Researcher perspective on state, gaps and opportunities

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Presentation overview

- Maturation of renal function
- Interplay of age and renal impairment
- What do we know about PK in pediatric renal insufficiency?
- Real-life practice

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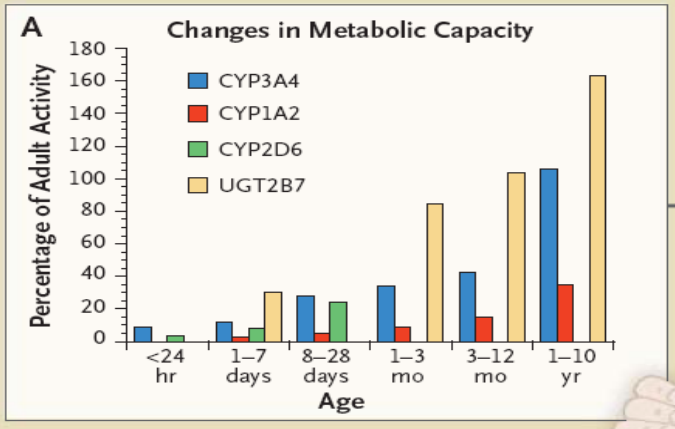

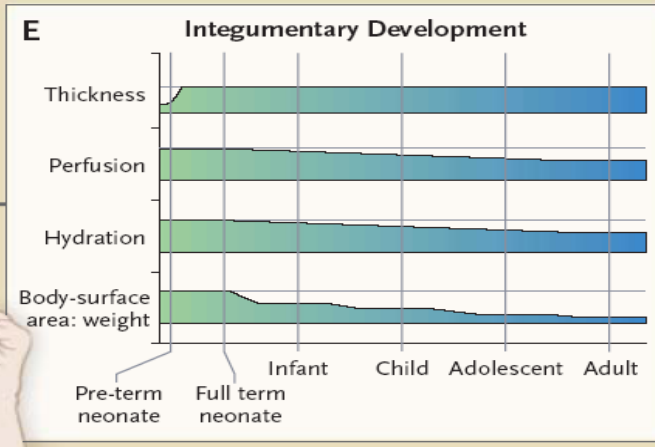

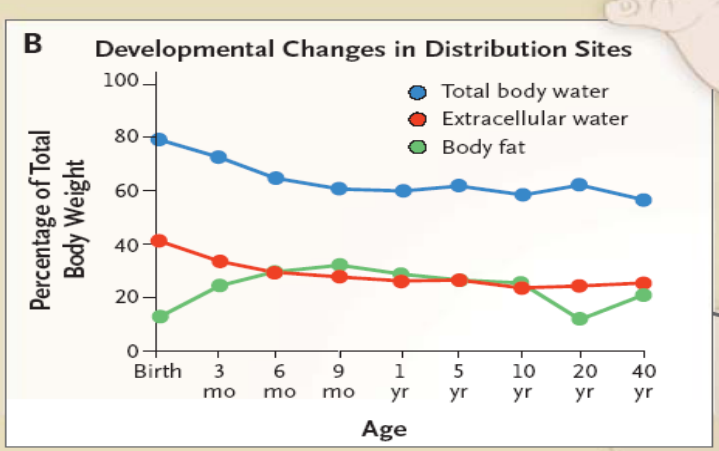

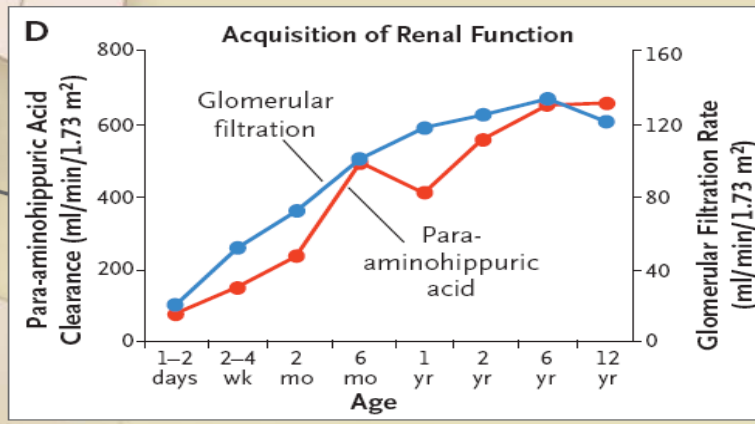

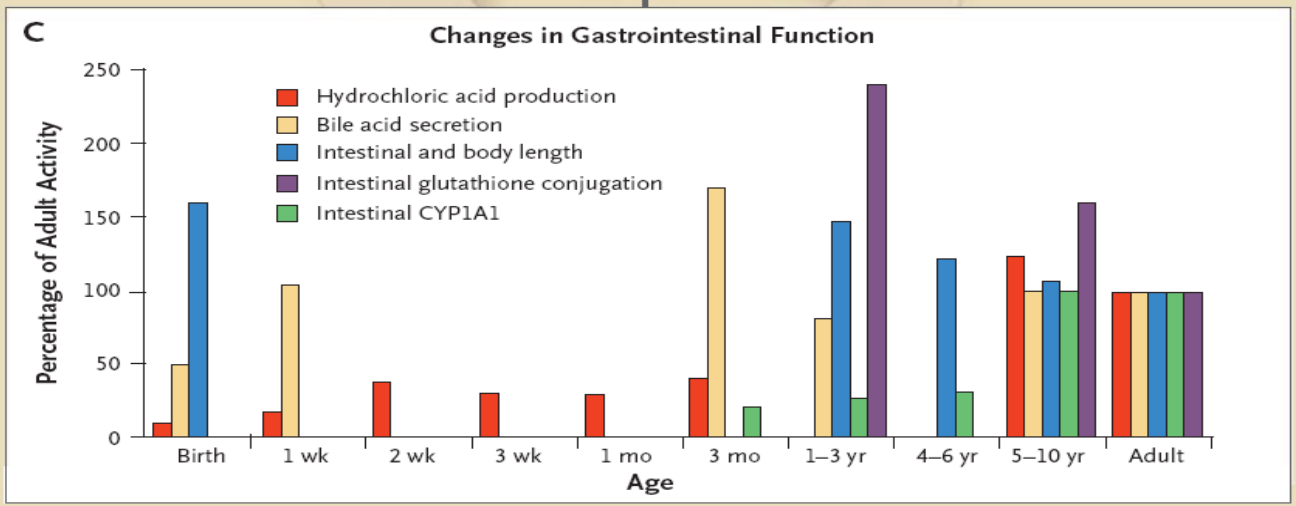

Kearns et al
NEJM, 2003

Extrapolation from adults to children

Review > Expert Opin Drug Metab Toxicol. 2022 Feb;18(2):99-113.
doi: 10.1080/17425255.2021.2027907. Epub 2022 Feb 25.

An Update on the Use of Allometric and Other Scaling Methods to Scale Drug Clearance in Children: Towards Decision Tables

Anne van Rongen [1], Elke Hj Krekels [1], Elisa Am Calvier [2], Saskia N de Wildt [3 4], An Vermeulen [5 6], Catherijne Aj Knibbe [1 7]

Choice of method (linear, allometry or PBPK models) dependent on:
age, drug elimination route (GFR, active tubular transport, binding plasma protein, fraction unbound

Extrapolation from adults to children

Table 1. Decision table for [illegible] scaling methods for renally cleared drugs through glomerular filtration (GF) and active tubular secretion (ATS) for typical children of different a[illegible]

	1 day[1]	1 mo[illegible][1]	6 months	1 year	2 years	5 years	15 years
GF of d[illegible]s bindin[illegible] albu[illegible]	If $f_{u,adults} > 0.34$ PBPK	LinearBW	AS0.75	**AS0.75**	**AS0.75**	**AS0.75**	AS0.75
	If $f_{u,adults} \leq 0.34$ LinearBW		**LinearBW**	LinearBW	LinearBW	LinearBW	LinearBW
GF of dru[illegible] binding to AAG	If $f_{u,adults} < 0.23$ OR $f_{u,adults} > 0.78$ PBPK	If $f_{u,adults} \leq$ [illegible] AS0.7[illegible]	All $f_{u,adults}$ values AS0.75	All $f_{u,adults}$ values **AS0.75**	All $f_{u,adults}$ values **AS0.75**	**AS0.75**	AS0.75
	[illegible]f $f_{u,adults}$ 0.23-0.78 [illegible]W	If f[illegible] > 0.34 [illegible]inearBW	If $f_{u,adults} \geq 0.34$ Lin[illegible]	If $f_{u,adults} \geq 0.34$ LinearBW	If $f_{u,adults} \geq 0.34$ LinearBW	LinearBW	LinearBW
ATS	OCT2	OCT2					
	OAT1	OAT1	OAT1				
	OAT3	OAT3	OAT3	OAT3			
	Pgp	Pgp					

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Van Rongen et al. Expert Opin Drug [illegible]etab Toxicol 2022 Feb;18(2):99-113

Can we predict a dose with modeling?

Systems data	Trial design	Drug data

Maximum likelihood estimation of renal transporter ontogeny profiles for pediatric PBPK modeling

J. Porter Hunt[1] | Samuel Dubinsky[2] | Autumn M. McKnite[1] | Kit Wun Kathy Cheung[3] | Bianca D. van Groen[4] | Kathleen M. Giacomini[5] | Saskia N. de Wildt[6,7] | Andrea N. Edginton[2] | Kevin M. Watt[1]

No of male/female

Physiologically-based pharmacokinetic model

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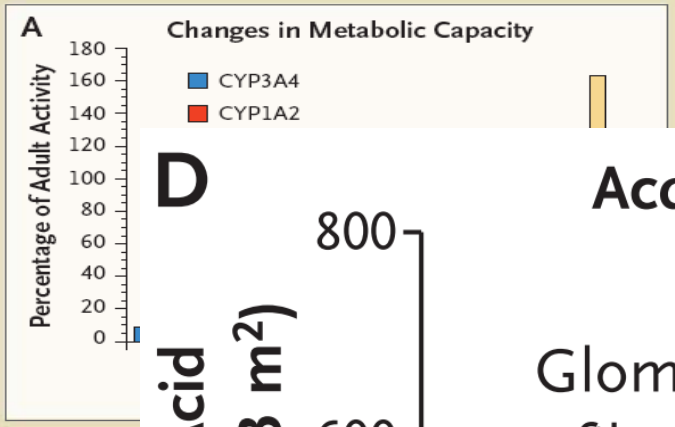
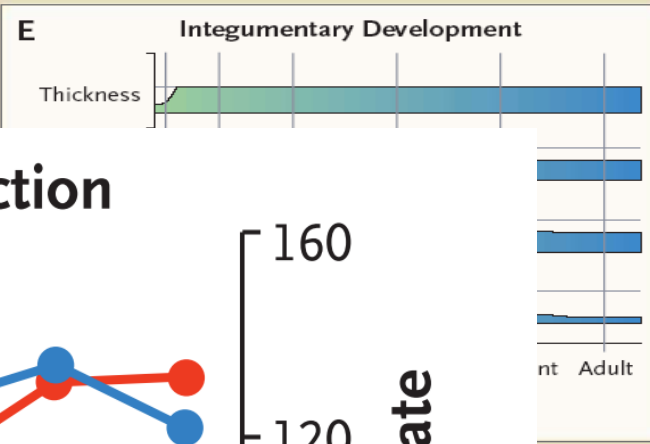
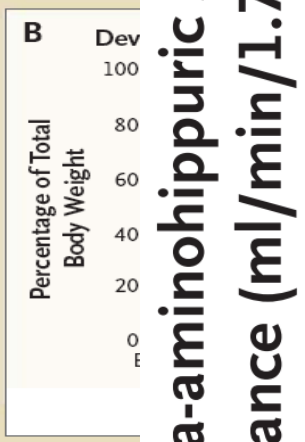
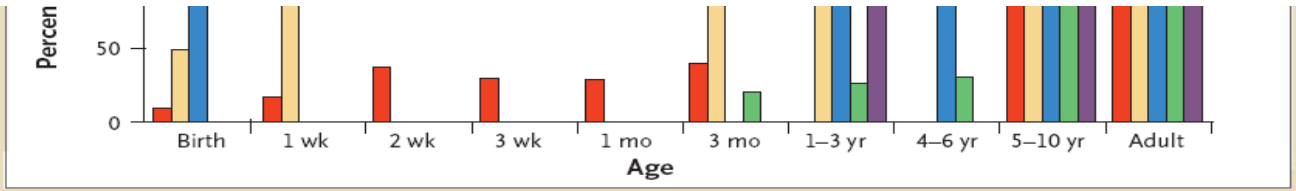

A
Changes in Metabolic Capacity
CYP3A4
CYP1A2
Percentage of Adult Activity
180
160
140
120
100
80
60
40
20
0


E
Integumentary Development
Thickness
nt
Adult


B
Dev
Percentage of Total Body Weight
100
80
60
40
20
0

D
Acquisition of Renal Function
Para-aminohippuric Acid Clearance (ml/min/1.73 m²)
800
600
400
200
0
Glomerular filtration
Para-aminohippuric acid
160
120
80
40
0
Glomerular Filtration Rate (ml/min/1.73 m²)
1–2 days
2–4 wk
2 mo
6 mo
1 yr
2 yr
6 yr
12 yr
Age


Percen
50
0
Birth
1 wk
2 wk
3 wk
1 mo
3 mo
1–3 yr
4–6 yr
5–10 yr
Adult
Age

Kearn
NEJM

What is GFR reference value in term infants?

Maturation of Glomerular Filtration Rate in Term-Born Neonates: An Individual Participant Data Meta-Analysis

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

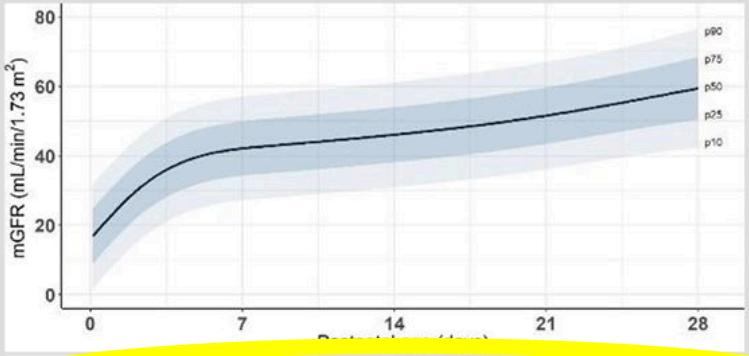
METHODS

- Individual participant data meta-analysis
- 48 studies, 881 neonates
- Definition of GFR reference values
- Update of Schwartz coefficient

eGFR(ml/min/1.73m2)=(k*height (cm))/serum creatinine(mg/dl)

OUTCOME

GFR doubled in the first five days after birth from 20 to 41 ml/min/1.73m^2, then more gradually increased to 59 ml/min/1.73m^2 by four weeks of age.



A coefficient of 0.31 led to accurate eGFR determination.

Conclusion
Our mGFR reference values and updated coefficient for the Schwartz equation can help to identify altered GFR in term-born neonates.

doi: 10.1681/ASN.2021101326

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Smeets N et al. J Am Soc Nephrol. 2022 Jul;33(7):1277-1292

FDA workshop Dec 2023

U.S. FOOD & DRUG ADMINISTRATION

ADEPT 8: Workshop on Drug Dosing in Pediatric Patients with Renal Impairment

Nov 30-Dec 1, 2023, Washington DC

J Pediatr. 2025 Apr 23:114624. doi: 10.1016/j.jpeds.2025.114624. Online ahead of print.

The ADEPT 8 Workshop: Drug Dosing in Pediatric Patients with Renal Impairment

Shamir Tuchman [1], Yeruk Mulugeta [2], George J Schwartz [3], Guido Filler [4], Saskia N de Wildt [5], Kirtida Mistry [6], Martina Sahre [7], Elimika Pfuma Fletcher [7], Karim Azer [8], Bakri J Alzarka [9], Sabrina Rahman Archie [10], Su-Young Choi [11], Mona Khurana [12], Lynne P Yao [2], Deepa H Chand [13]

The Smeets equation, a refinement for the updated Schwartz equation, was developed from measured GFR and provides an equation that can be used to estimate GFR in patients from 2 days of age until 1 month of age.

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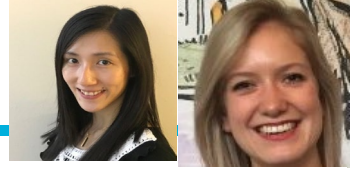
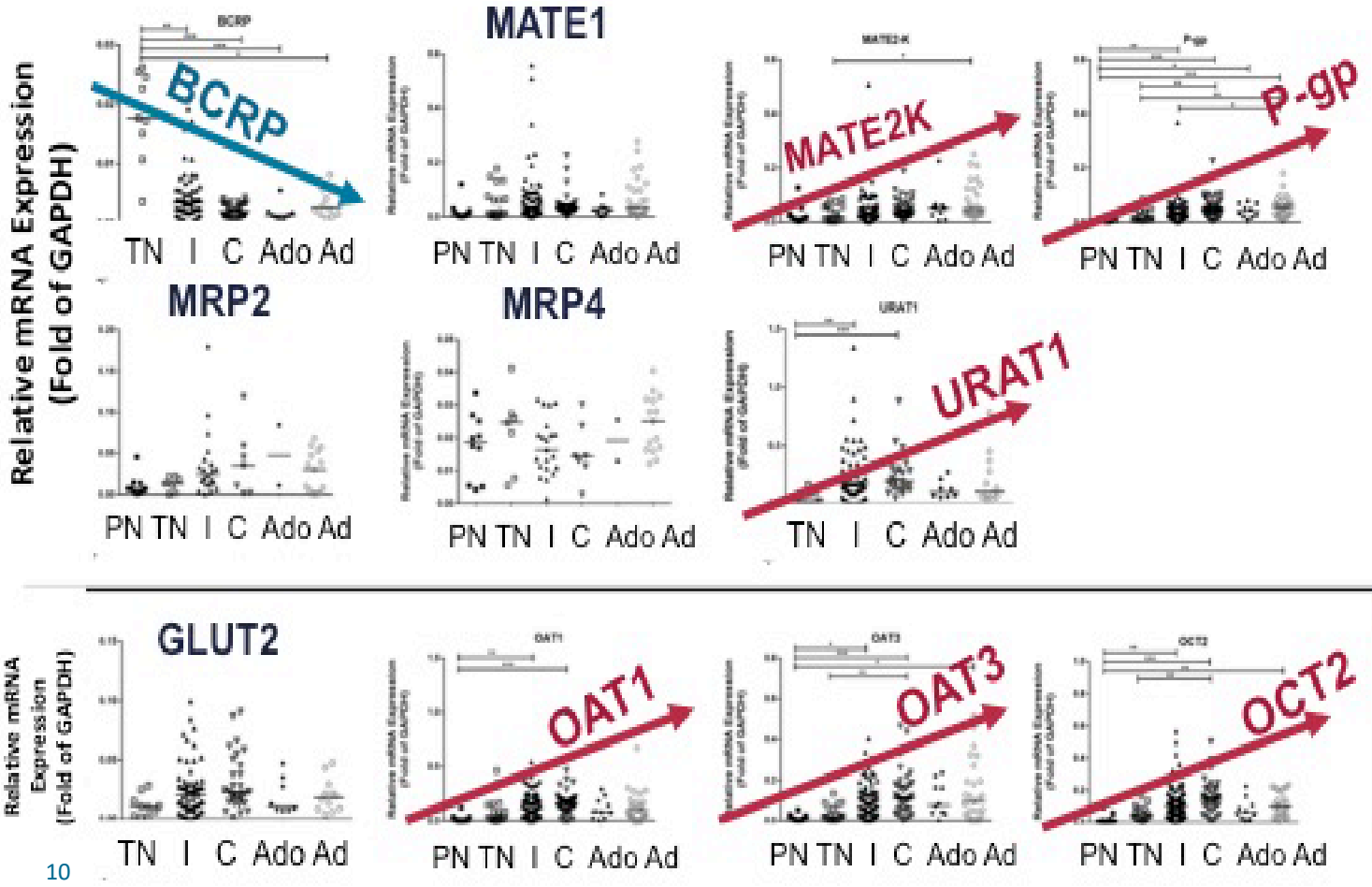
Maturation of Renal transporter



Transcript levels of 7 out of 11 transporters showed age-dependent changes



PN = Preterm Neonates
TN = Term Neonates
I = Infants
C = Children
Ado = Adolescents
Ad = Adults

Cheung, van Groen et al, Clin Pharmacol Ther. 2019 Nov;106(5):1083-1092

Including transporter ontogeny improves PK

Maximum likelihood estimation of renal transporter ontogeny profiles for pediatric PBPK modeling

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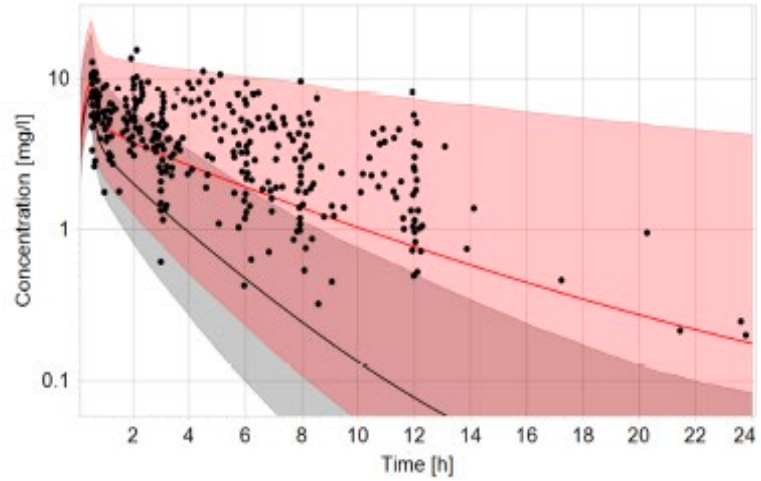

Ciprofloxacin PK
Preterm neonates (n=60, 25-41 wks PMA)

Black-grey = NO transporter ontogeny

Red-pink = WITH transporter ontogeny

CPT Pharmacometrics Syst Pharmacol, 2024 Apr;13(4):576-588

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Discussion points

- We need sound pediatric systems data, focus on (preterm) neonate
- PD receptor ontogeny is knowledge gap
- Biomarkers (lab/clinical) need age-specific reference values
- Multi-stakeholder consensus on maturation patterns is needed
- To reduce academic brain-drain shared appointments with industry or regulator should be encouraged

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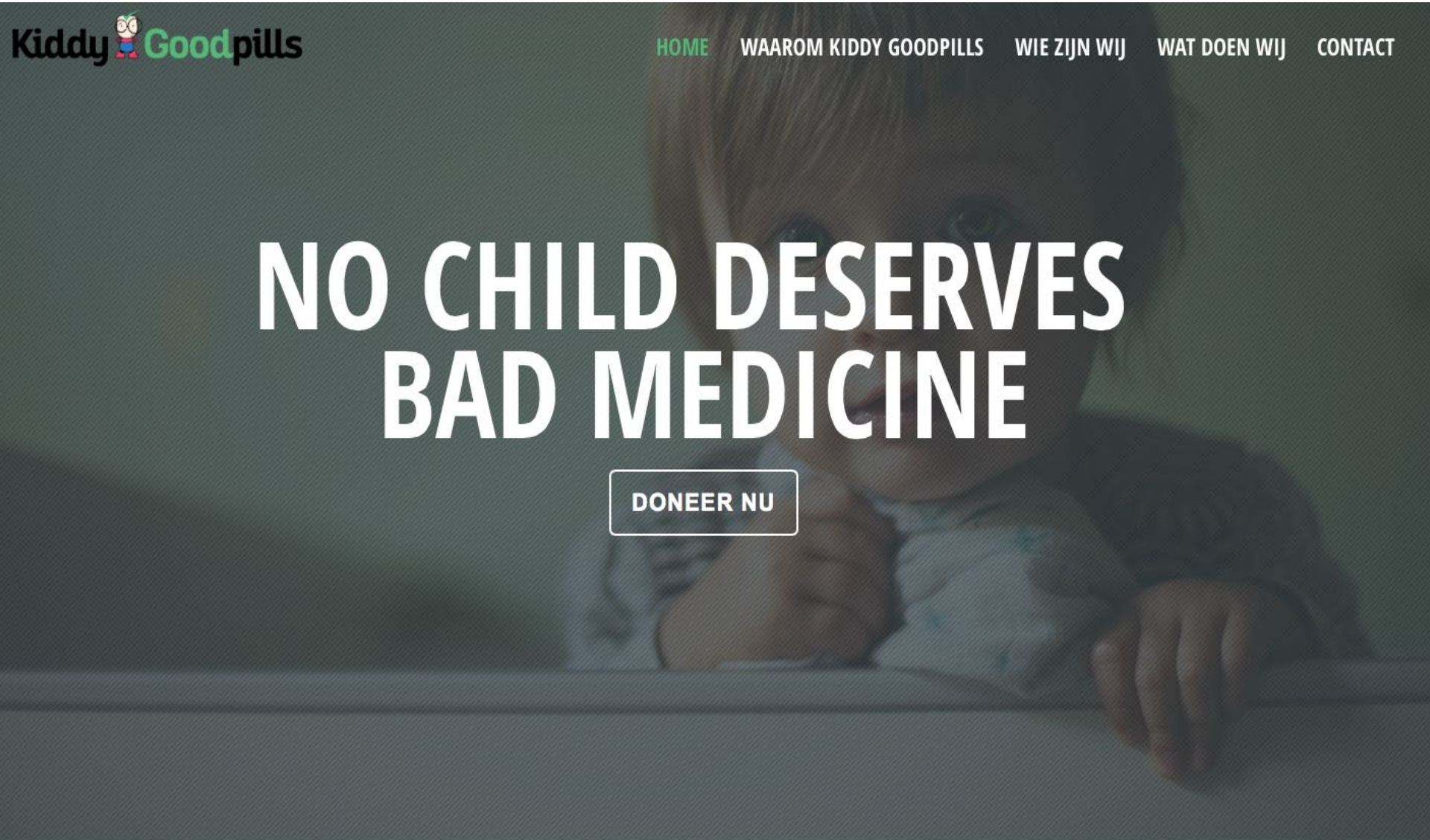
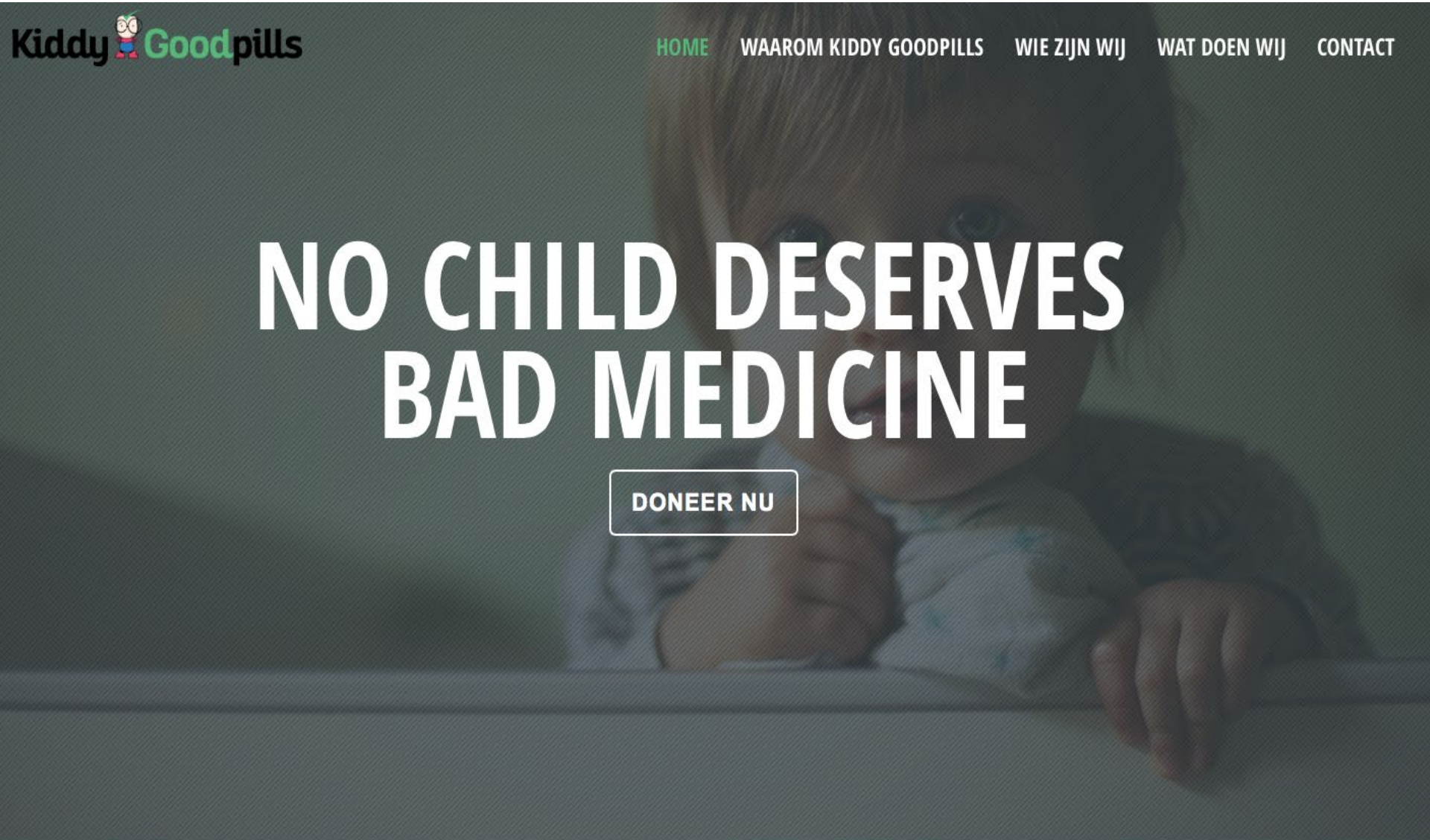
Kathy Giacomini
Kathy Cheung

FDA, USA
Shamir Tuchman
Deepa Chand
Lynne P Yao
Huang SM

Questions?


Kiddy Goodpills
HOME
WAAROM KIDDY GOODPILLS
WIE ZIJN WIJ
WAT DOEN WIJ
CONTACT
NO CHILD DESERVES
BAD MEDICINE
DONEER NU

Questions?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