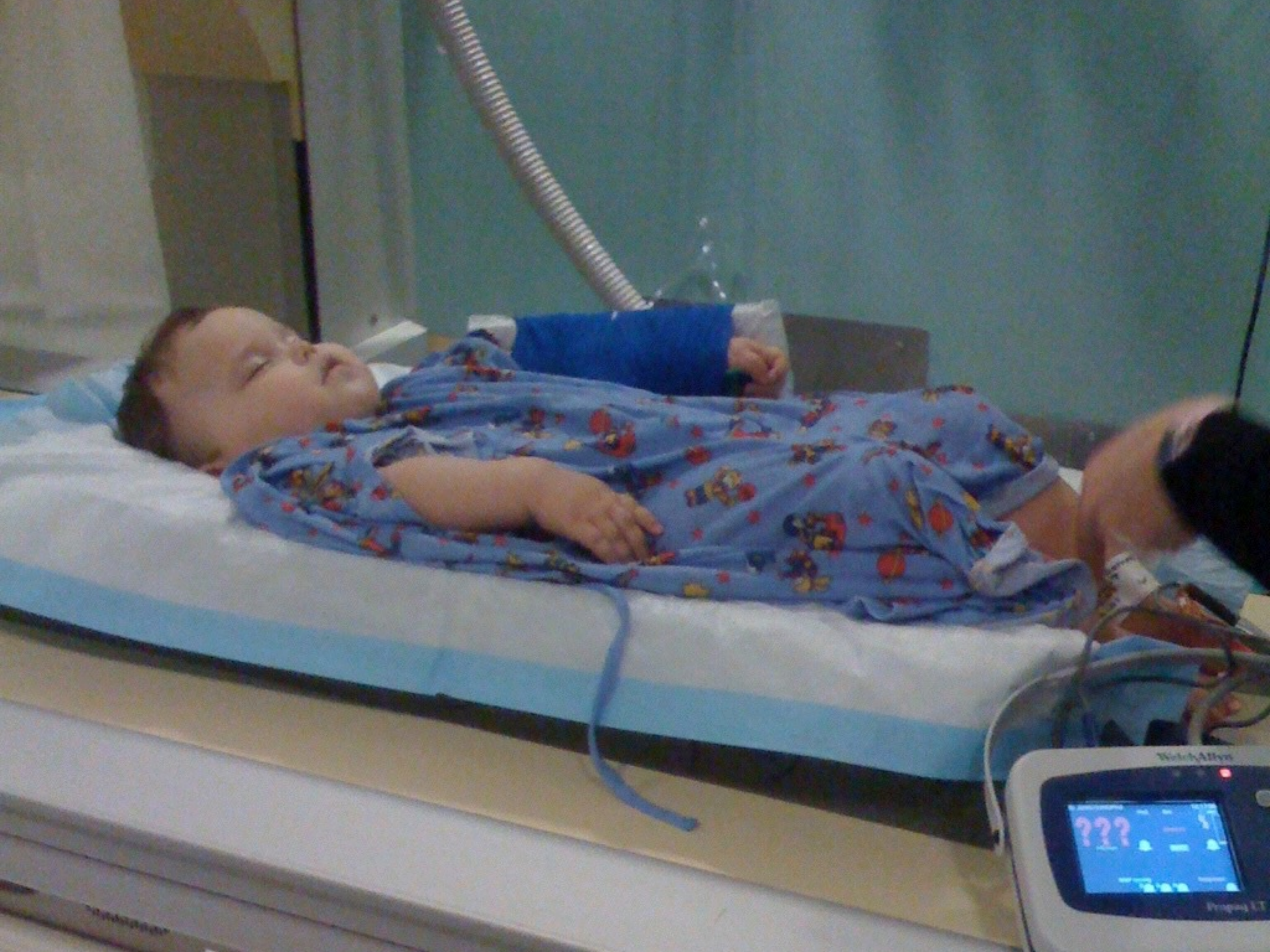
What can a Community of one do?

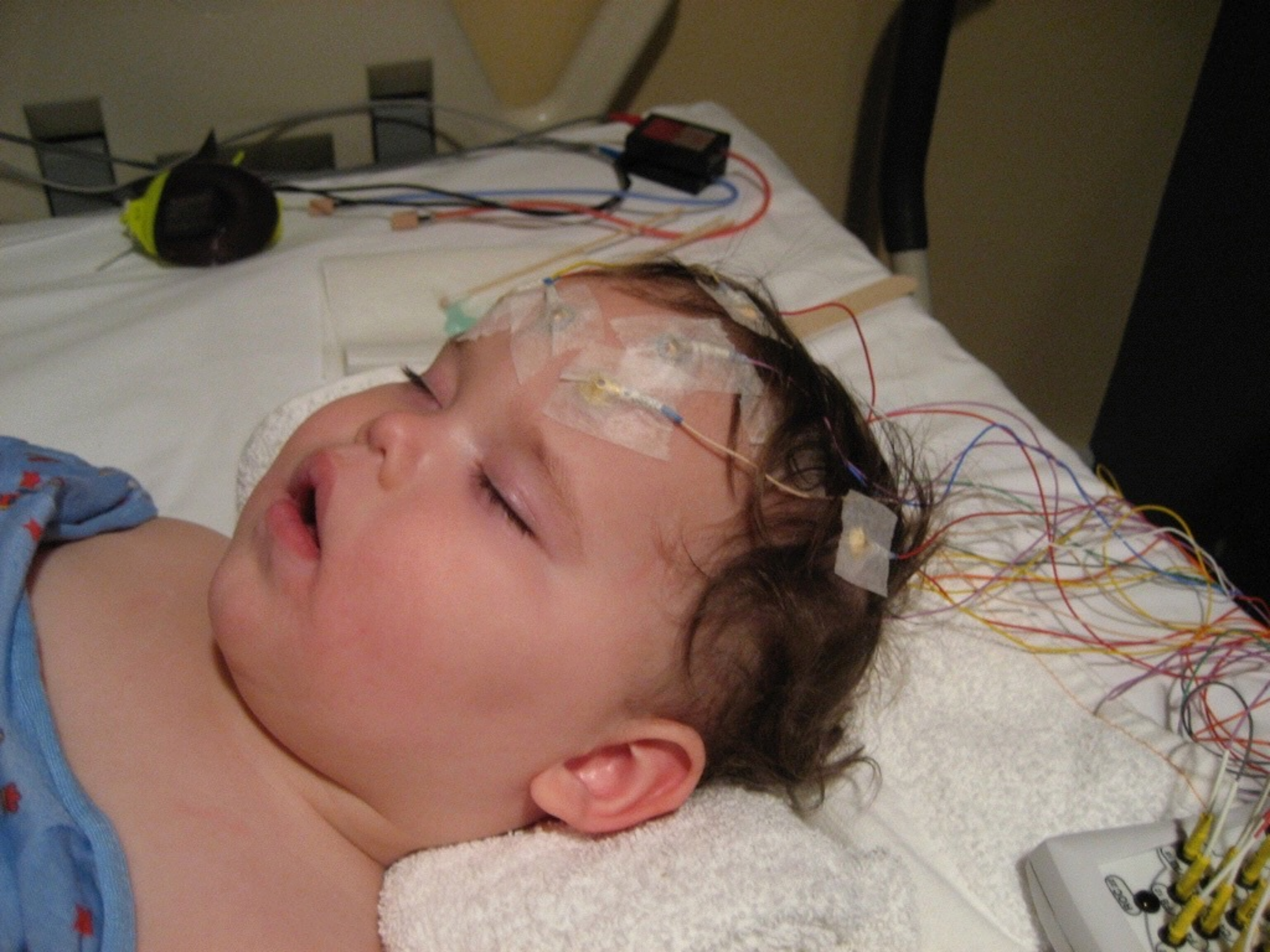
How do you create a Community?

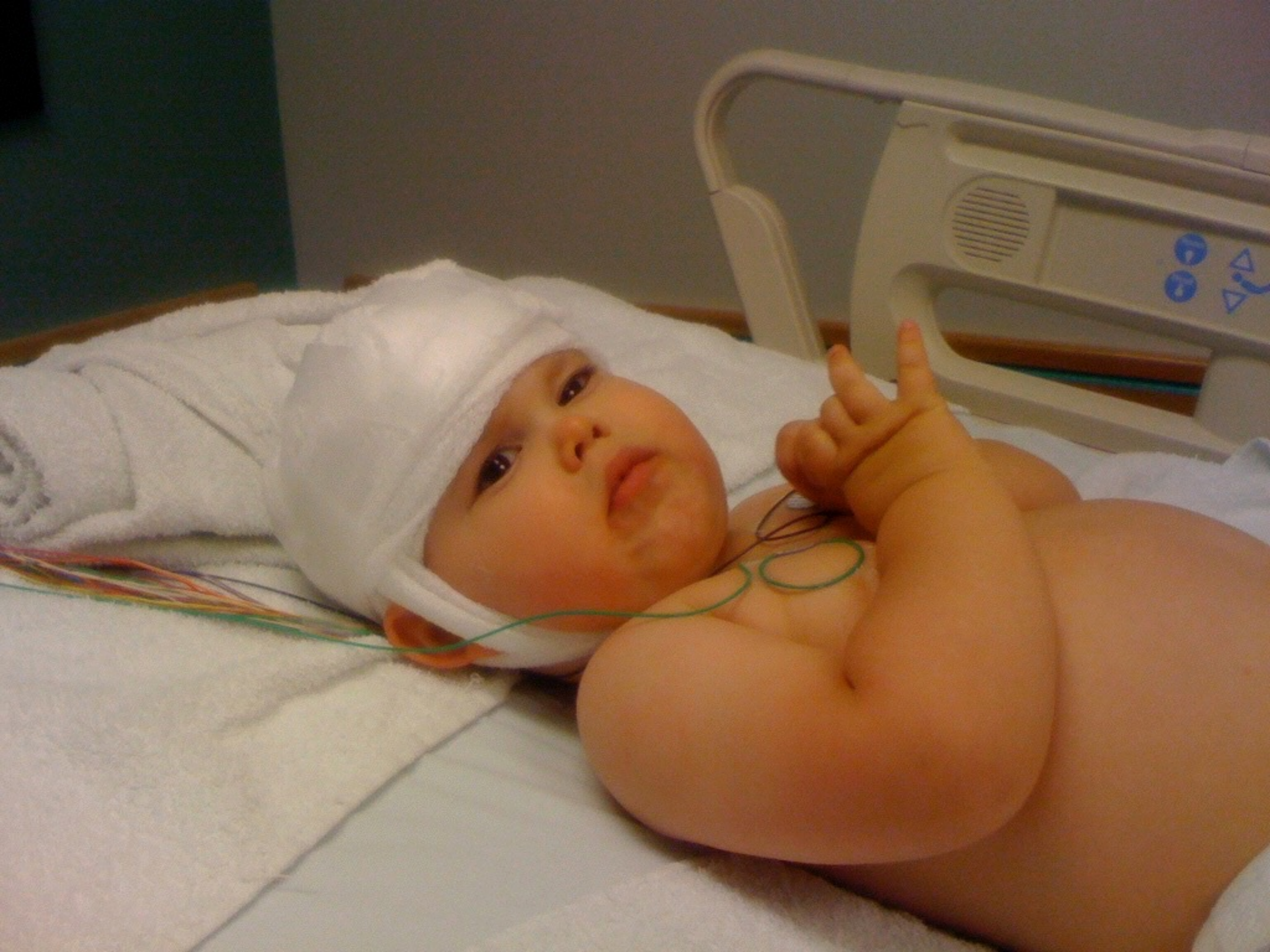
What can a Community do?

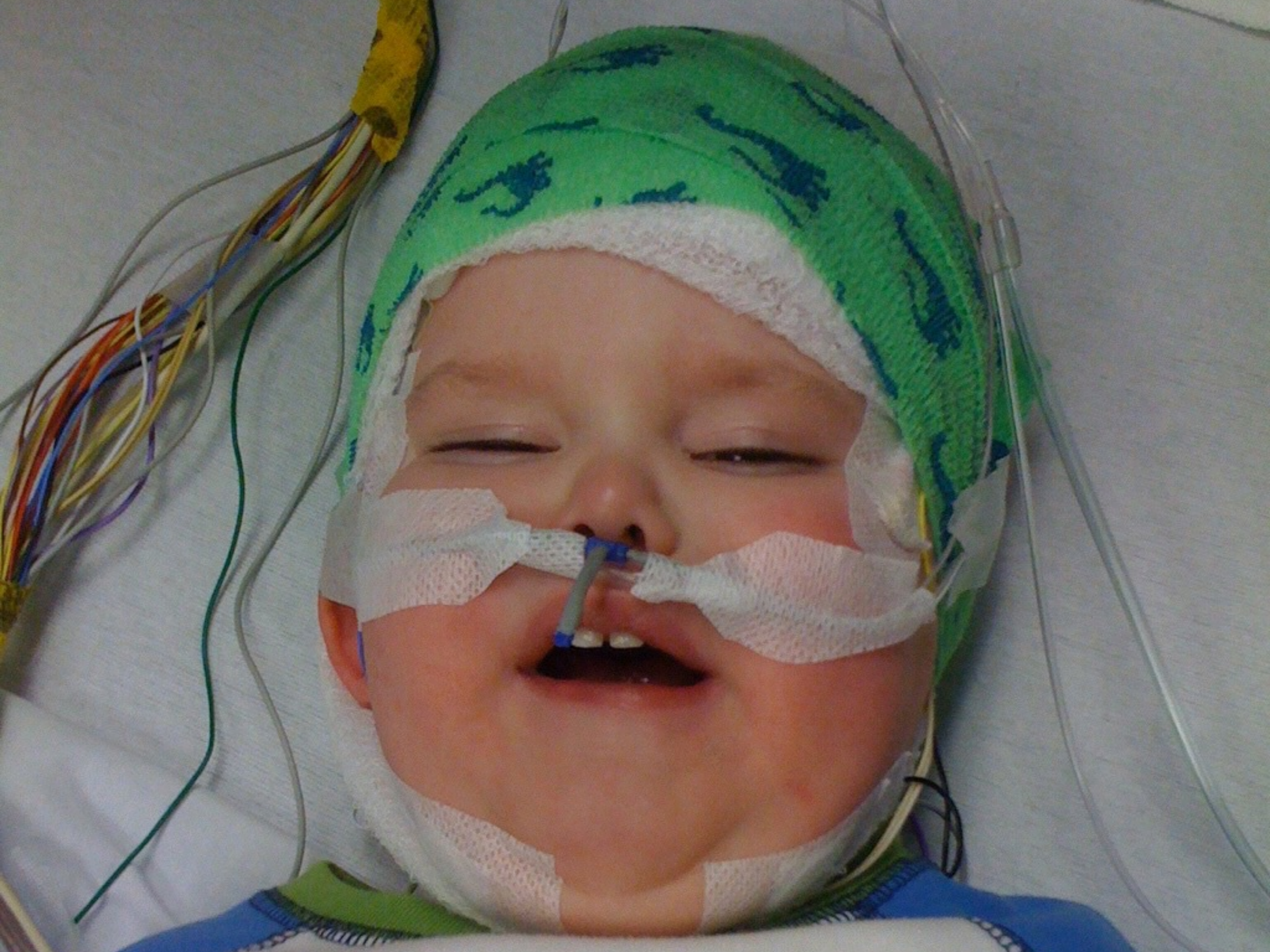
“Undiagnosed island”

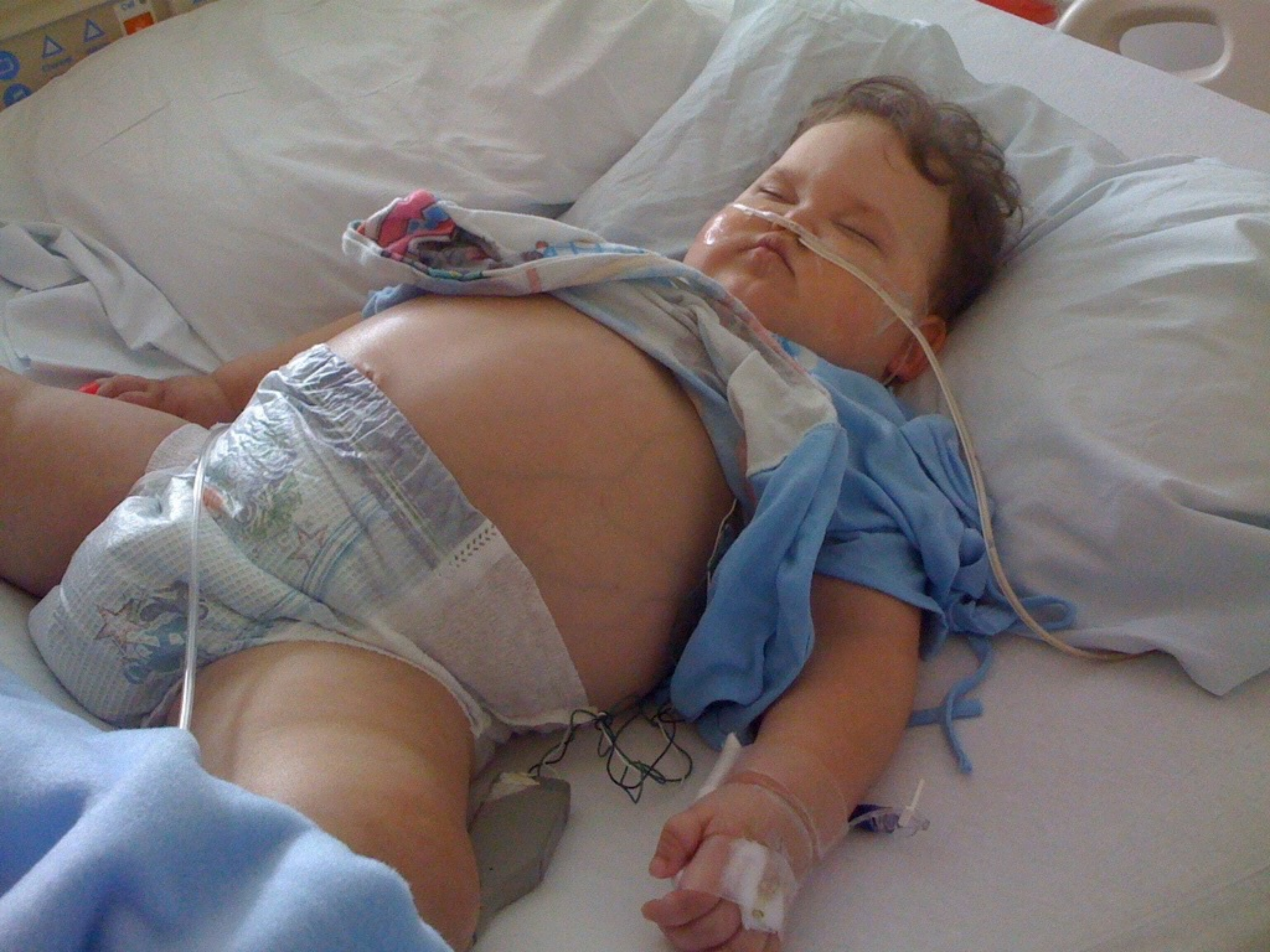


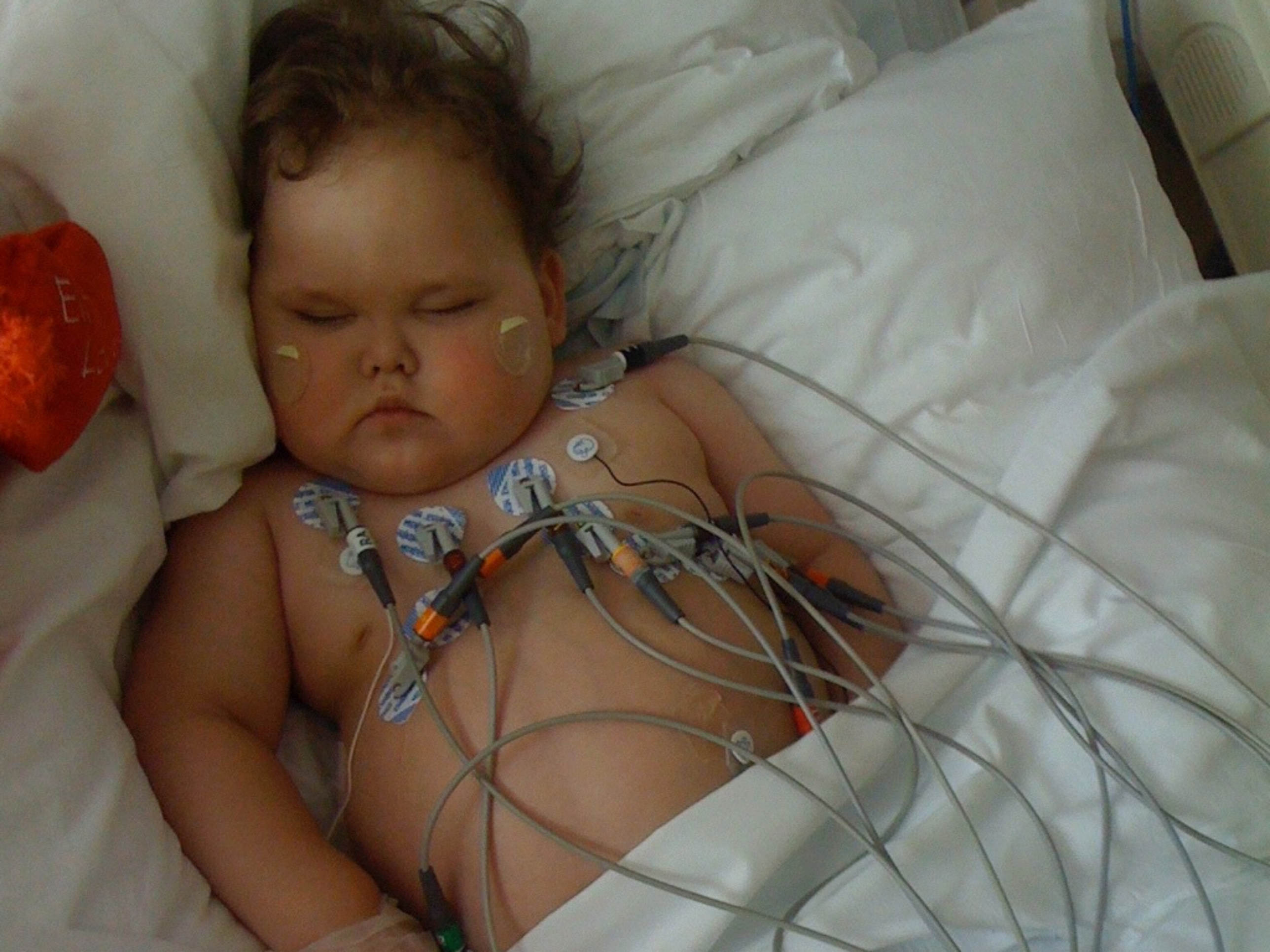












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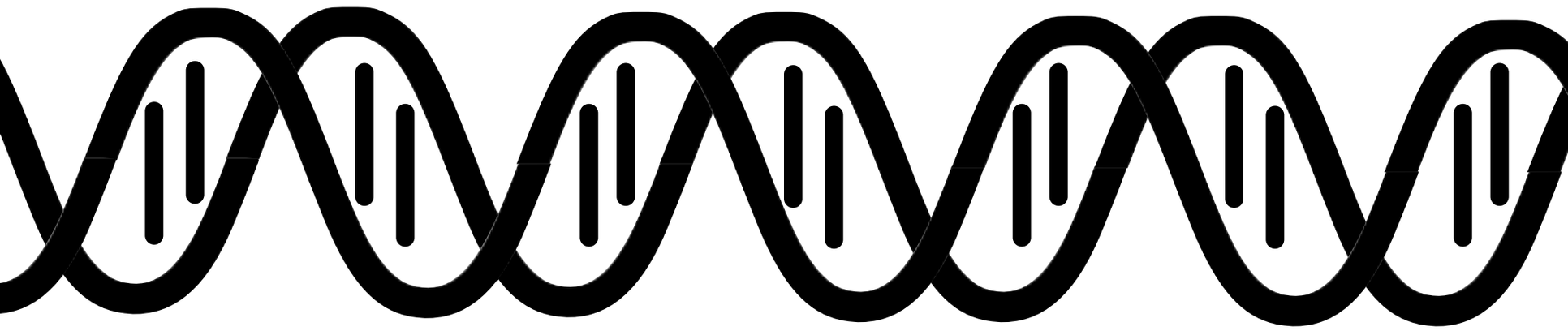
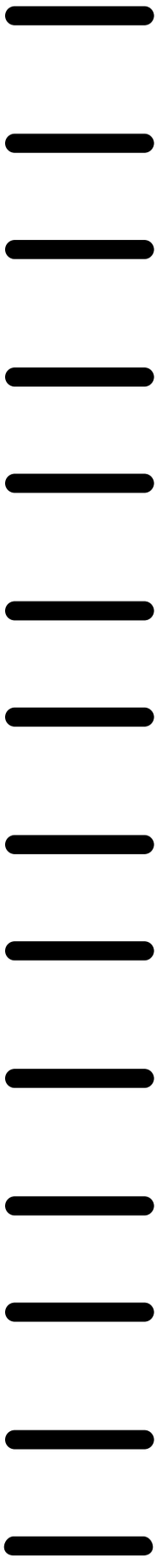
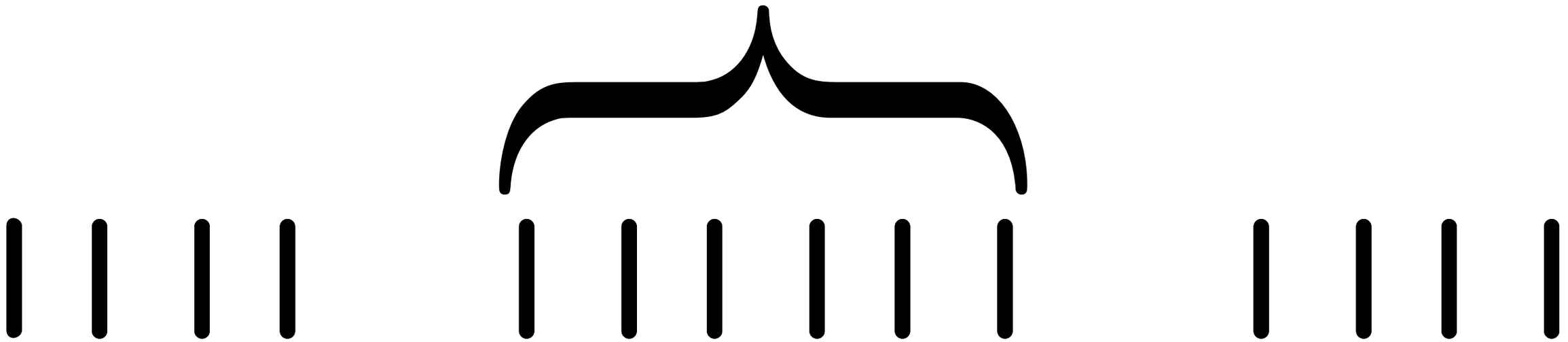
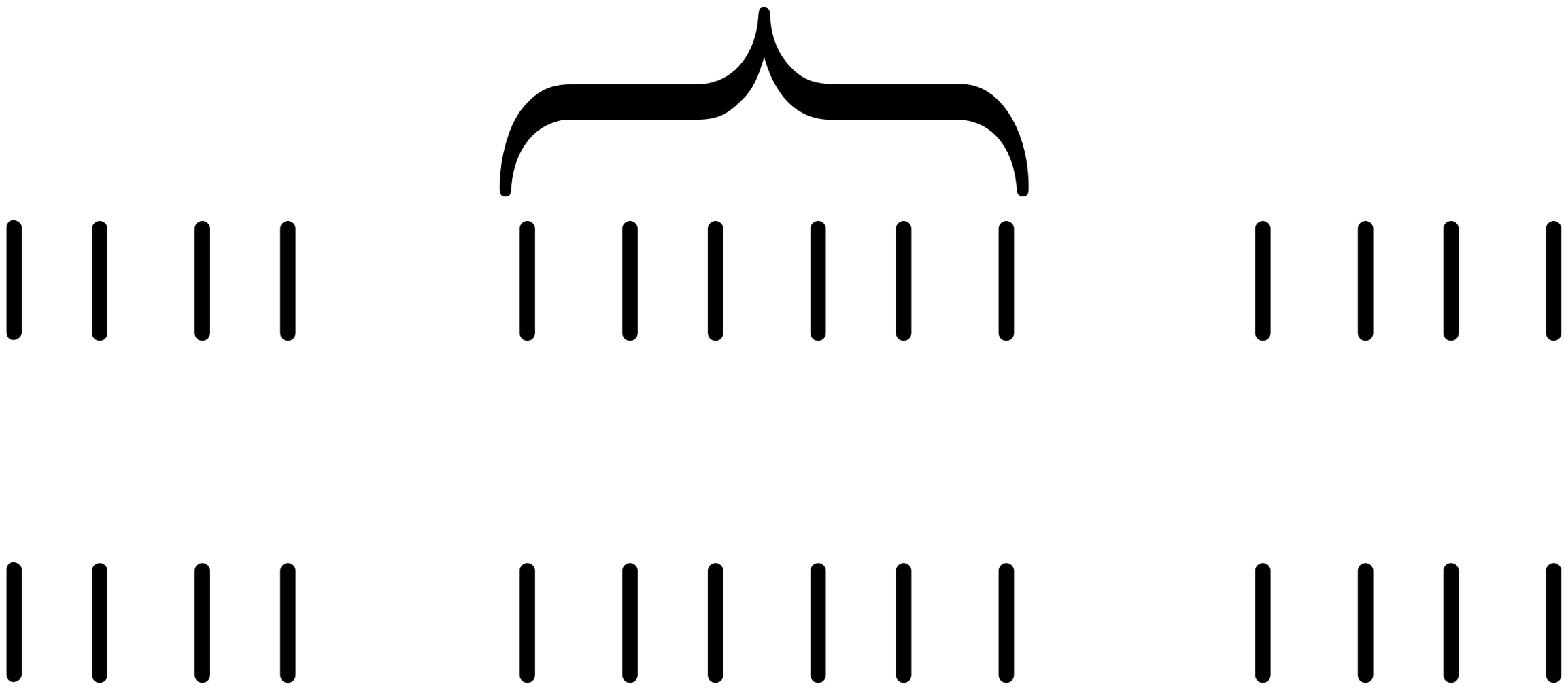




NGLY1



NGLY1



NGLY1

What if $n = 1$?

“Not actionable.”

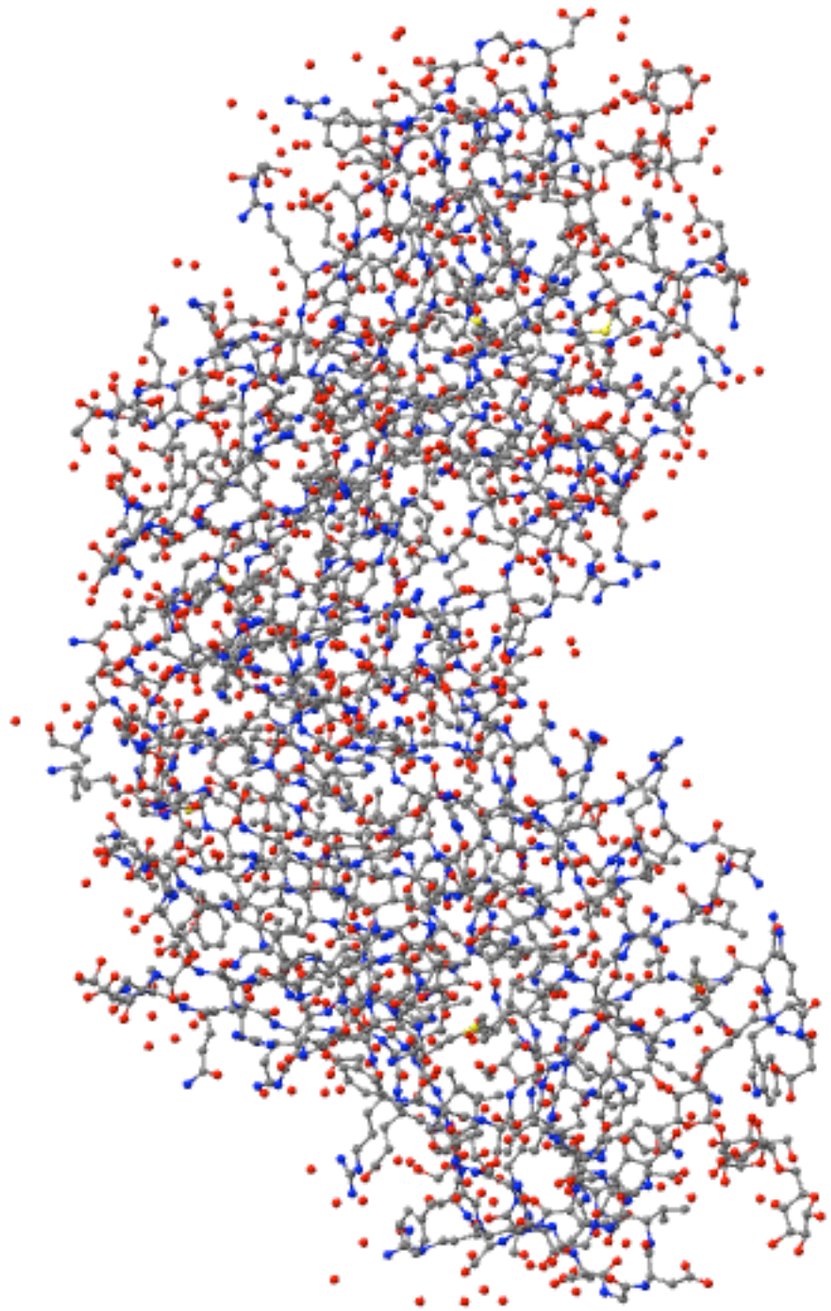
Aftermath

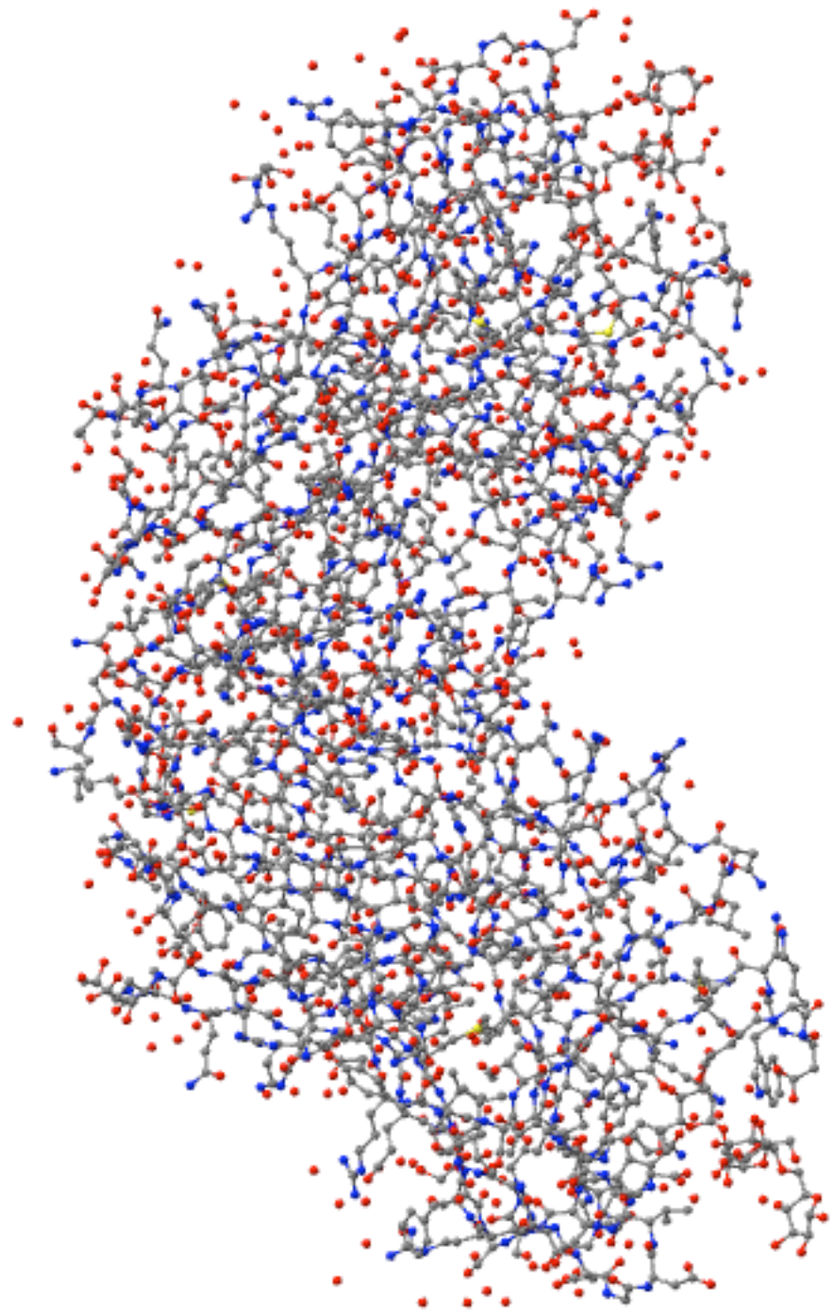

NGLY1

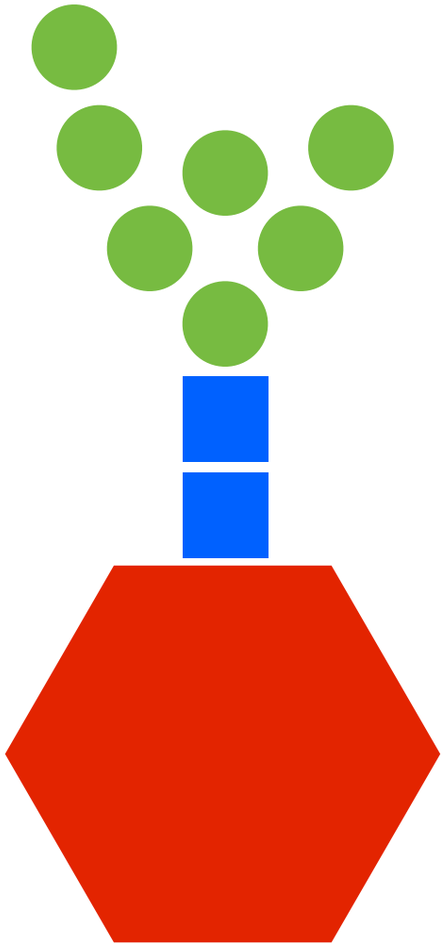
The science *is* the medicine.

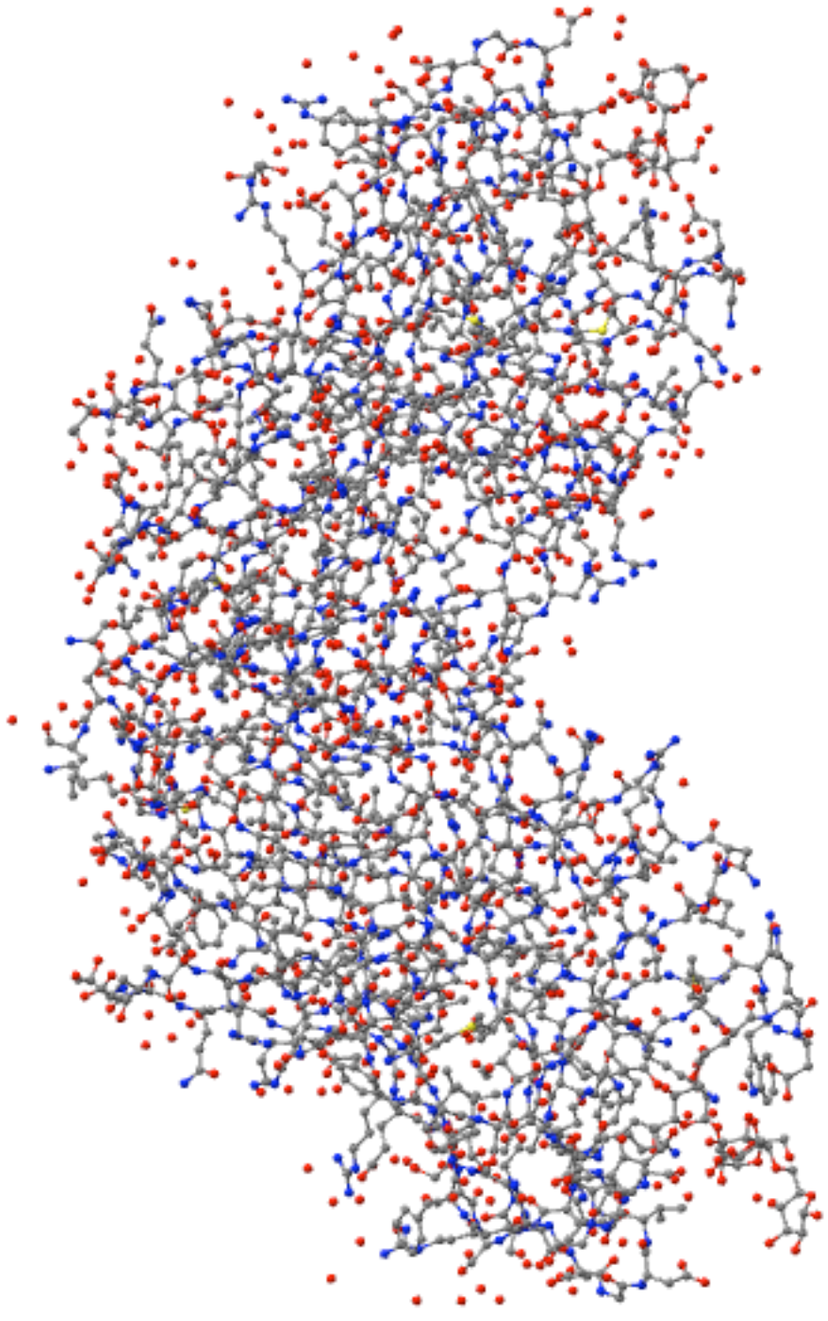

John "Rocket" Williams IV

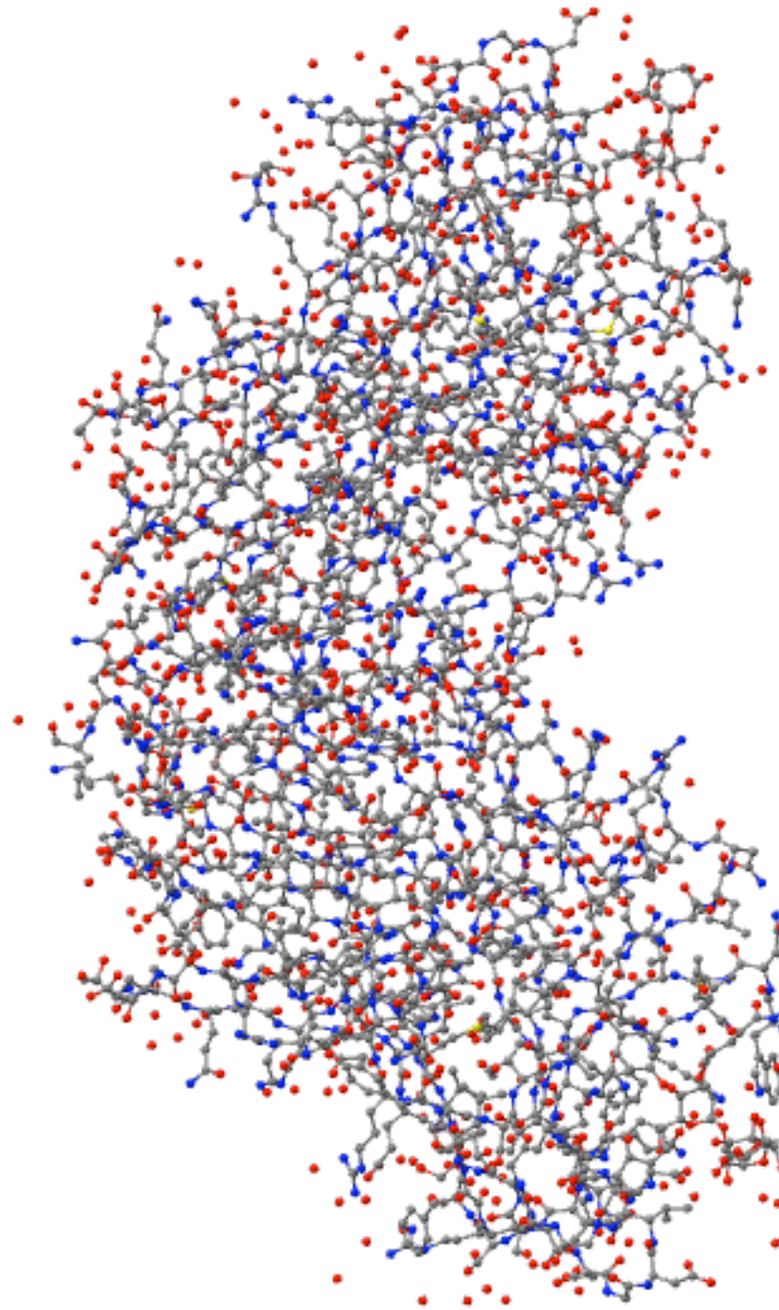
NGLY1

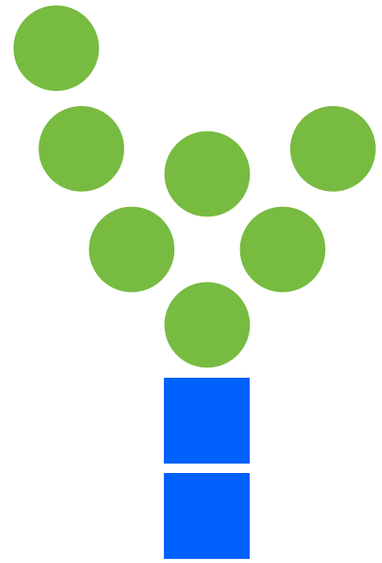


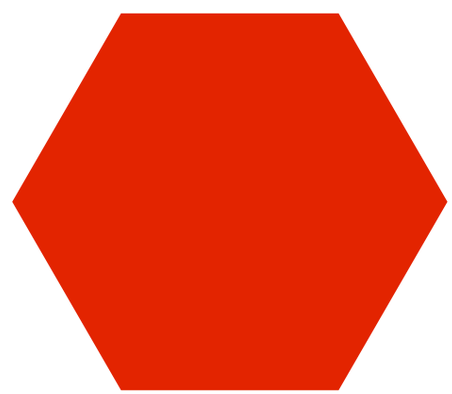


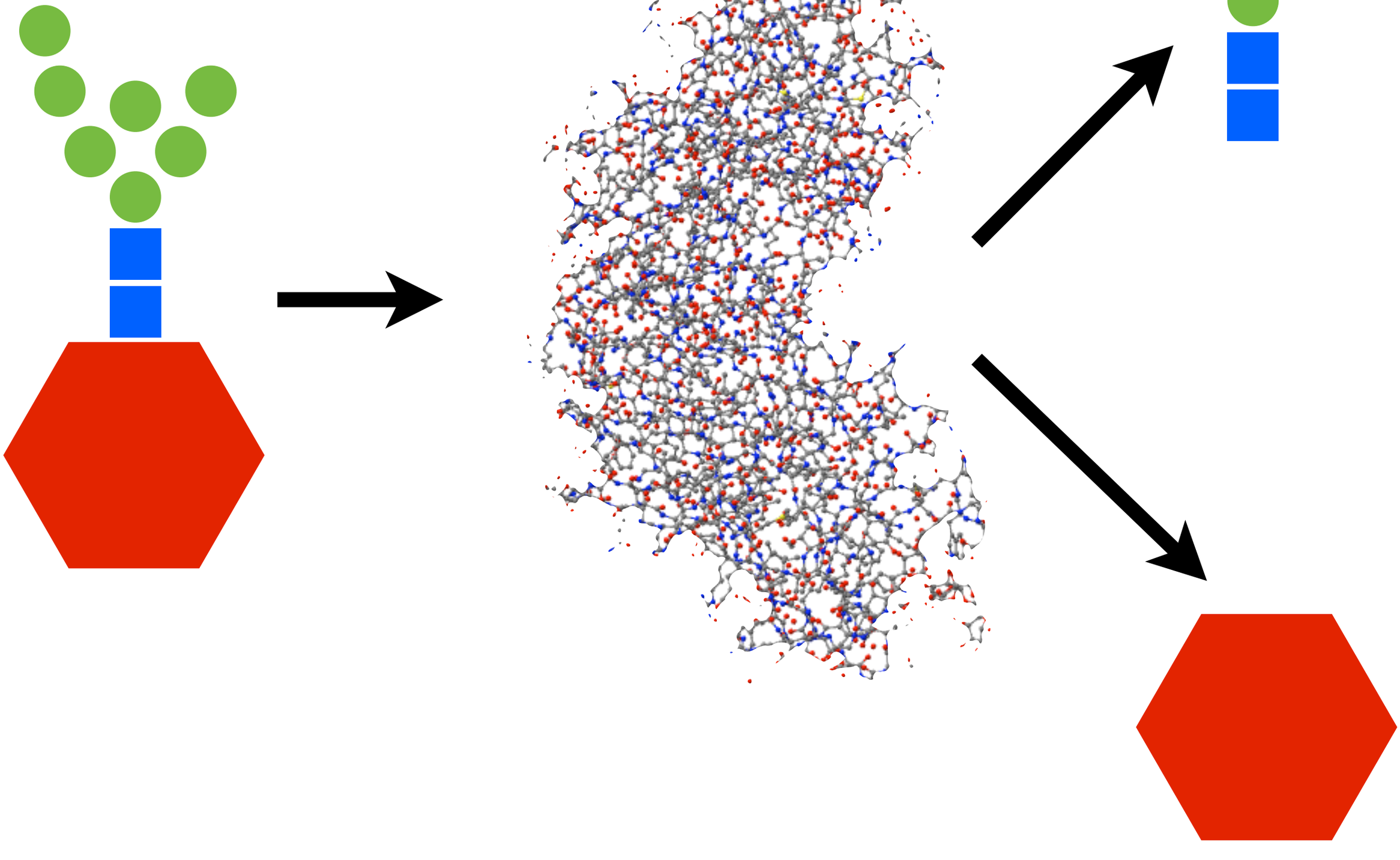


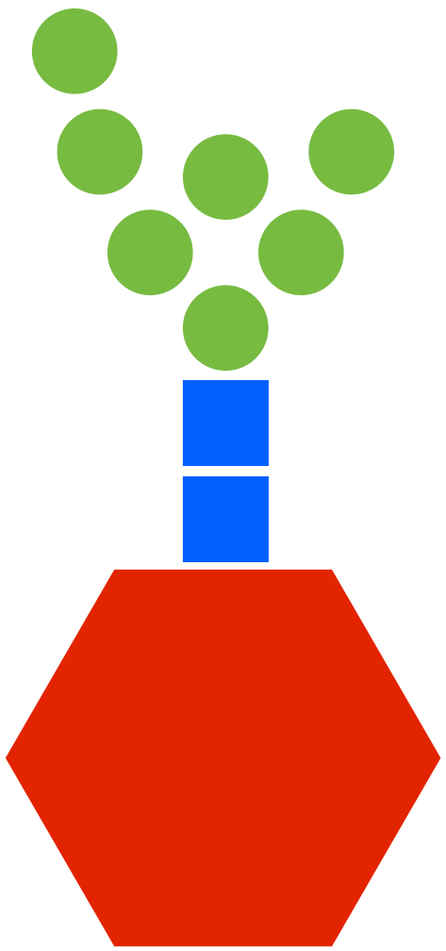


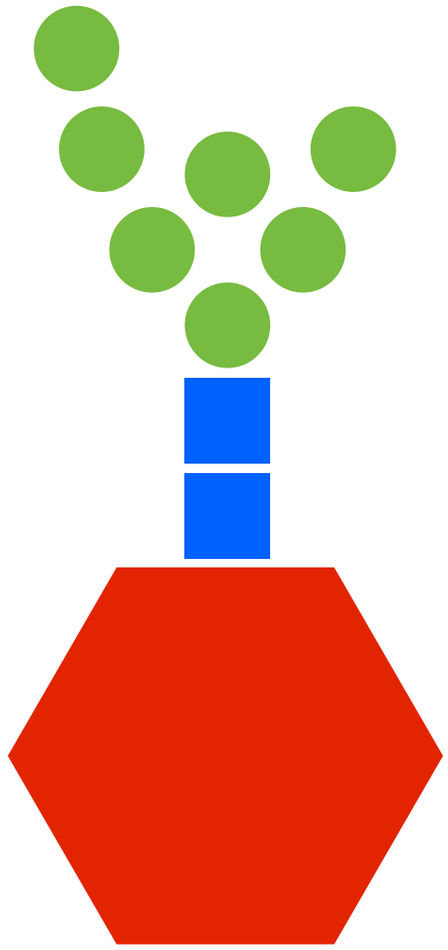


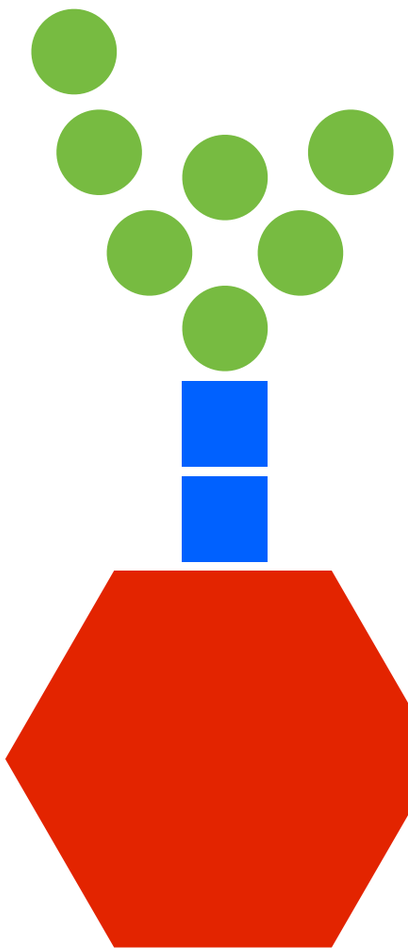












“We can’t do this alone.”

“Let’s find the others.”

Hunting down my son's killer

I found my son's killer.

It took three years.

But we did it.

Not quite like this.

2,000,000

Google NGLY1

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About 12,000 results (0.43 seconds)

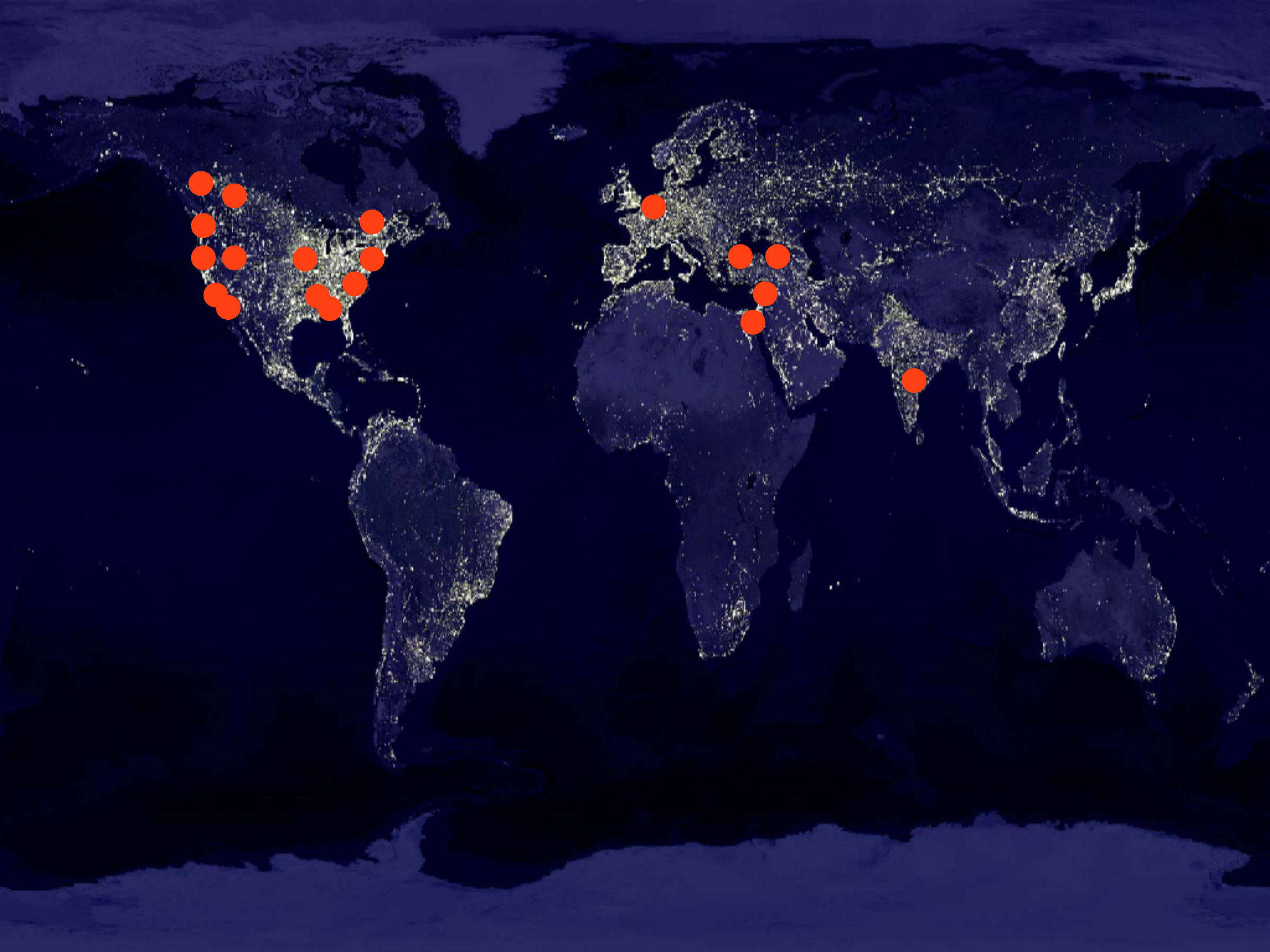
NGLY1 Gene - GeneCards | **NGLY1** Protein | **NGLY1** Antibody
www.genecards.org/cgi-bin/carddisp.pl?gene=**NGLY1**
Complete information for **NGLY1** gene (protein-coding), N-glycanase 1, including: function, proteins, disorders, pathways, orthologs, and expression.

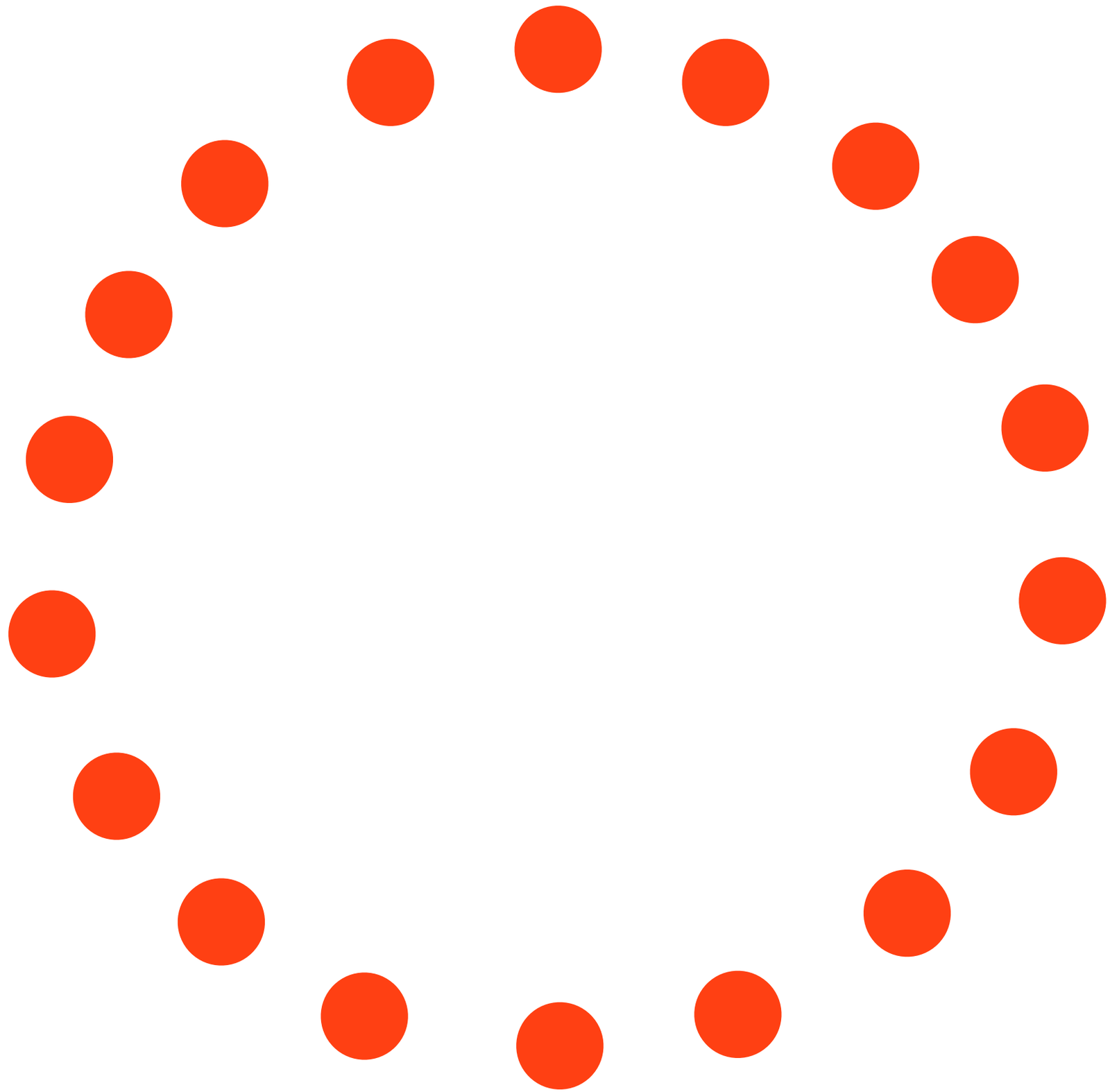
NGLY1 - Wikipedia, the free encyclopedia
en.wikipedia.org/wiki/**NGLY1** Wikipedia
Peptide-N(4)-(N-acetyl-beta-glucosaminyl)asparagine amidase is an enzyme that in humans is encoded by the **NGLY1** gene.

NGLY1 N-glycanase 1 [Homo sapiens (human)]
www.ncbi.nlm.nih.gov/gene/55768 National Center for Biotec...
5 days ago - This gene encodes an enzyme that catalyzes hydrolysis of an N(4)-(acetyl-beta-D-glucosaminyl) asparagine residue to ...

OMIM Entry - * 610661 - N-GLYCANASE 1; **NGLY1**
www.omim.org/610661 OMIM : Online Mendelian...
Jun 12, 2013 - (2000) identified several homologs of yeast Png1, including human **NGLY1**. In yeast, Png1 was expressed in both the cytoplasm and nucleus.

Hunting down my son's killer - Matt Might
matt.might.net/articles/my-sons-killer/
We discovered that my son inherited two different (thus-far-unique) mutations in the same gene--the **NGLY1** gene--which encodes the enzyme N-glycanase 1.





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NGLY1

HOME | ABOUT | RESEARCH | PATIENTS | TREATMENTS | PRESS | CONTACT

MEDICAL DISPATCH

ONE OF A KIND

What do you do if your child has a condition that is new to science?

BY SETH MNOOKIN

Matt Might and Cristina Casanova met in the spring of 2002, as twenty-year-old undergraduates at the Georgia Institute of Technology. Cristina was [illegible] est in philosophy; Matt was a shy computer geek obsessed with "Star Trek." At first Cristina took no notice of him, but [illegible]

worry. Matt and Cristina described Bertrand to friends as being "jiggly"; his body appeared always to be in motion, as if he were lying on a bed of Jell-O. He [illegible] to be in near-constant distress, and Matt's efforts to comfort him [illegible] Matt says. "I felt like a failure as a father." When the Mights [illegible] raised their concerns with Bertrand's

City, and the first available appointment fell on the same day as a mandatory faculty retreat. That afternoon, when Matt was able to check his phone, he saw that Cristina had left several messages. "I didn't listen to them," he told me in an e-mail. "I didn't have to. The number of them told me this was really bad."

Bertrand had brain damage—or at least, that was the diagnosis until an MRI revealed that his brain was perfectly normal. After a new round of lab work was done, Bertrand's doctors concluded that he likely had a rare, inherited movement disorder called ataxia-telangiectasia. A subsequent genetic screen [illegible] When Bertrand was fifteen months old, the Mights were told that urine screening suggested that

NGLY1 in The New Yorker!

Open science and social media were key in the discovery and growth of the NGLY1 rare disease community. Article by Seth Mnookin.

Dr. David Goldstein to direct Institute for Genomic Medicine at Columbia University

By Cristina on Saturday, October 25, 2014 Columbia , news No comments

Search

Do you know a NGLY1 patient?

If you know a patient with NGLY1-deficiency, or think you do, please contact us immediately.

You can reach us directly at info@ngly1.org

NGLY1 Symptoms

Global Developmental Delays

Movement Disorder

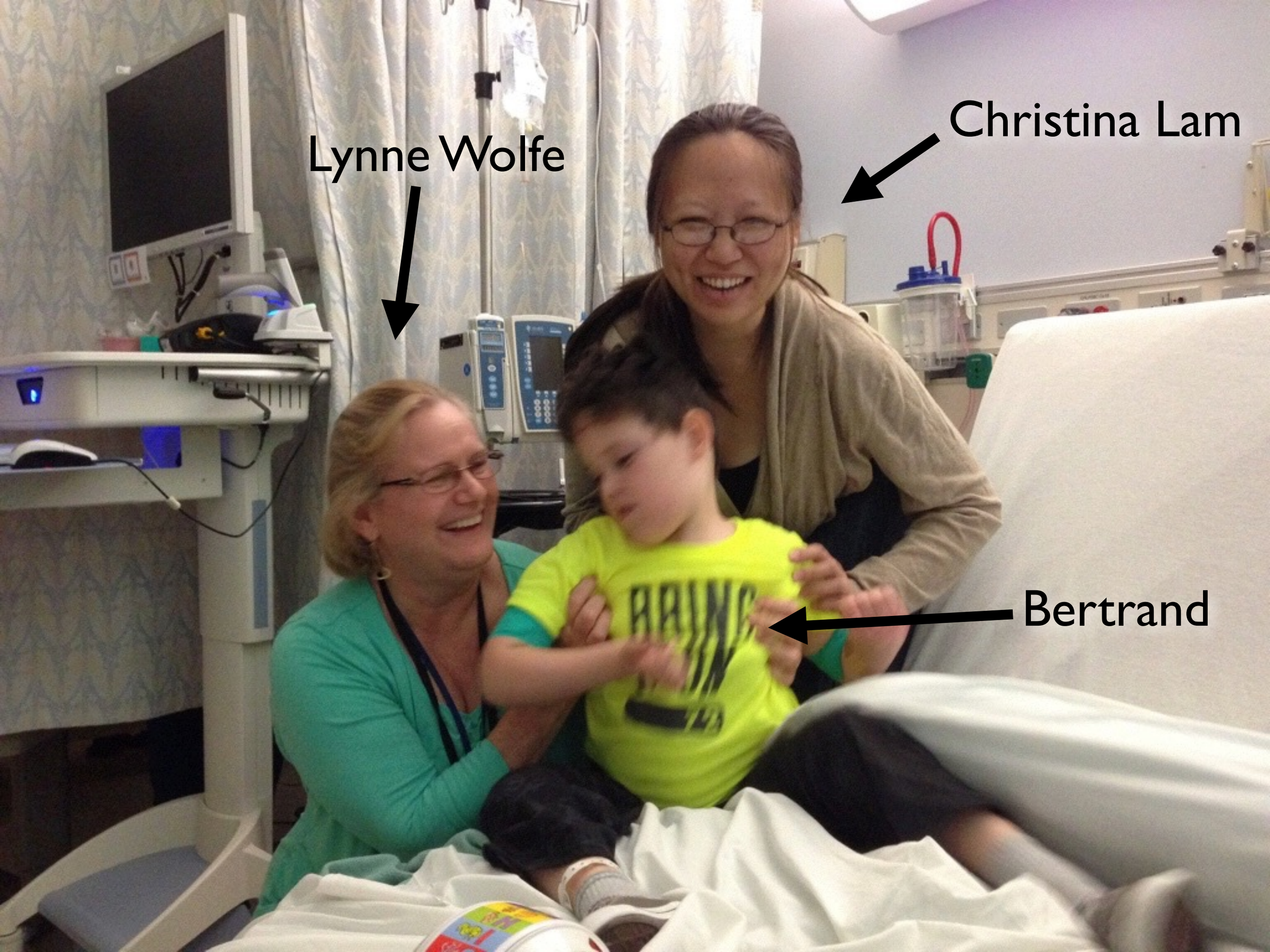
Hypotonia

Communities can push science!

Clinical research

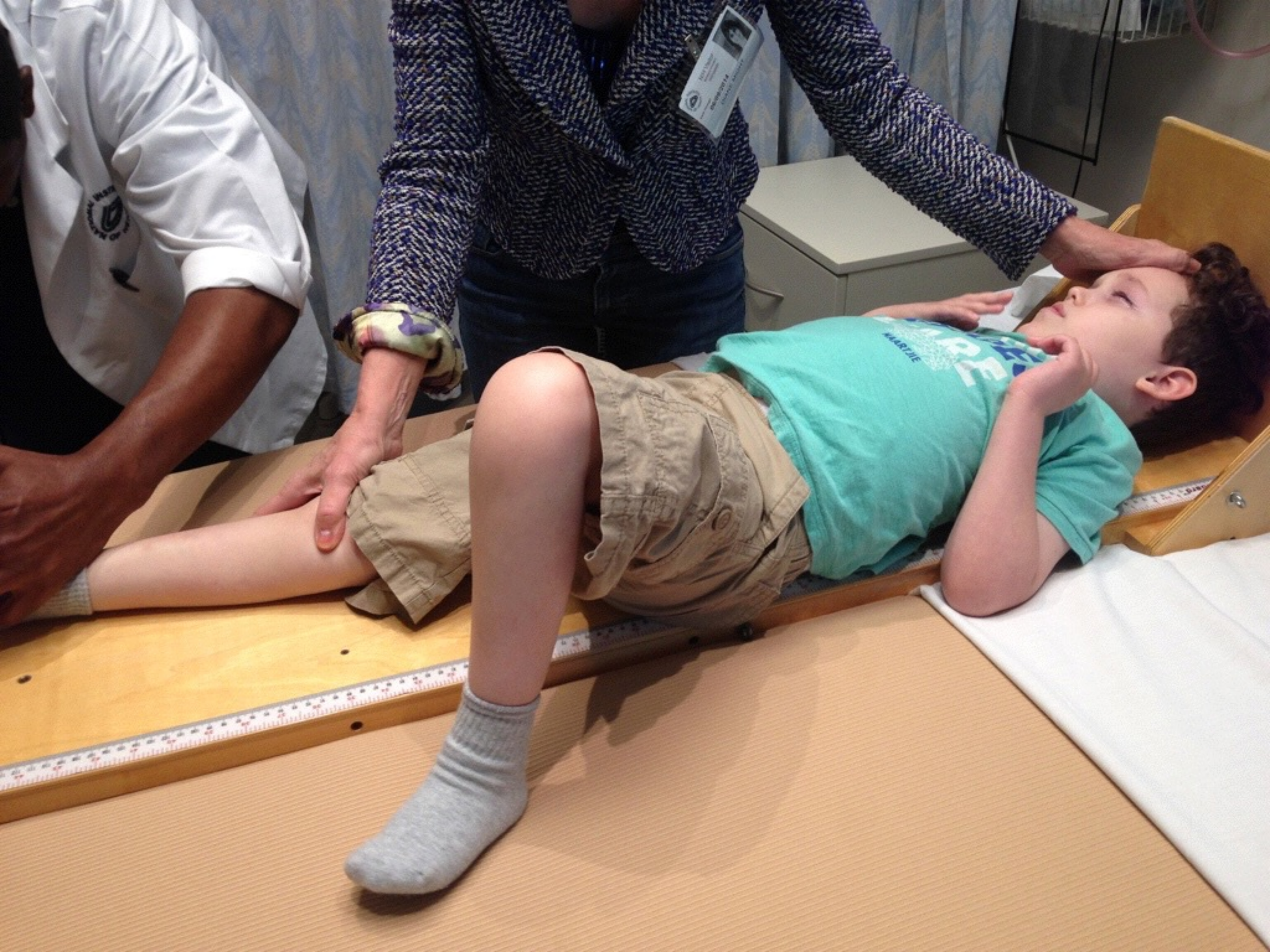
National Institutes of Health

Natural History


Lynne Wolfe
Christina Lam
Bertrand

Bill Gahl


PATIENT PORTAL




Check-In


DUDES


COOL
DUDES
CAPE
NAARTJIE


Pocket
Mask

Patient | Examination | Postprocessing | Documentation

MIGHT BERTRAND

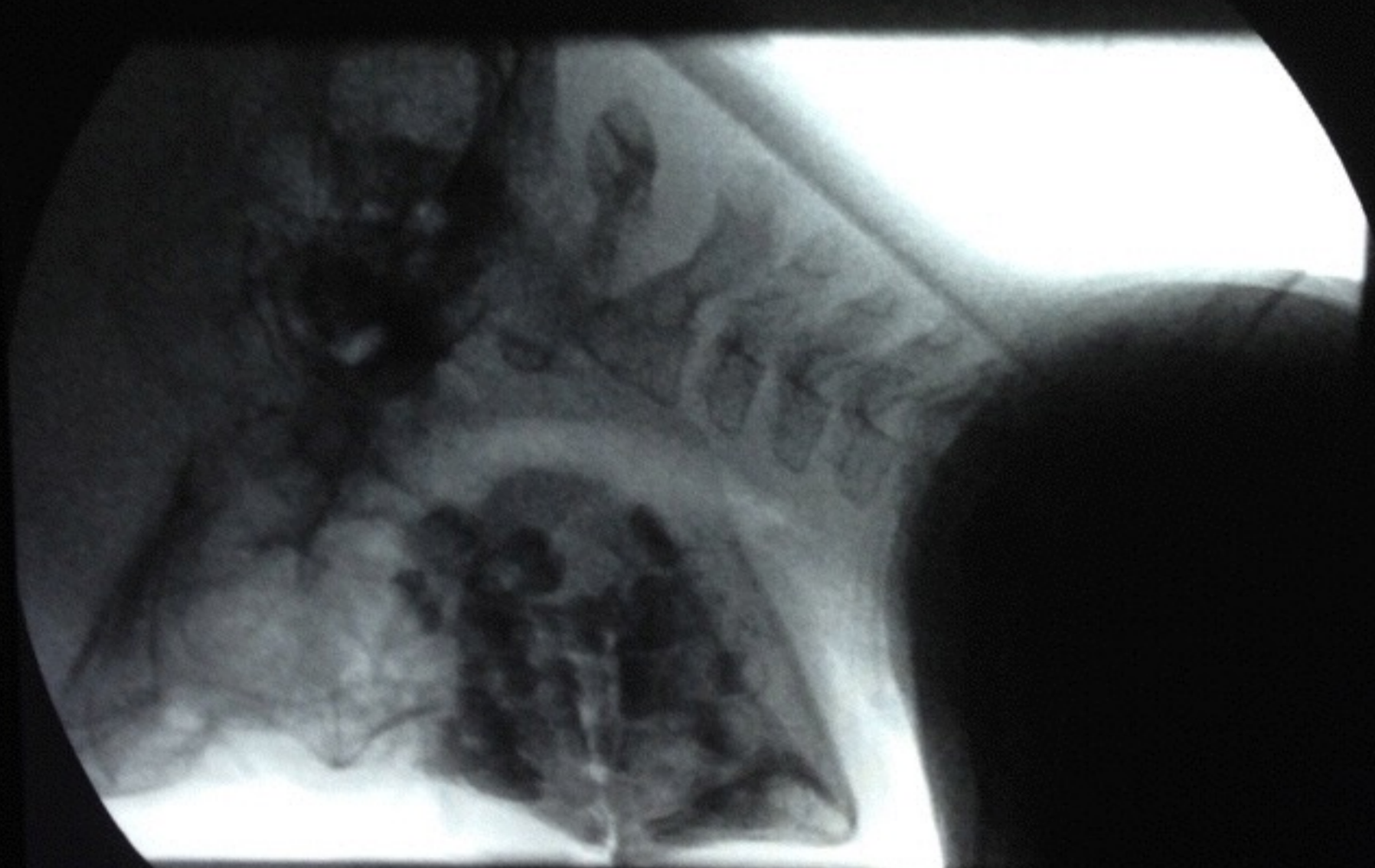
Barium
Single shot
Single shot
Continuous
25 f/s

1000

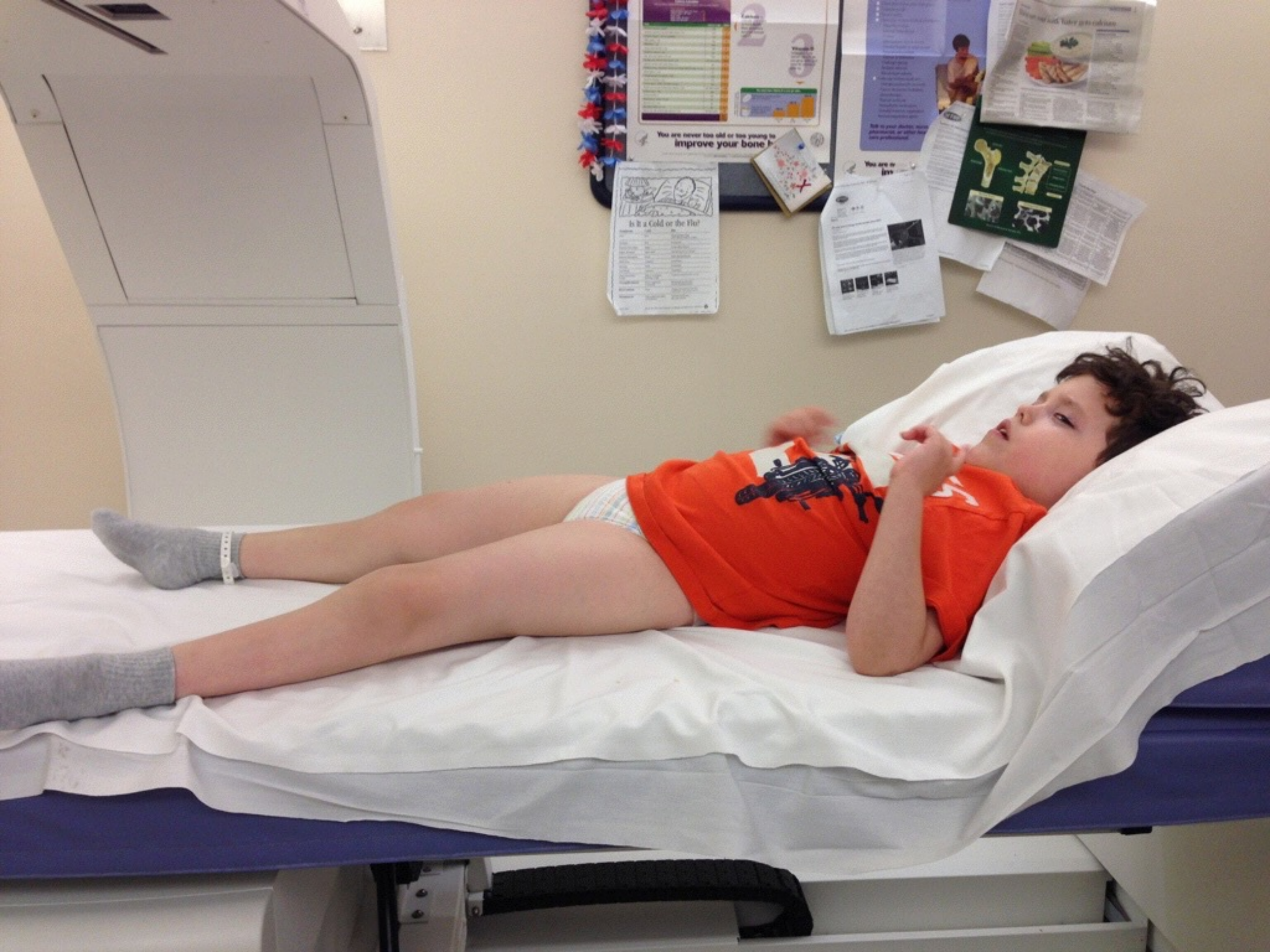
Control

Fluoro: Cu 0.0mm
Acquis: Cu 0.0mm
25.4 cGycm2

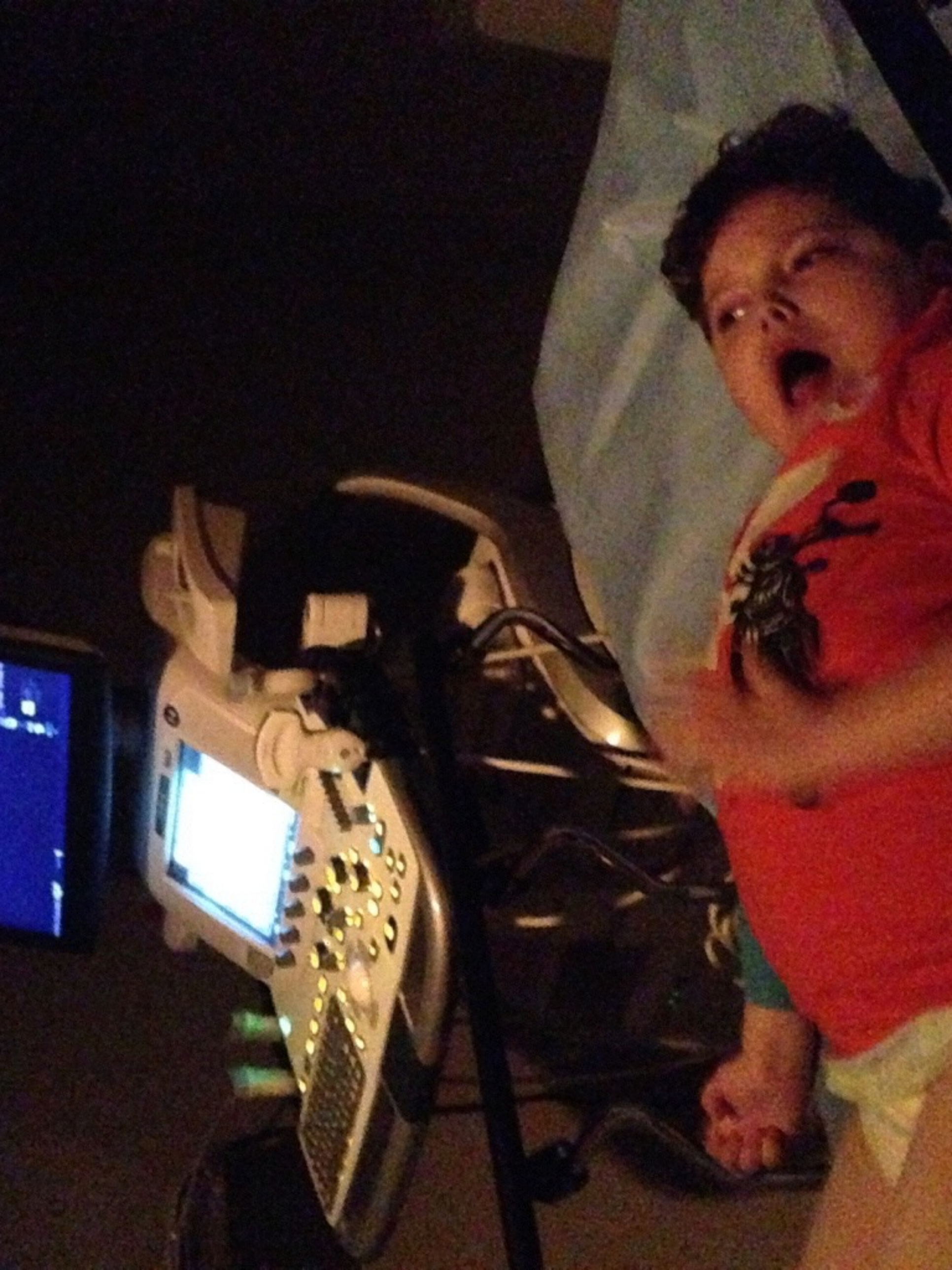
LIH



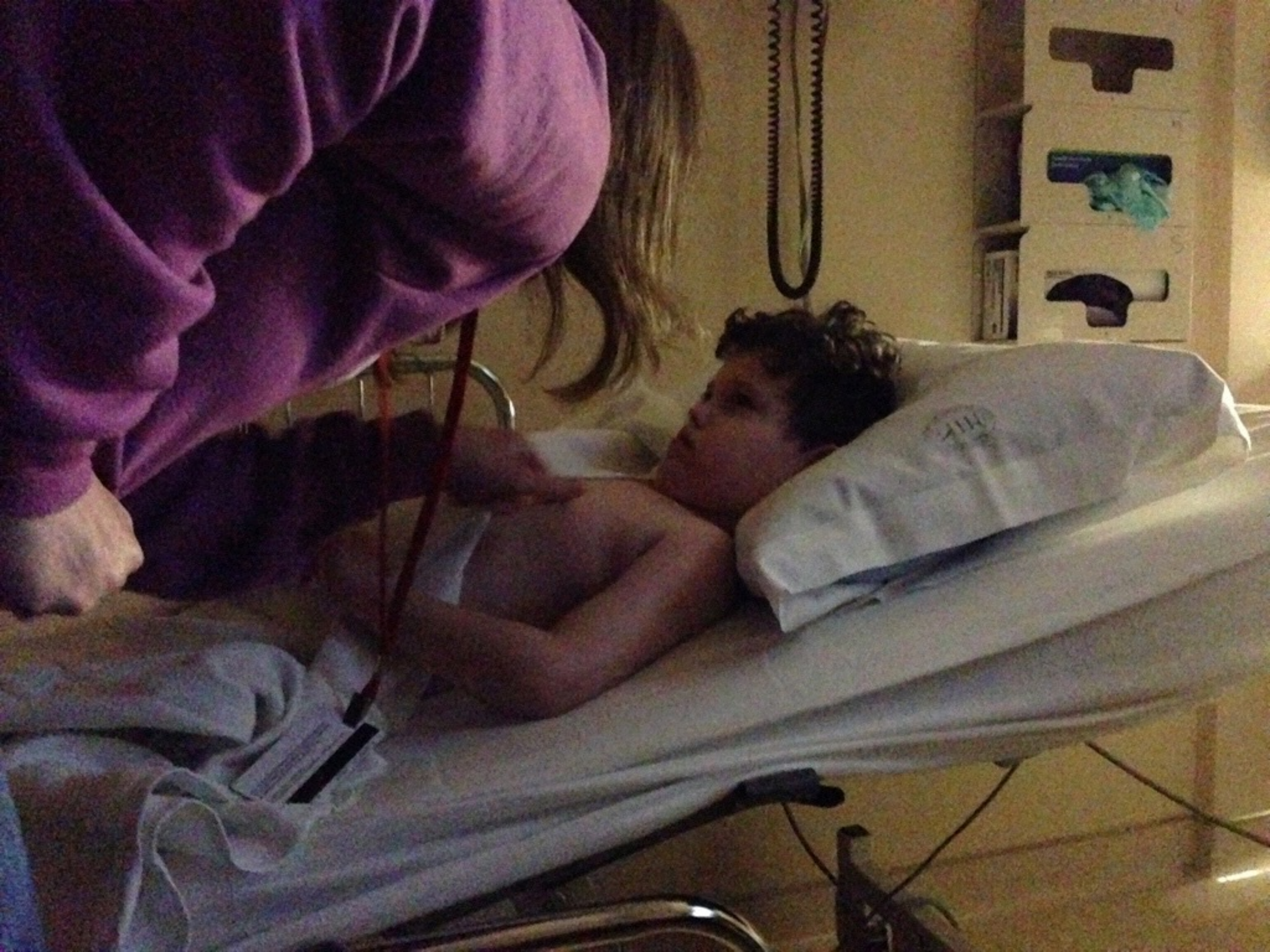

CYCLE


Is It a Cold or the Flu?


CYCLES
DELIVER TO

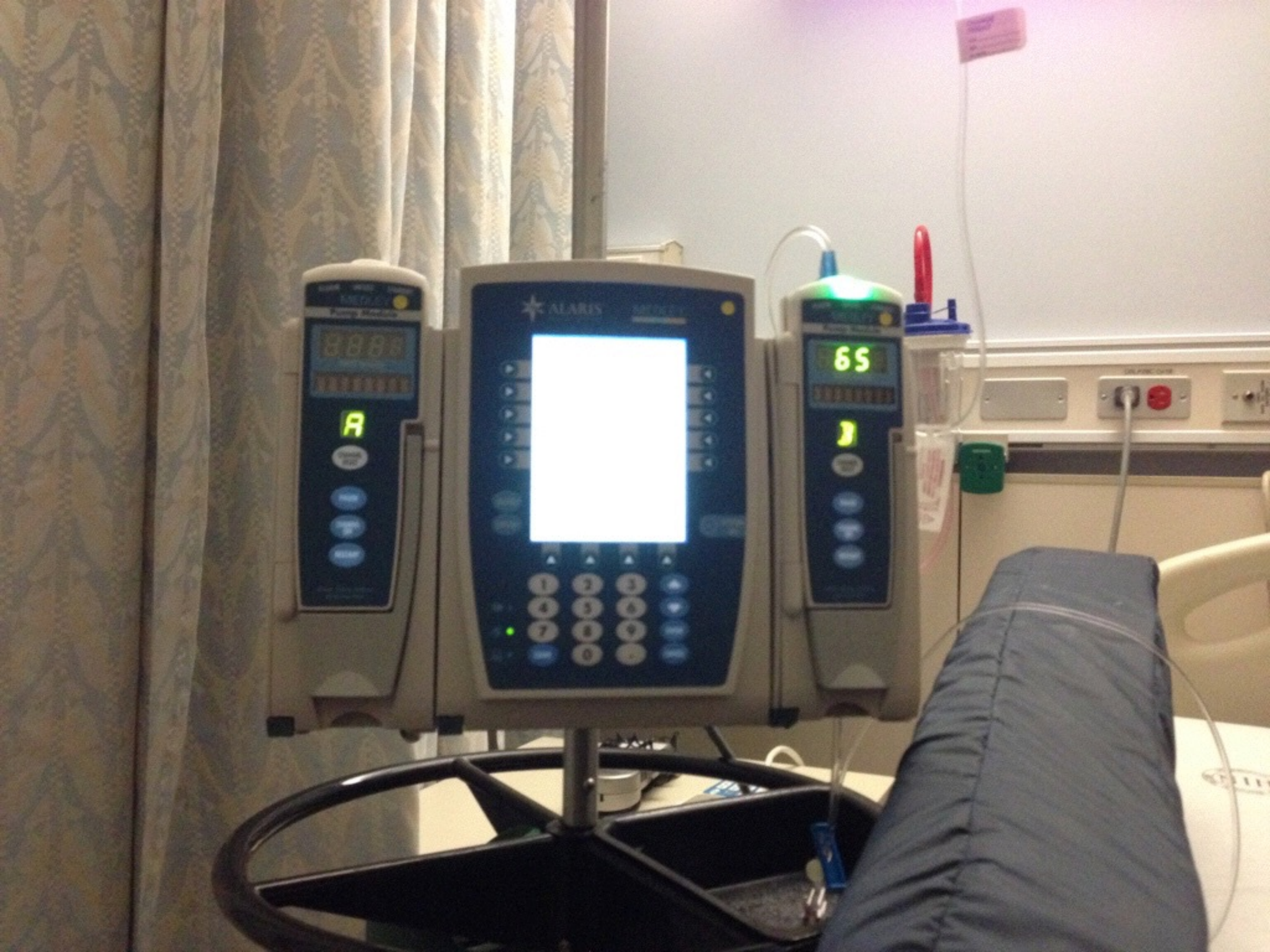



CYCLES



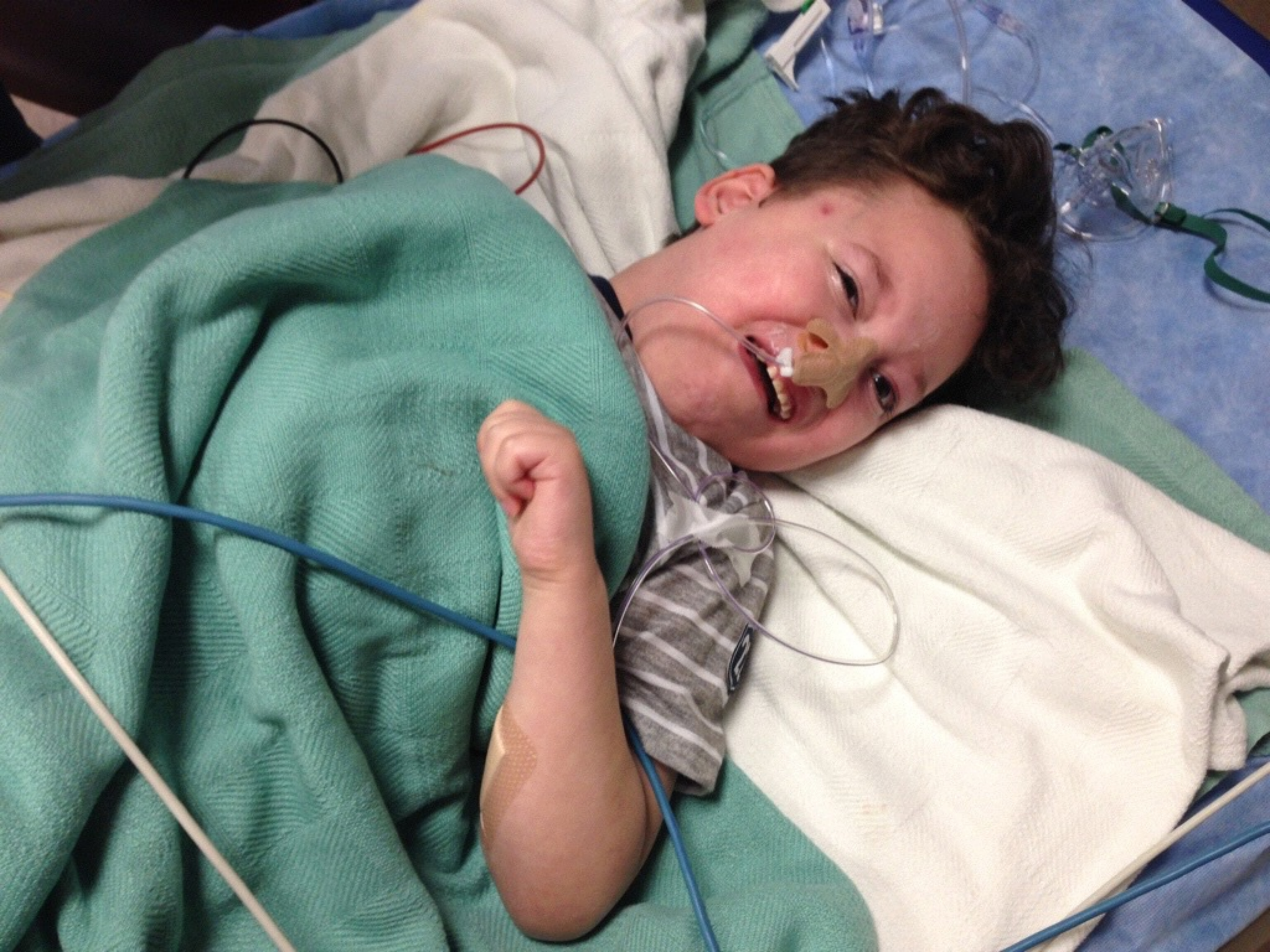

N.I.H. MEDICAL RECORD: U.S. GOVER
TO BE OPENED BY ADDRE
RAING

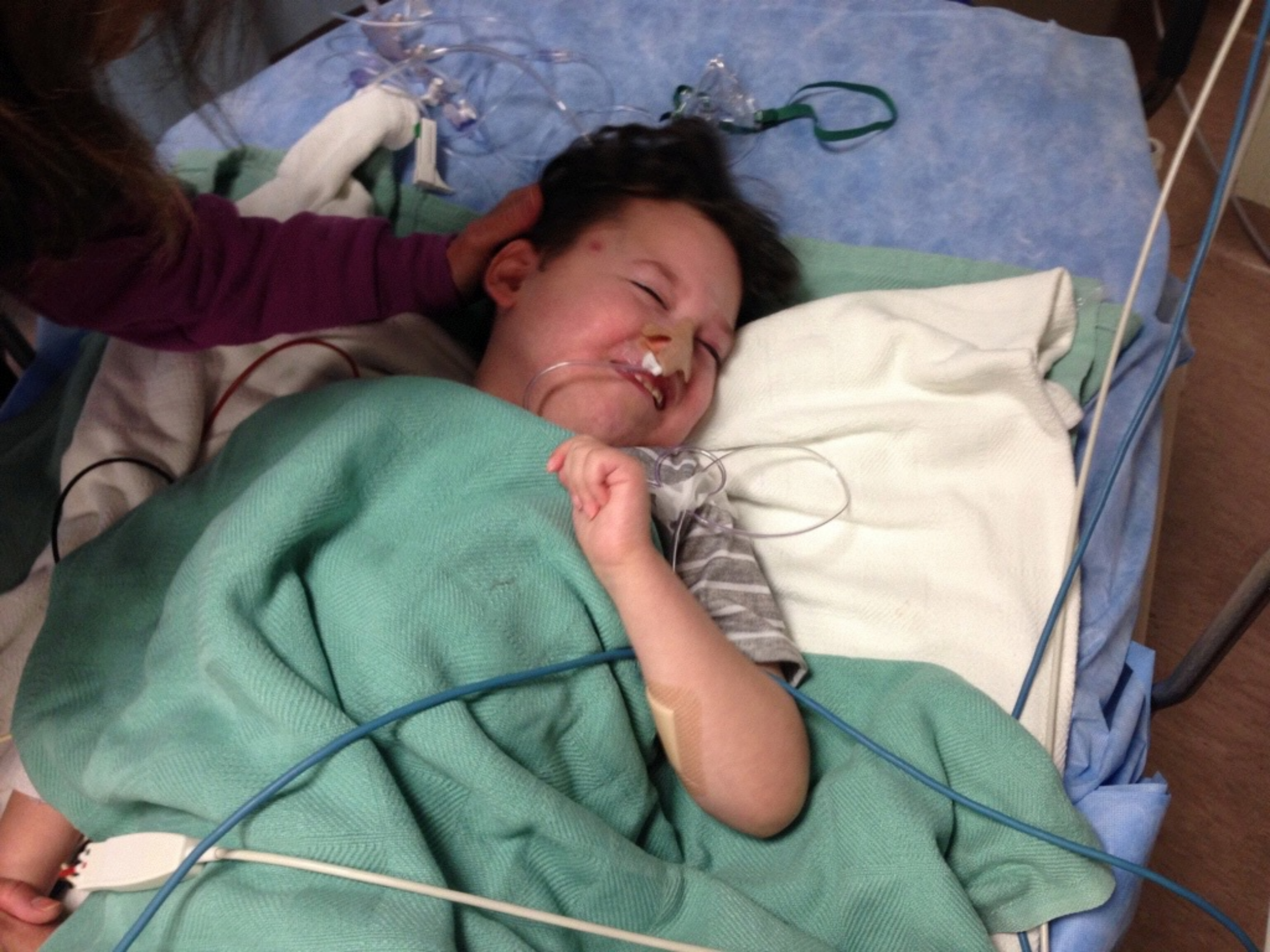

BRING

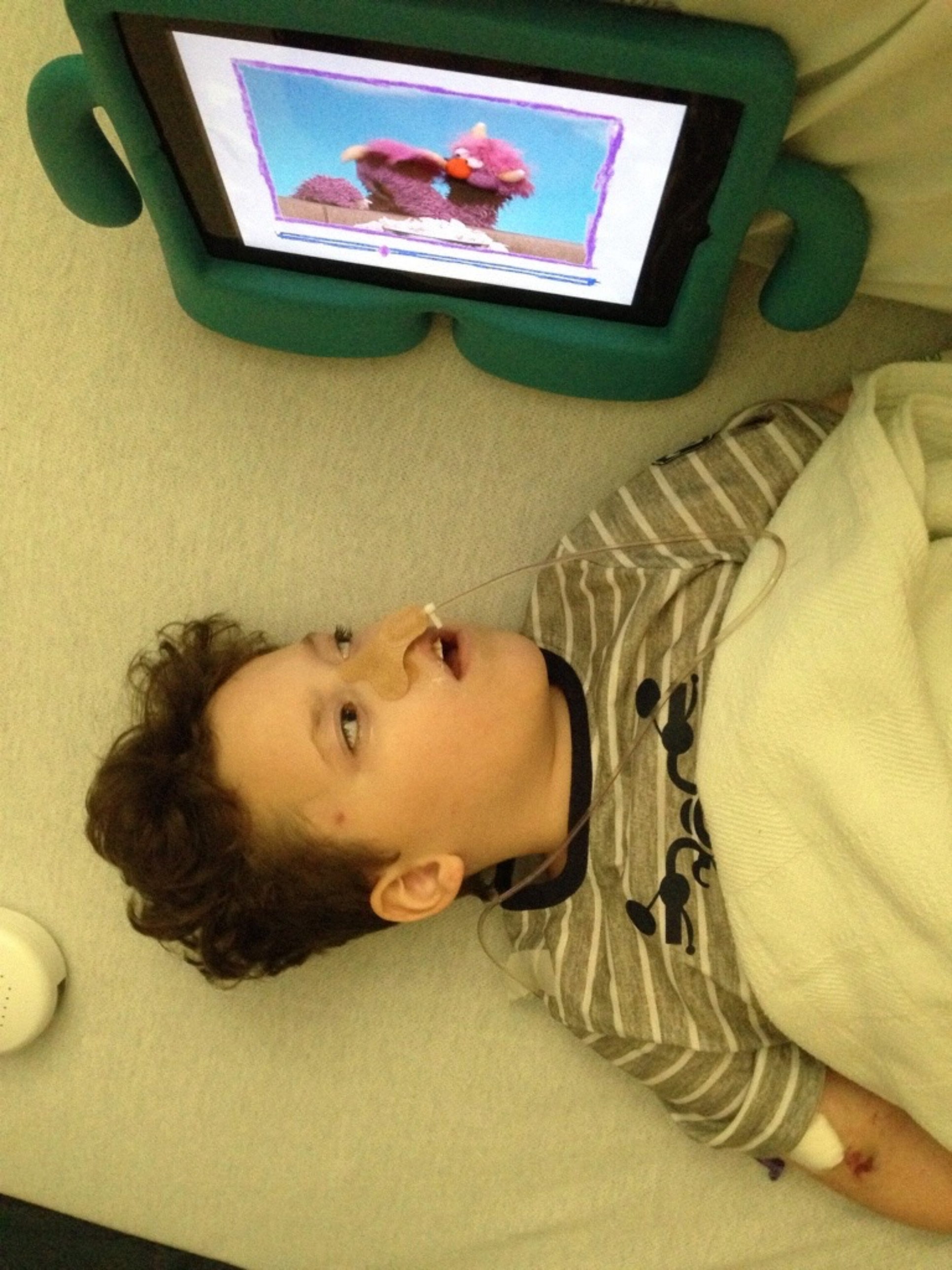

ALARIS
65

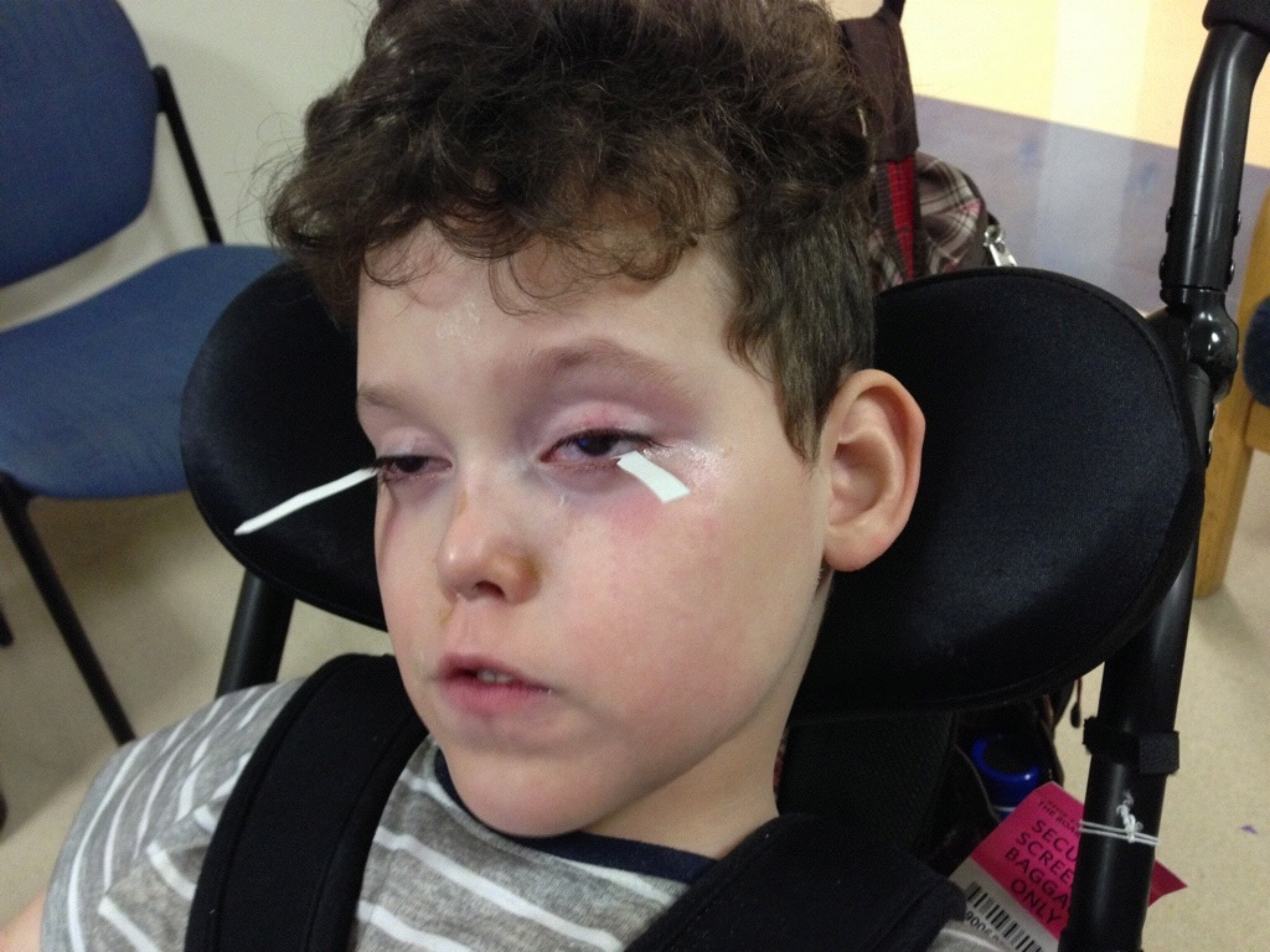

DELIVER TO
GOVERNMENT PROPERTY
ESSEE ONLY

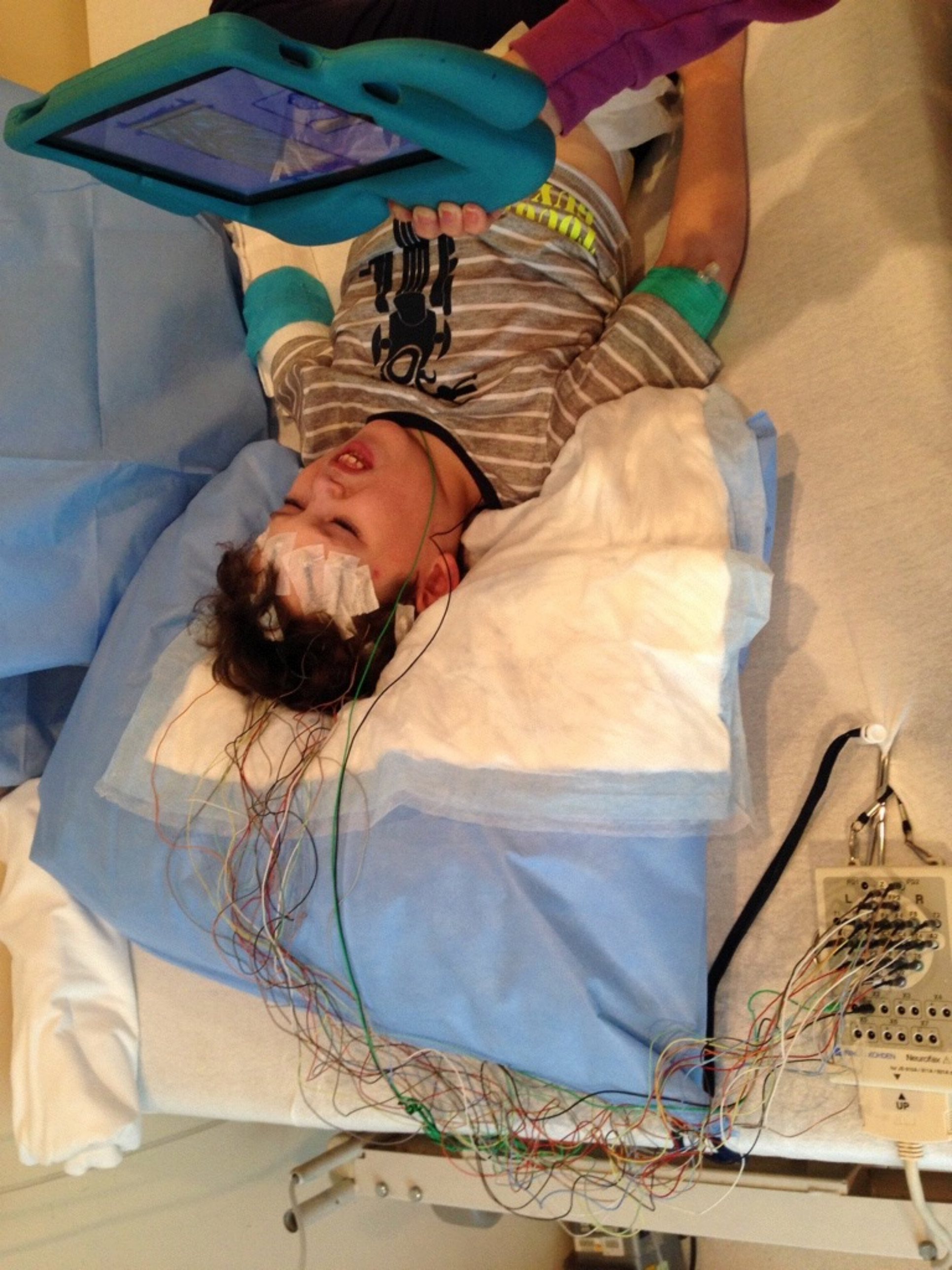

MAGNETOM Skyra
SIEMENS

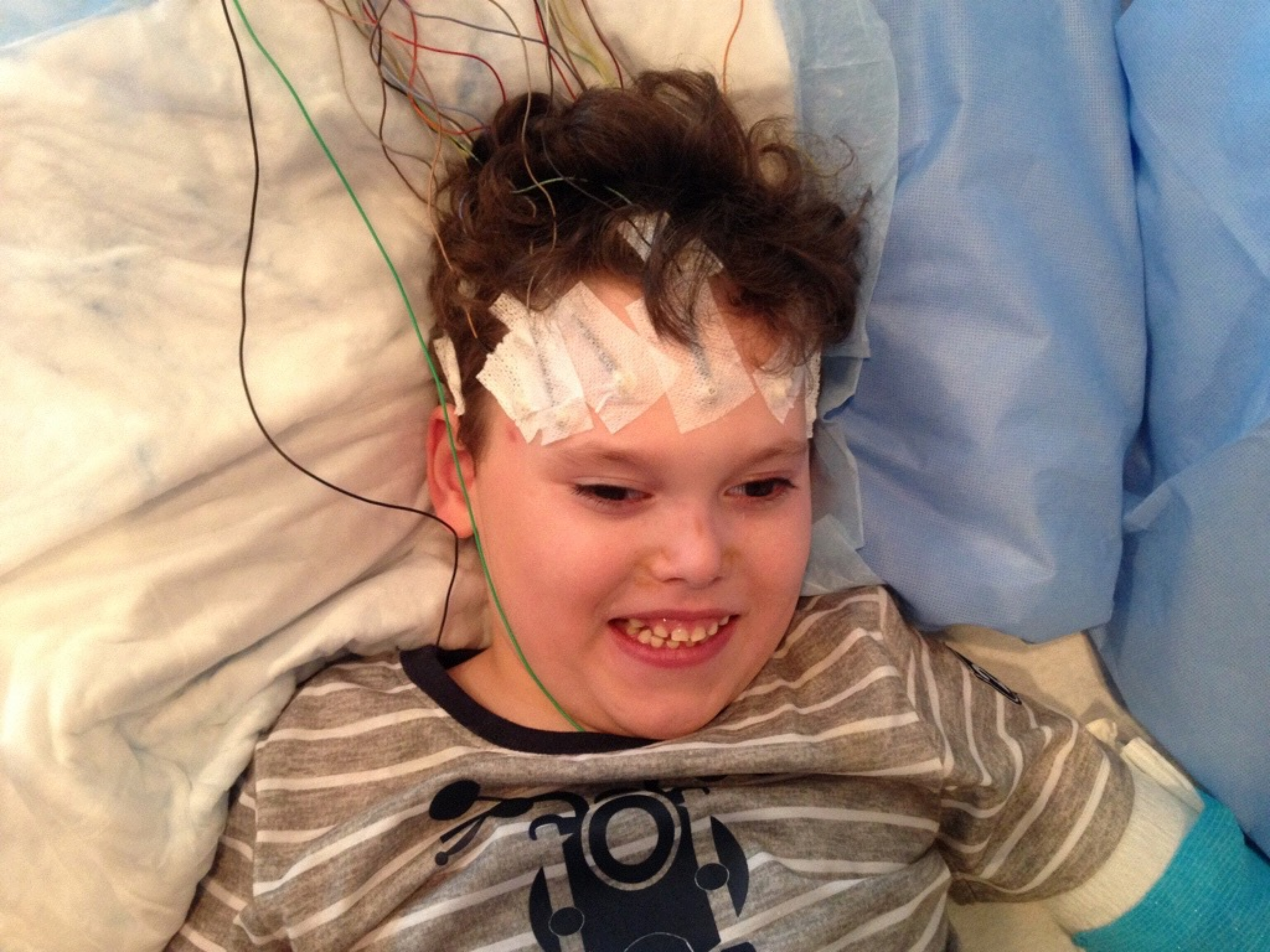


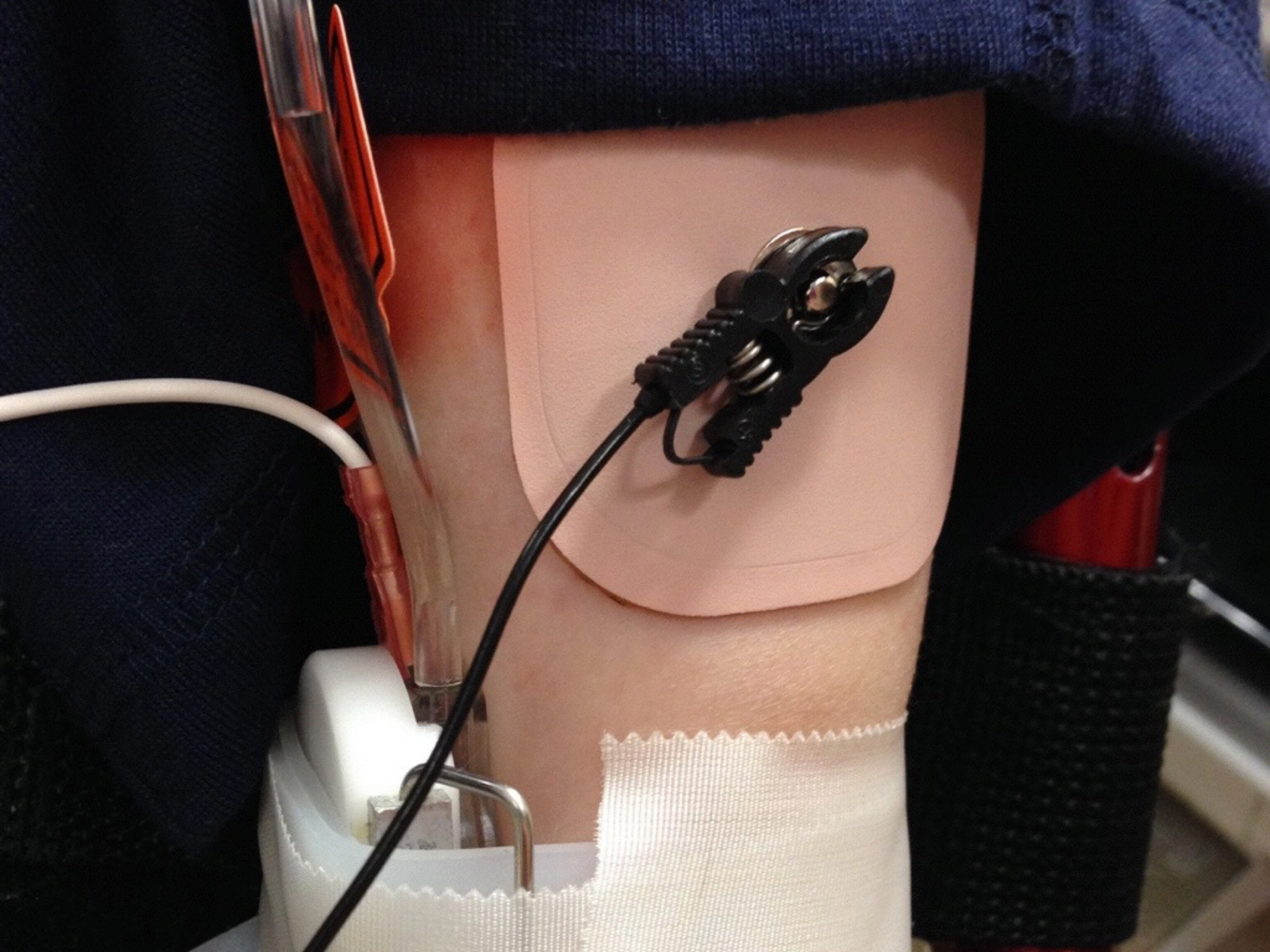


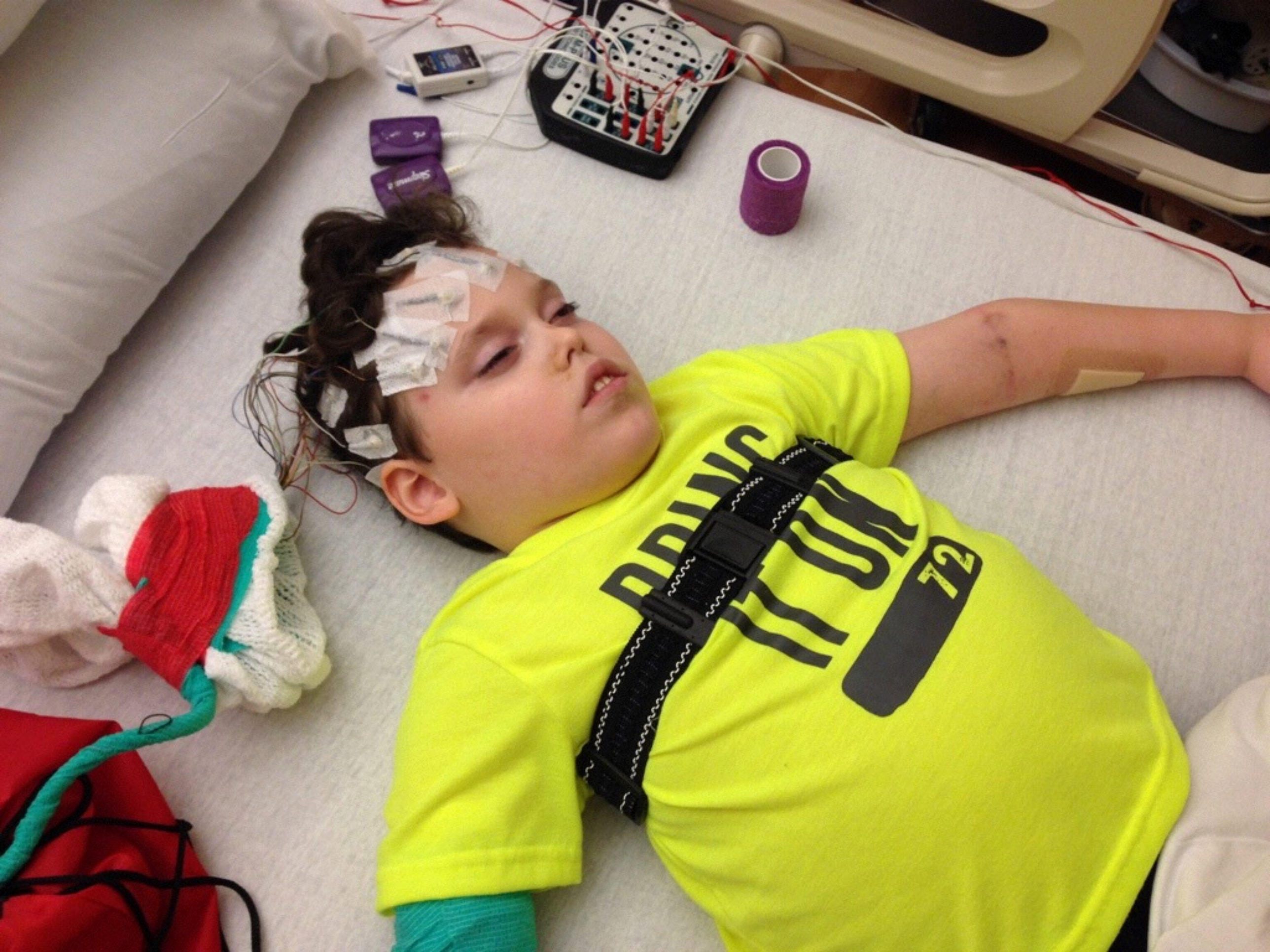


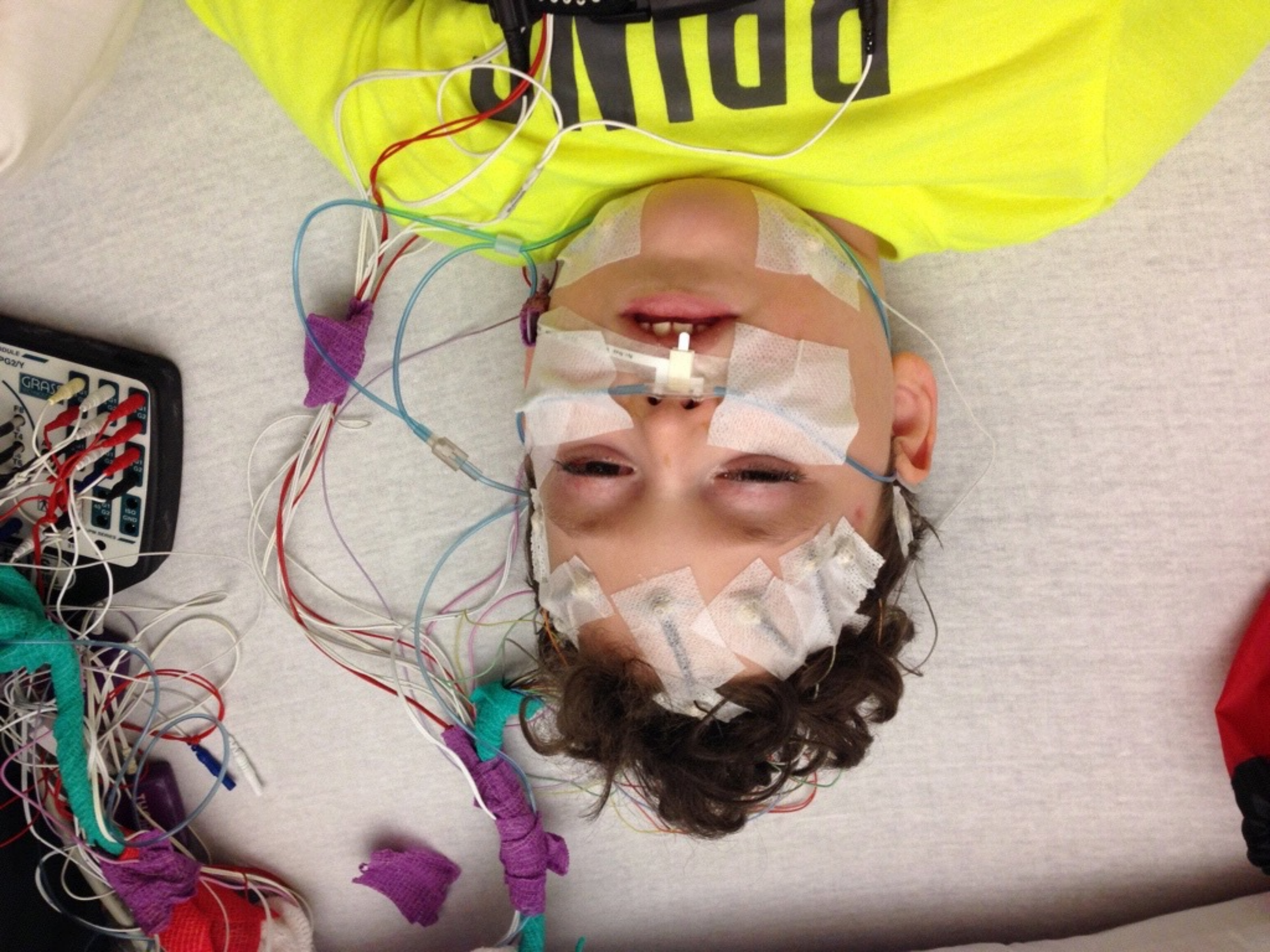


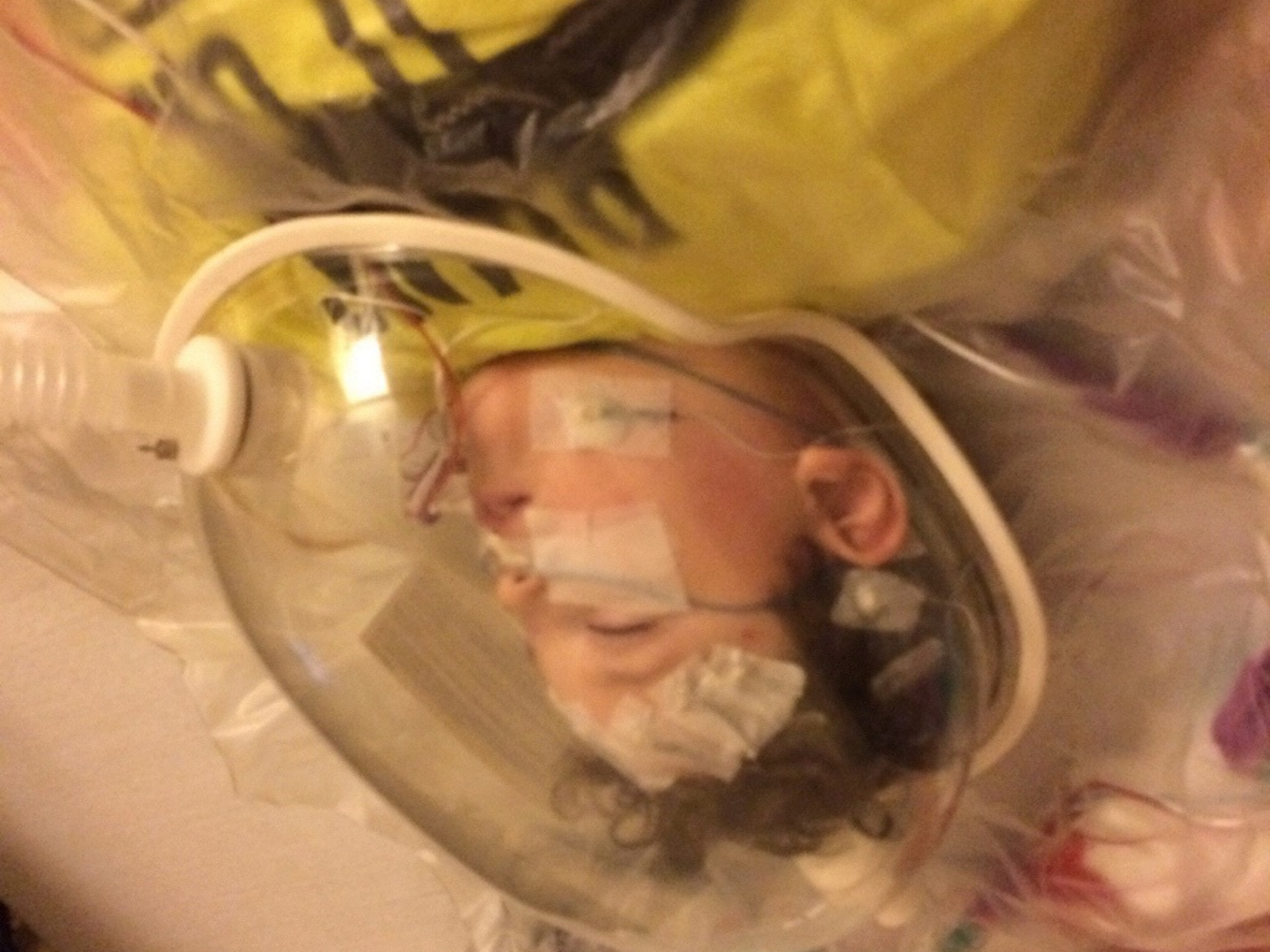










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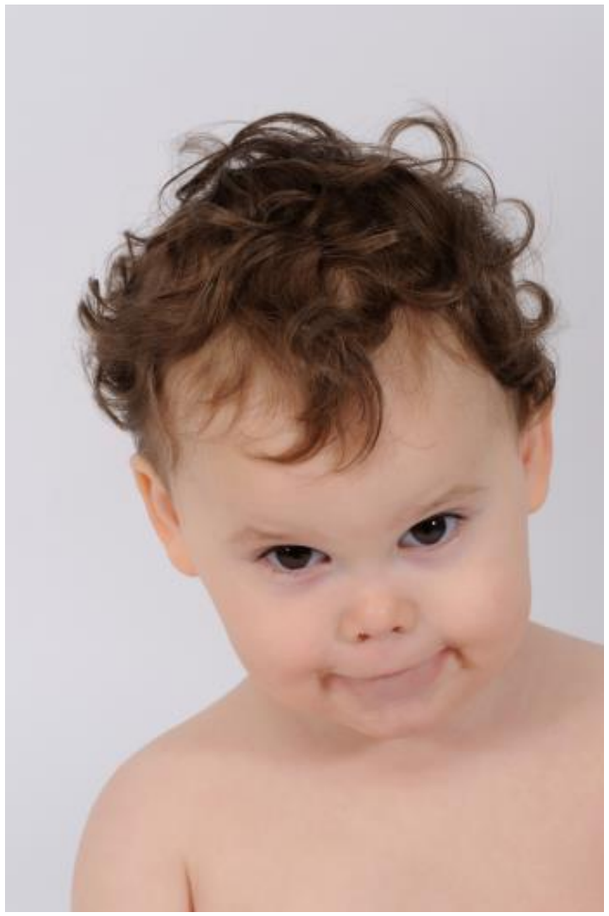
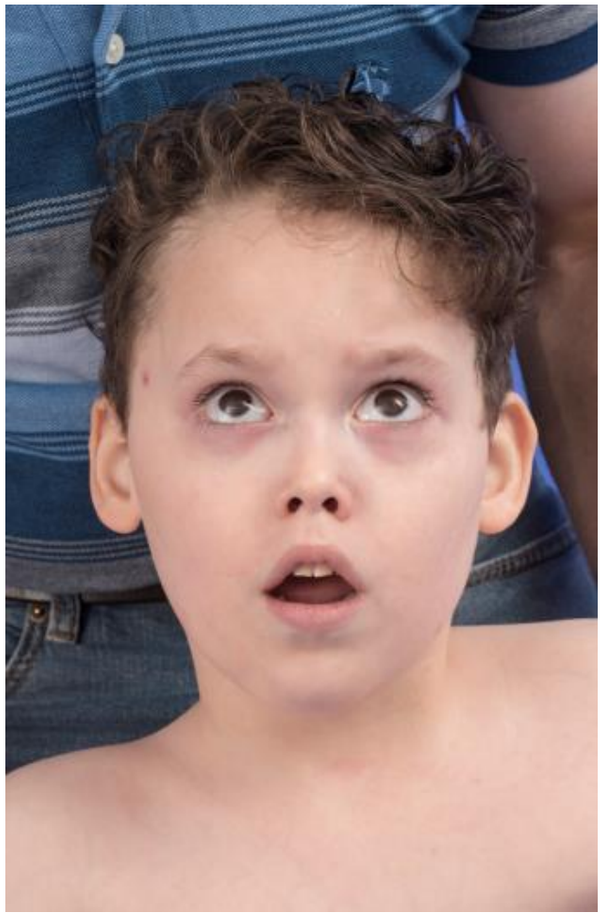
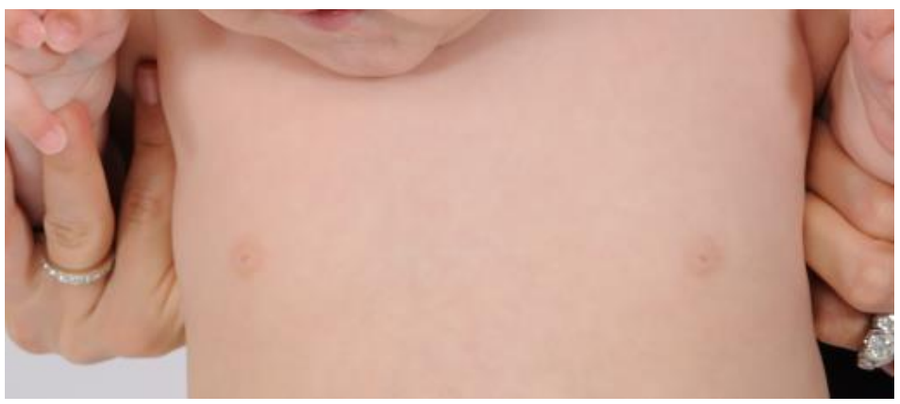
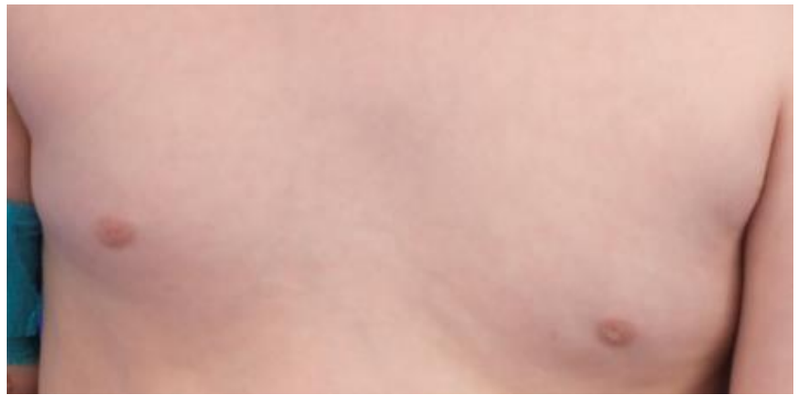
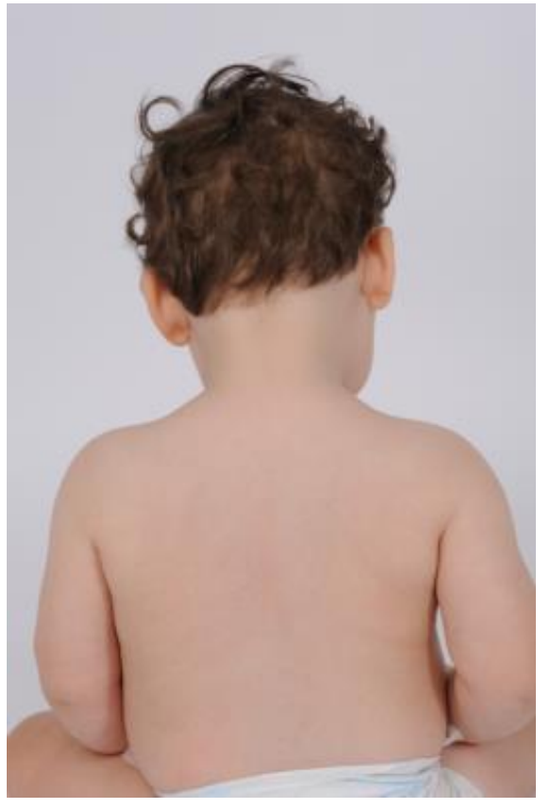
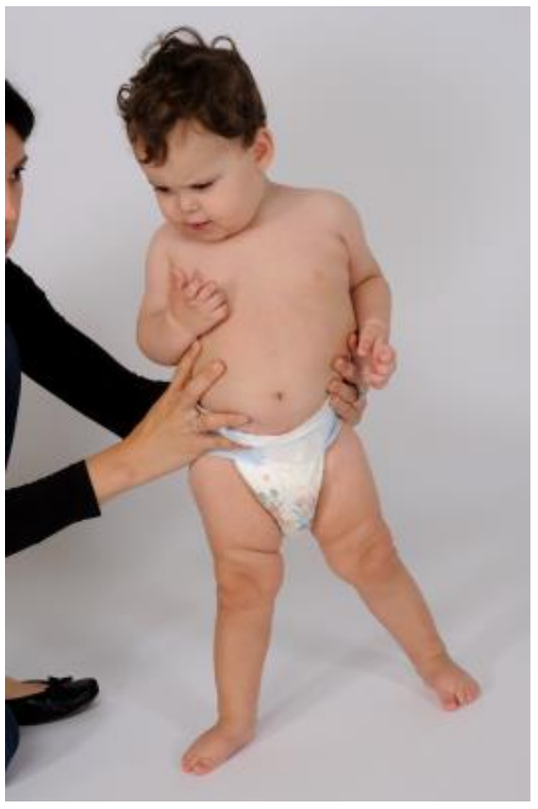




BRING
IT ON
72






BRING
IT ON
72

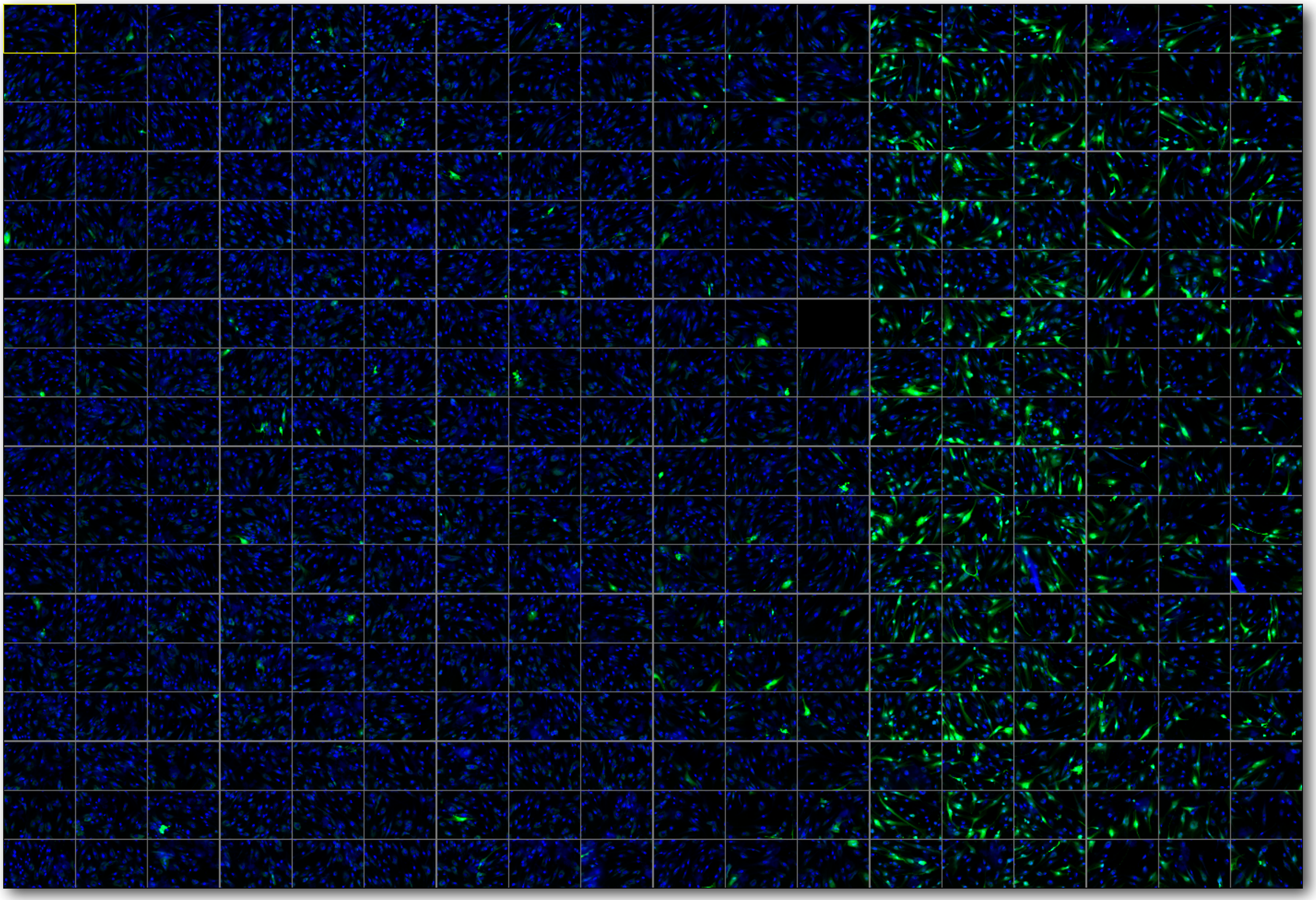

BRING
IT ON
72


BRING


BRING
72

Biomarkers!

High-throughput drug screening



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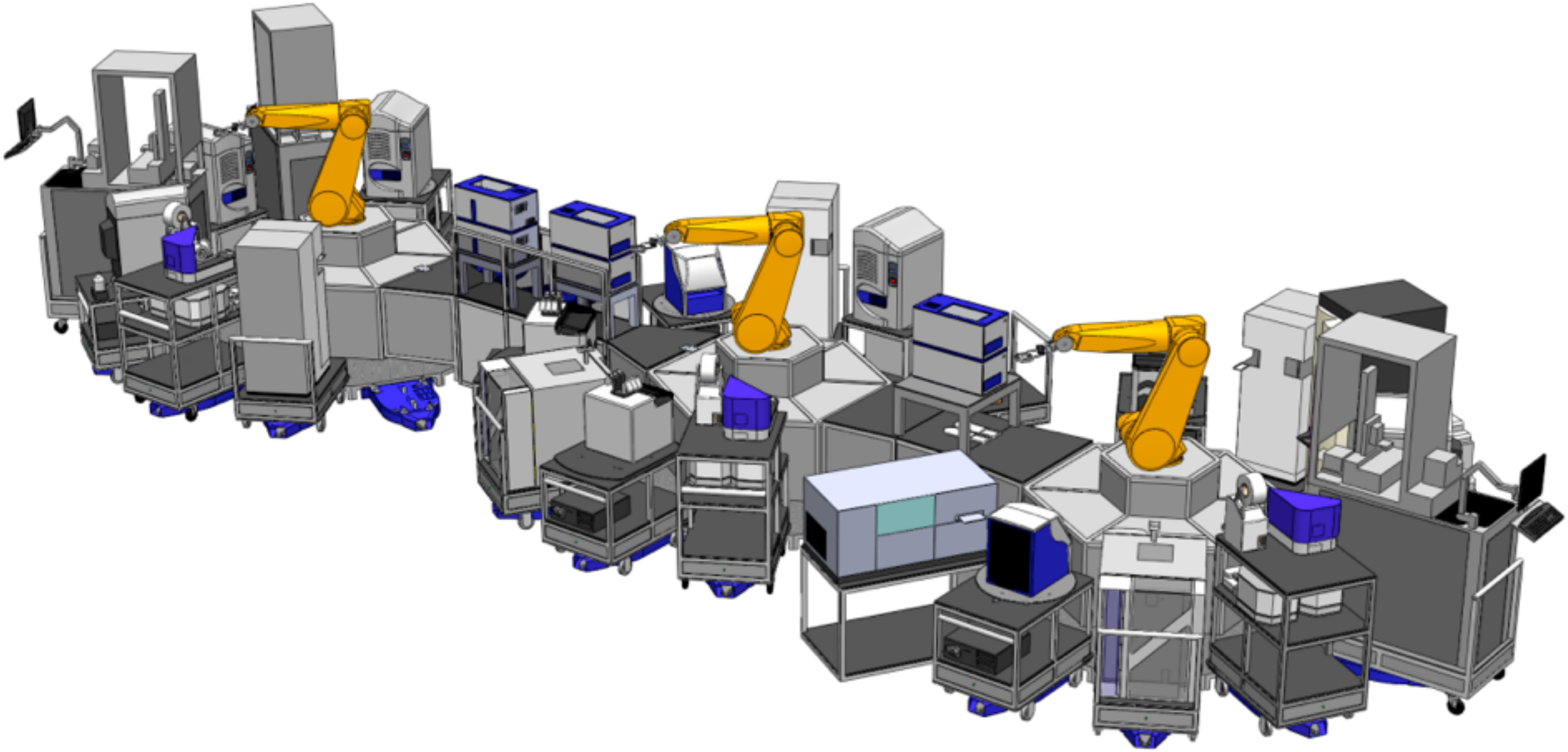

Transgenics


NUTRITIONAL
INNOVATIVE
Since KAL 1932
QUALITY
YEAST
Flakes
Vegan Friendly
PREMIUM • UNSWEETENED • FORTIFIED
Gluten Free
Wonderful Nutty Flavor
Non-GMO
NET WT. 22 oz. (624 g)

Biologics

Human NGLY1 full length protein (ab163212)

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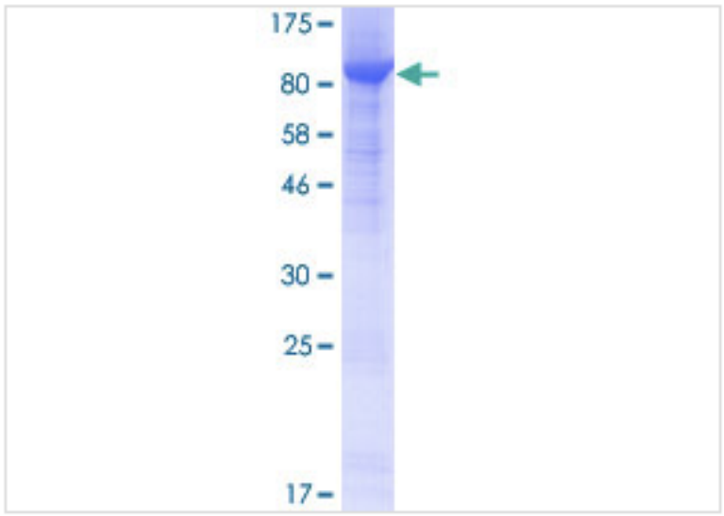
Datasheet



Datasheet | Specific References | Protocols

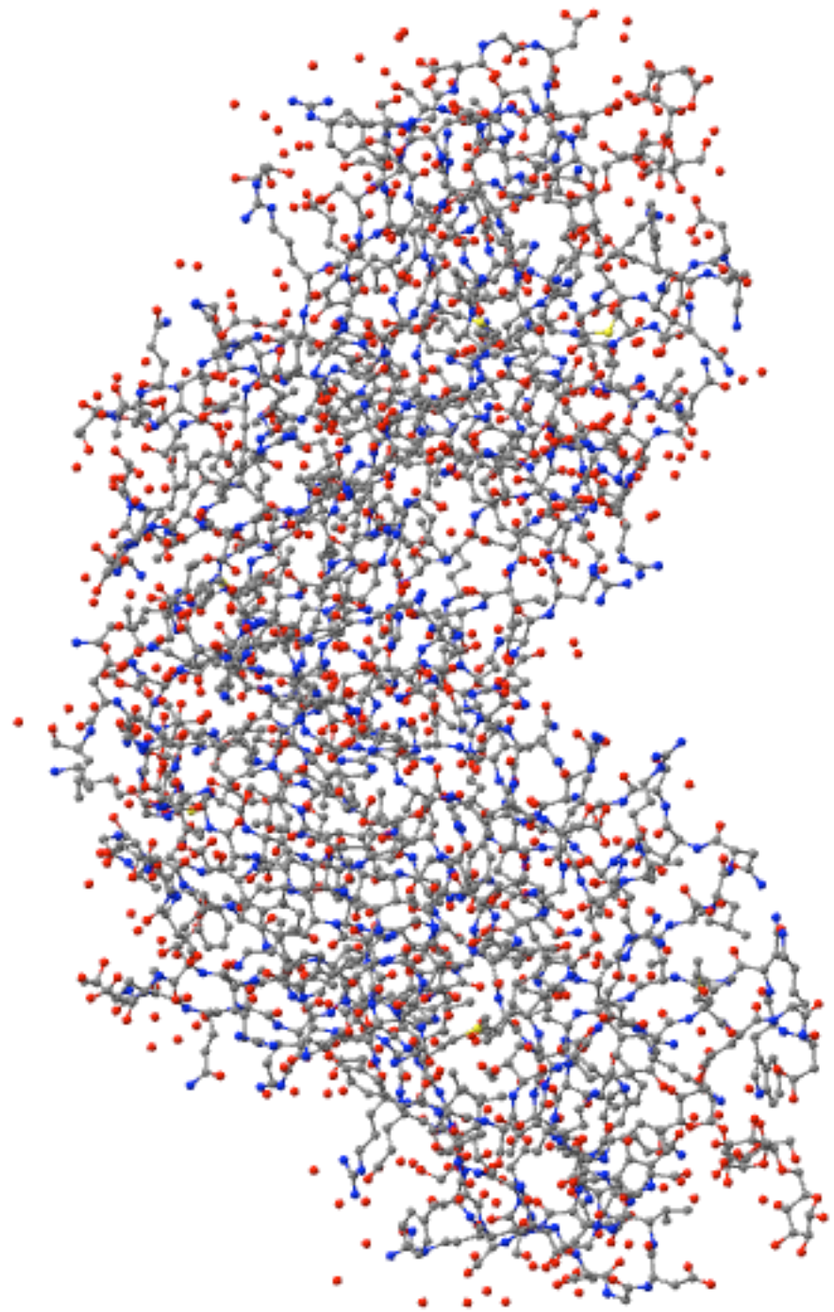
Overview

Customer reviews and FAQs

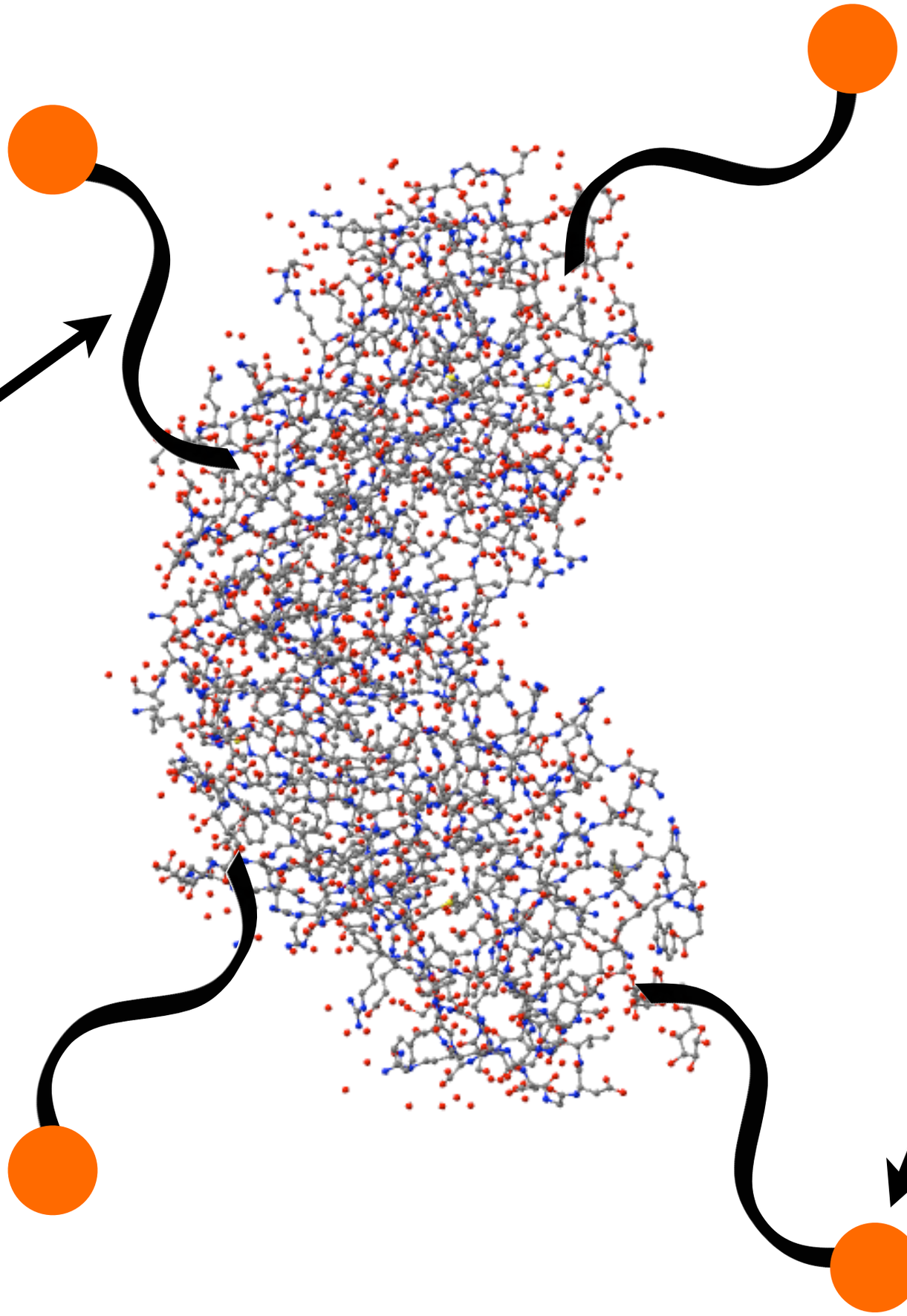
Product name	Human NGLY1 full length protein

Description

Nature	Recombinant
Source	Wheat germ
Amino Acid Sequence	
Species	Human



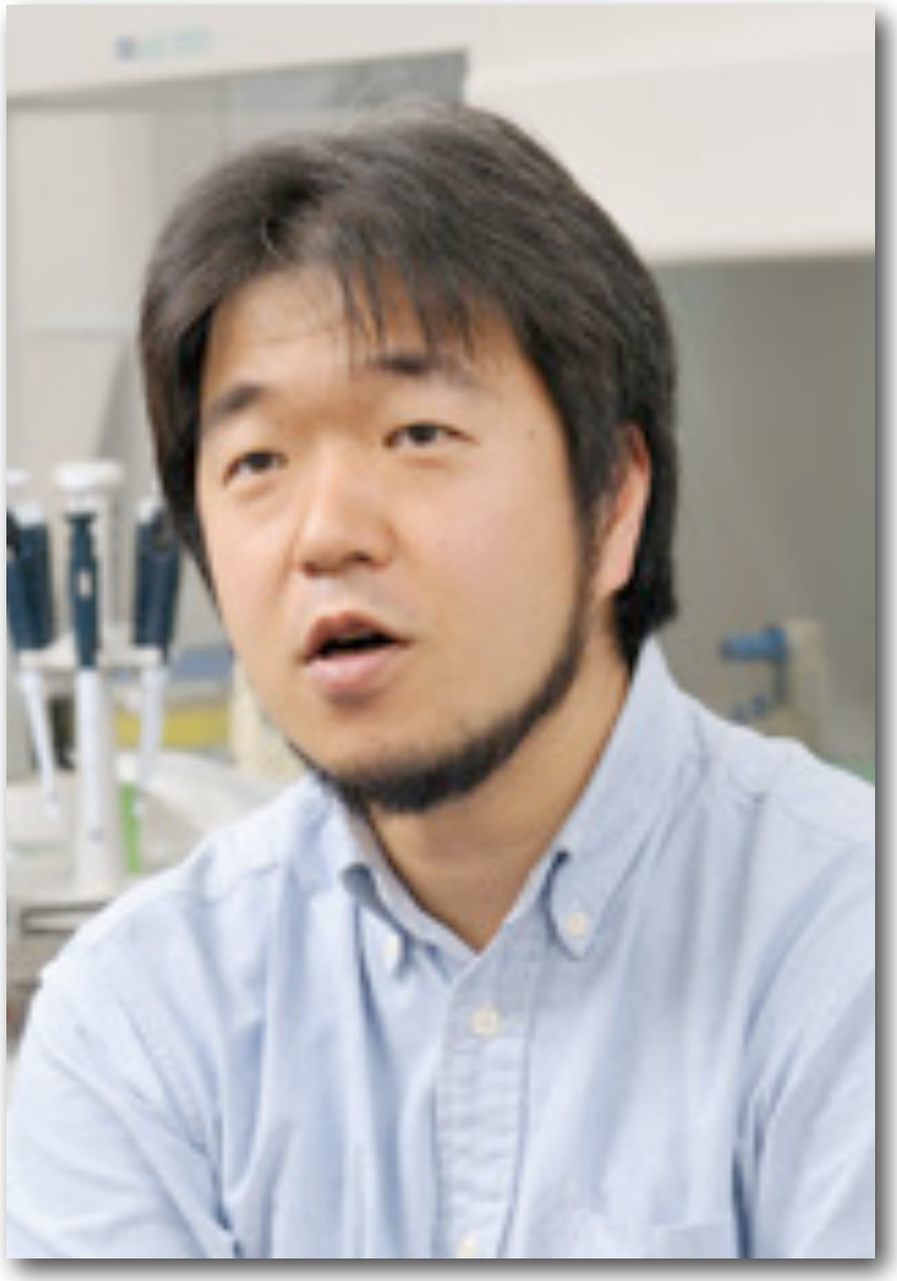
PEG polymer



TAT peptide

When suddenly…

a breakthrough



Suzuki

PNAS

Endo-β-*N*-acetylglucosaminidase forms *N*-GlcNAc protein aggregates during ER-associated degradation in Ngly1-defective cells

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Edited by David W. Russell, University of Texas Southwestern Medical Center, Dallas, TX, and approved December 30, 2014 (received for review August 1, 2014)

The cytoplasmic peptide:N-glycanase (PNGase; Ngly1 in mice) is a deglycosylating enzyme involved in the endoplasmic reticulum (ER)-associated degradation (ERAD) process. The precise role of Ngly1 in the ERAD process, however, remains unclear in mammals. The findings reported herein, using mouse embryonic fibroblast (MEF) cells, that the ablation of *Ngly1* causes dysregulation of the ERAD process. Interestingly, not only delayed degradation but also the deglycosylation of a misfolded glycoprotein was observed in *Ngly1*$^{-/-}$ MEF cells. The unconventional deglycosylation reaction was found to be catalyzed by the cytosolic endo-β-*N*-acetylglucosaminidase (ENGase), generating aggregation-prone *N*-GlcNAc proteins. The ERAD dysregulation in cells lacking *Ngly1* was restored by the additional knockout of ENGase gene. Thus, our study underscores the functional importance of Ngly1 in the ERAD process and provides a potential mechanism underlying the phenotypic consequences of a newly emerging genetic disorder caused by mutation of the human *NGLY1* gene.

PNGase (Ngly1) | ENGase | protein aggregates | glycoprotein | ERAD

Endoplasmic reticulum (ER)-associated degradation (ERAD) constitutes one of the quality control mechanisms for newly synthesized proteins in the ER. The ERAD process involves a series of events, including aberrant domain recognition, ubiquitination, translocation from the ER to the cytosol, and degradation by proteasomes. Numerous lines of evidence point to the existence of an ERAD system dedicated to N-linked glycoproteins; in this system, specific N-glycan structures dictate the folding status of client glycoproteins (1, 2). Once glycoproteins in the ER lumen are targeted for degradation, they are retrotranslocated into the cytosol, where the 26S proteasome plays a central role in their degradation (3). During the degradation process, N-glycans are removed by the action of the cytoplasmic peptide:N-glycanase (PNGase) (4–6).

Activity of the cytoplasmic PNGase was first described in mammalian cells (7, 8), and the gene encoding cytoplasmic PNGase (*PNG1* in yeast; *Ngly1*/*NGLY1* in mice/human) is widely distributed throughout eukaryotes (9). The functional importance of cytoplasmic PNGase in the ERAD process is evident in yeast (10–13). On the other hand, the suppression of *Ngly1* gene expression by siRNA in mammalian cells resulted in a reduced deglycosylation of T-cell receptor α subunit (TCRα) or MHC class I heavy chain, whereas no significant delay in their degradation was observed (14, 15). Moreover, Z-VAD-fmk, a pan-caspase inhibitor, was shown to inhibit cytoplasmic PNGase activity in vivo, but it did not impede the degradation of MHC class I heavy chain (16). Consequently, the functional importance of the cytoplasmic PNGase remains elusive in mammalian cells.

PNGase-mediated deglycosylation generates free oligosaccharides in the cytosol (17). Recent evidence suggests that a nonlysosomal degradation pathway exists for these cytosolic free glycans (17). This degradation process involves cytosolic endo-β-*N*-acetylglucosaminidase (ENGase) (18, 19). Although the ENGase is believed to be involved in the catabolism of cytosolic free oligosaccharides, recent evidence shows that it can deglycosylate glycoproteins in vivo to generate *N*-GlcNAc–bearing proteins in *Arabidopsis thaliana* (20), raising the possibility that this enzyme may also act as a deglycosylation enzyme for misfolded glycoproteins in the cytosol (21, 22) (Fig. 1*A*).

Recently, patients harboring mutations on the *NGLY1* gene, an ortholog of the cytoplasmic PNGase in mammalian cells (23), have been described (24, 25). Although this observation emphasizes the functional importance of this protein in mammalian cells, mechanistic insight into the phenotypic consequences of these patients remains unclarified. In this study, we established an ERAD model substrate, RTAΔm, and demonstrated that the delay in its degradation was evident in *Ngly1*$^{-/-}$ mouse embryonic fibroblast (MEF) cells. Interestingly, the delay was canceled by additional gene knockout of ENGase. The degradation of RTAΔm in double-knockout cells remains proteasome-dependent, clearly indicating that the presence of an N-glycan on RTAΔm did not affect the efficiency of proteasomal degradation. Moreover, the occurrence of *N*-GlcNAc–modified RTAΔm in *Ngly1*$^{-/-}$ MEF cells was identified by MS analysis, demonstrating that the ENGase-mediated

Significance

In the endoplasmic reticulum (ER), N-glycans on glycoproteins play important roles in dictating the folding status of proteins by a sophisticated N-glycan–dependent protein quality control machinery. In this study we identified the dysregulation of ER-associated degradation (ERAD) in cells that were defective in the cytosolic deglycosylating enzyme, Ngly1. ERAD dysregulation was caused by an unexpected deglycosylating activity of endo-β-*N*-acetylglucosaminidase, another cytosolic deglycosylation enzyme, and this action resulted in the intracellular formation of protein aggregates. Our results clearly point to the critical role of N-glycans even in cytosolic events of the ERAD process by controlling the conformation/solubility of proteins. This study may also provide a potential mechanism for explaining the pathology of a human genetic disorder caused by mutations in the *NGLY1* gene.

Author contributions: C.H. and Tadashi Suzuki designed research; C.H., Y.H., A.H., Y.M.-N., J.S., H.F., Y.F., Takehiro Suzuki, and N.D. performed research; Y.H., A.H., Y.M.-N., and Y.F. contributed new reagents/analytic tools; C.H., Y.H., A.H., J.S., H.F., Y.F., Takehiro Suzuki, N.D., and Tadashi Suzuki analyzed data; and C.H. and Tadashi Suzuki wrote the paper.

The authors declare no conflict of interest.

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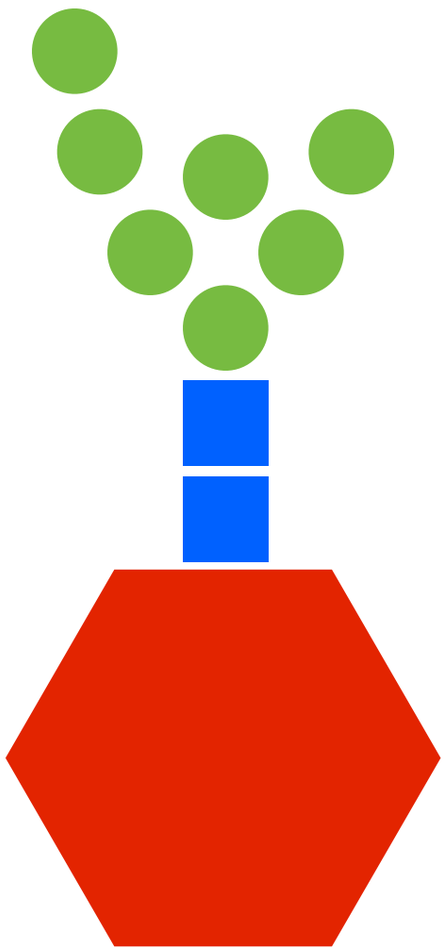

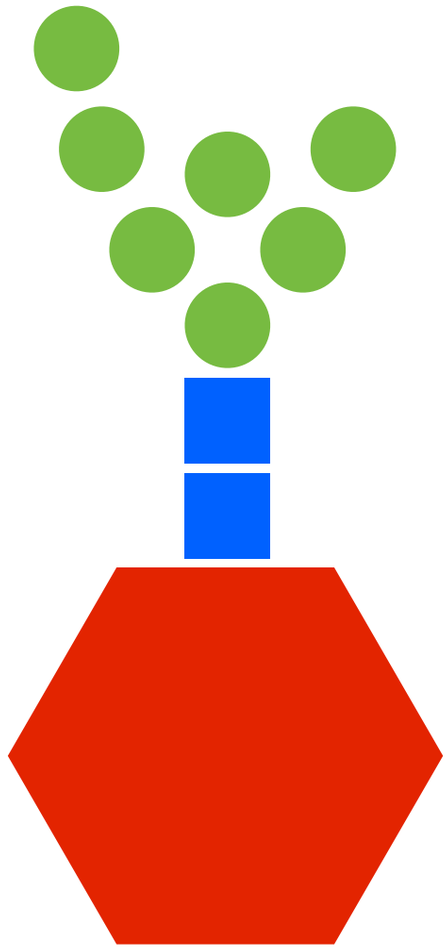

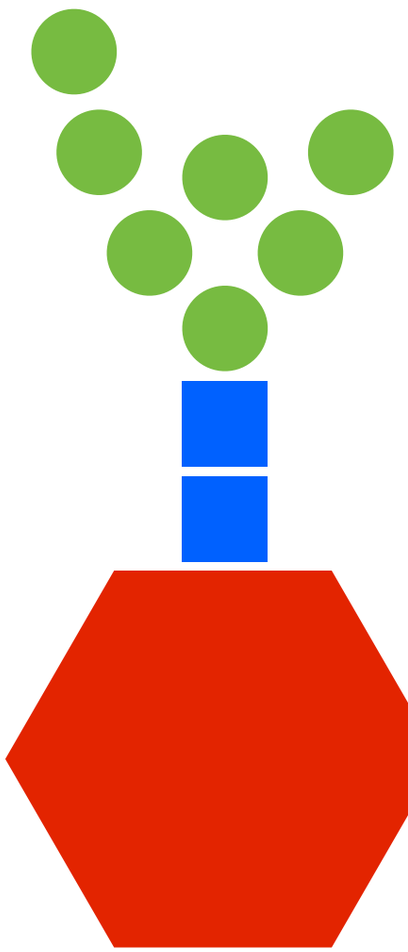

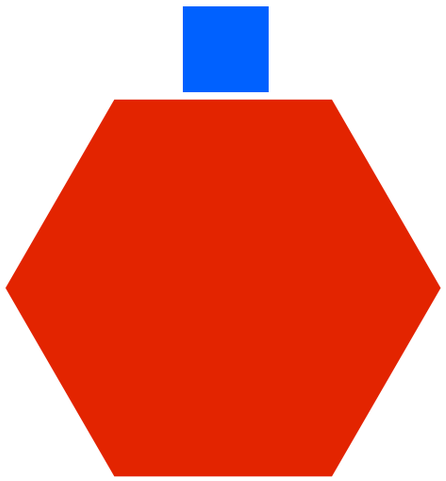

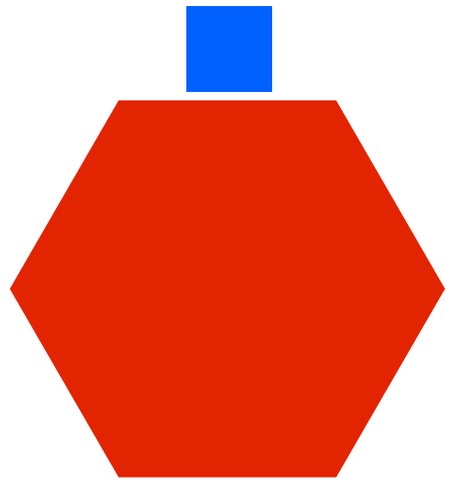

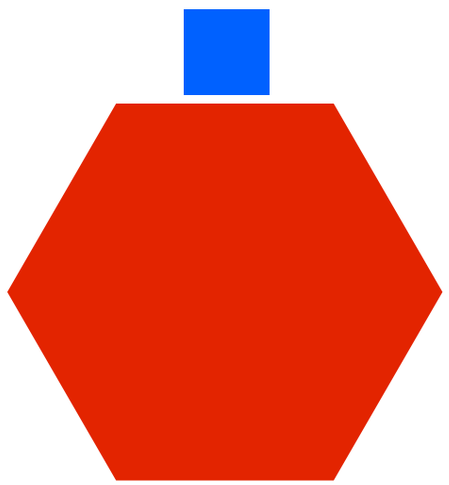

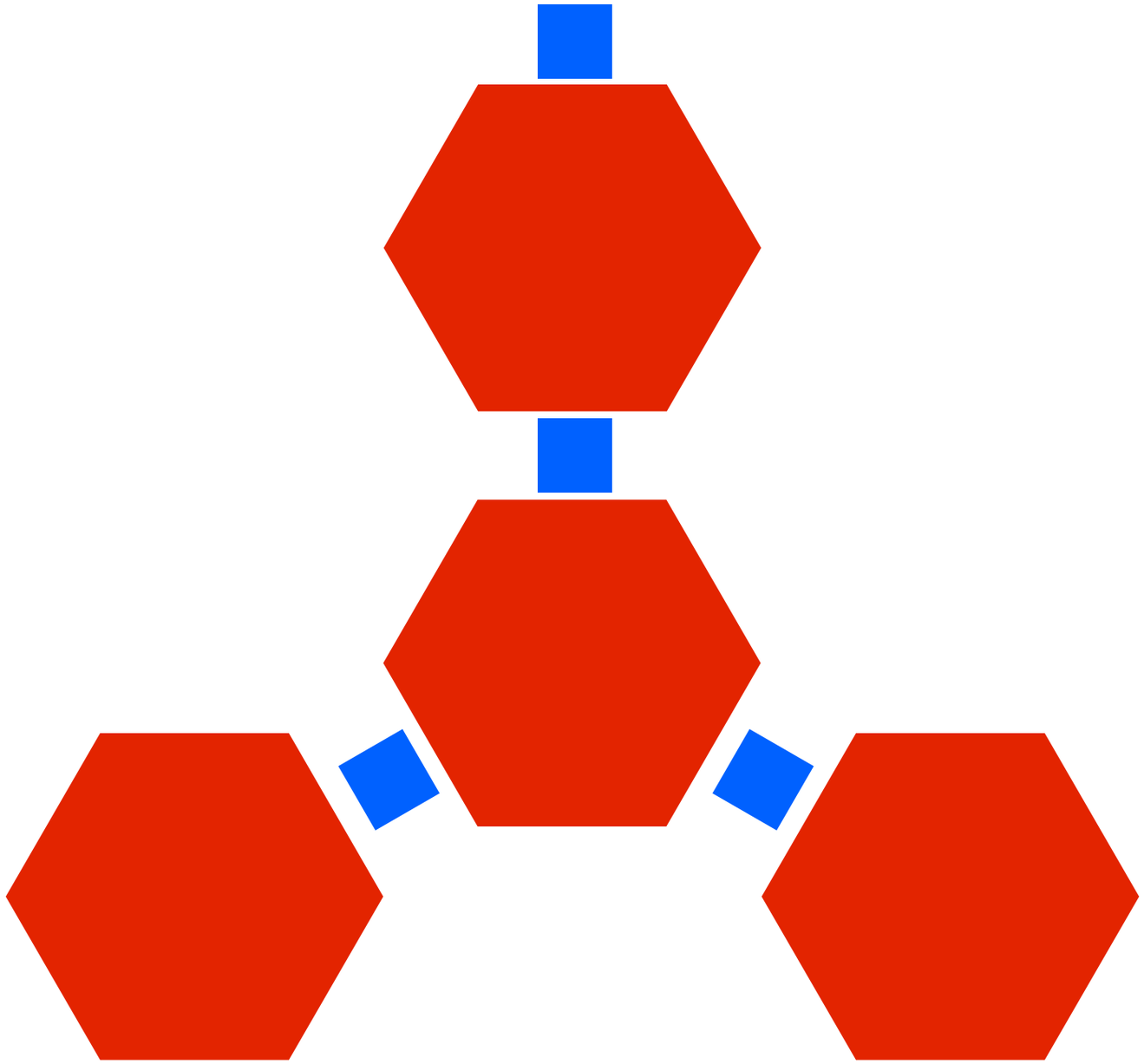

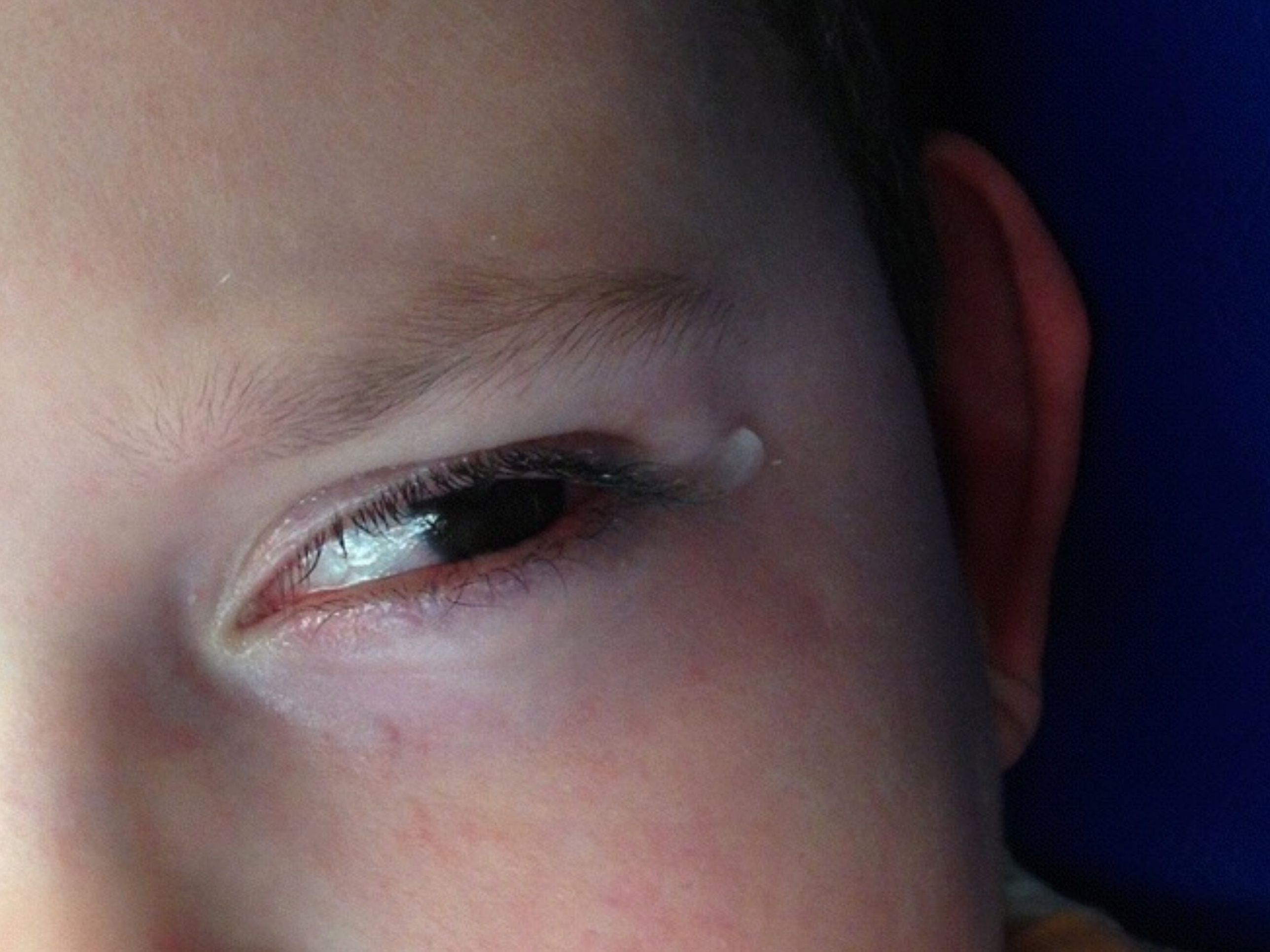

HIV

Ebola

NGLY1

MS

Diabetes

“Community breakthroughs”

Replicable?

Yes

MILO'S JOURNEY

....looking for companions

Reaching out

This page is for parents, doctors, or researchers who may know of other children like our son, Milo. If you know of a similar case, please get in touch with us. The more cases we have, the more opportunities we will have to improve our understanding of his condition and facilitate research that can help him and others.

Find out more

- What this site is for
- Case study:

Finding others like our Milo

Currently, at age 3, Milo's primary challenges are global developmental delay and significant hypotonia. He has had surgical repairs for a minor cleft in his soft palate, for ptosis, for C1 stenosis, for a tethered

The Stop Sign in Aidan's Genes (PURA GENE)

I have something special to show you, a little piece of yourself.

But first let me tell you why it's so incredible to me.

My son Aidan was born 13 years ago with an undiagnosed developmental disability so for 13 years I've been watching human development in slow motion. The strength of our muscles, the authority of the brain, the power of the body to heal. The same brain that's made it difficult for him to walk and impossible for him to speak, has also given him the cognitive ability and dexterity to drive a power wheelchair and find other ways to communicate.

For 13 years Aidan's medical team has been searching for a cause of his medical issues. For 13 years we've come up empty handed.

Until now.

Six months ago Aidan's whole exome was sequenced and we found two genetic mutations.

All knowledge is actionable.

The knowledge enables community.

The community drives action.

Thank you!

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