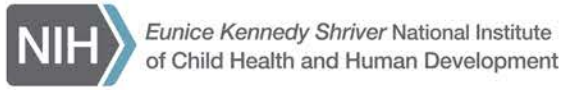
The **MPRINT** Hub: Advancing Frontiers in Health through **M**aternal and **P**ediatric p**R**ecision **I**n **T**herapeutics

A collaborative effort of the Obstetric and Pediatric Pharmacology and Therapeutics Branch

Aaron C. Pawlyk, Ph.D., Branch Chief

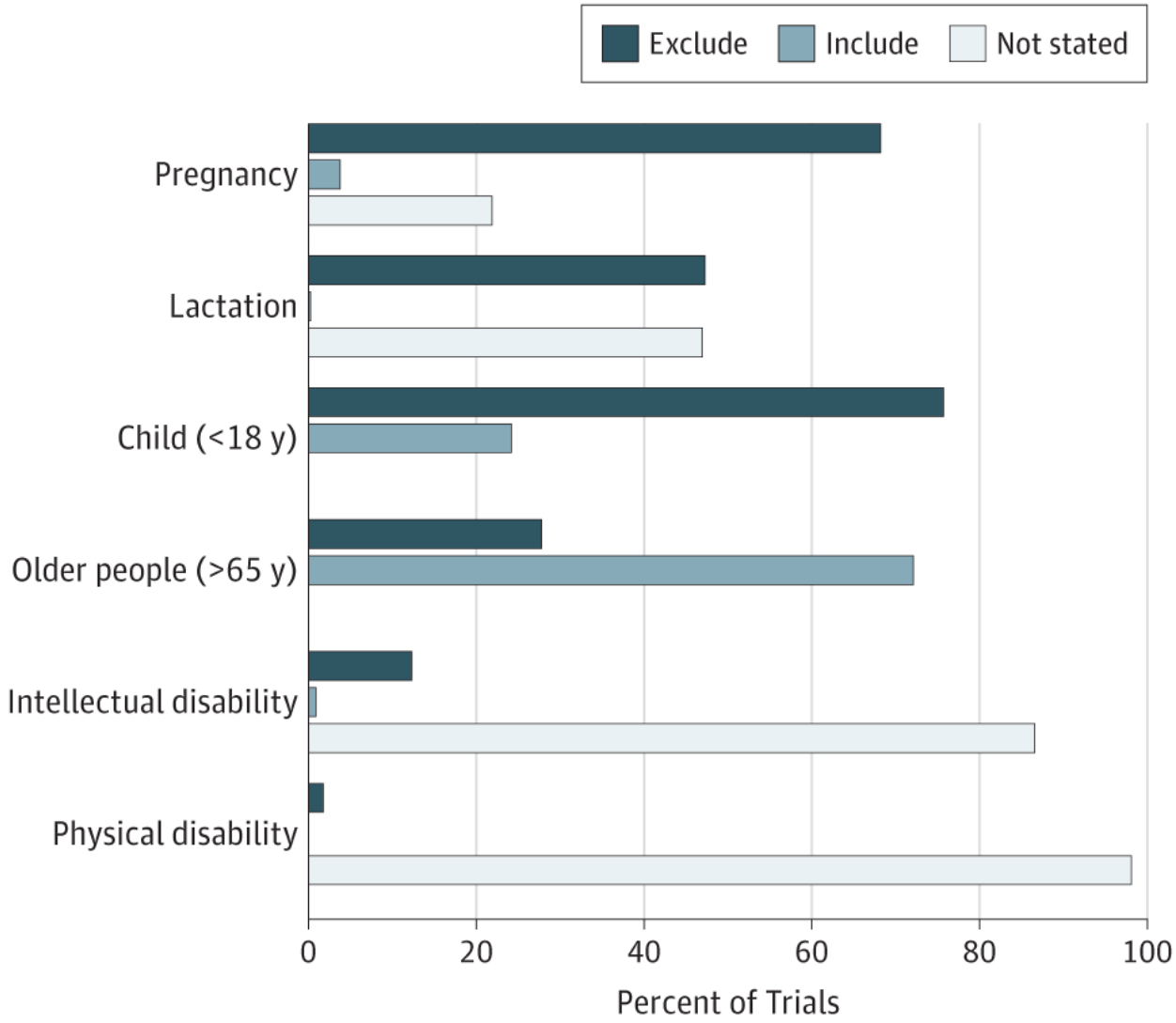


The Problem

Physicians and patients must sometimes make decisions on medication and vaccine use without rigorously conducted regulatory studies and approval.

Underrepresented Groups in Research

Up to 59% of the U.S. population comprises people who typically are not included in research studies (pregnant women, children, older people, and those with intellectual and physical disabilities).



Spong CY, Bianchi DW. Improving Public Health Requires Inclusion of Underrepresented Populations in Research. JAMA. 2018;319(4):337–338. doi:10.1001/jama.2017.19138

Why are Pregnant Persons and Children Underrepresented?

- Real and perceived ethical concerns
- Real and perceived concerns over safety risk
- Practical challenges to inclusion in clinical trials
- Lack of workforce experienced with these populations

The MPRINT Hub is a new initiative that continues OPPTB's efforts to provide new knowledge, tools, and training to address these factors.

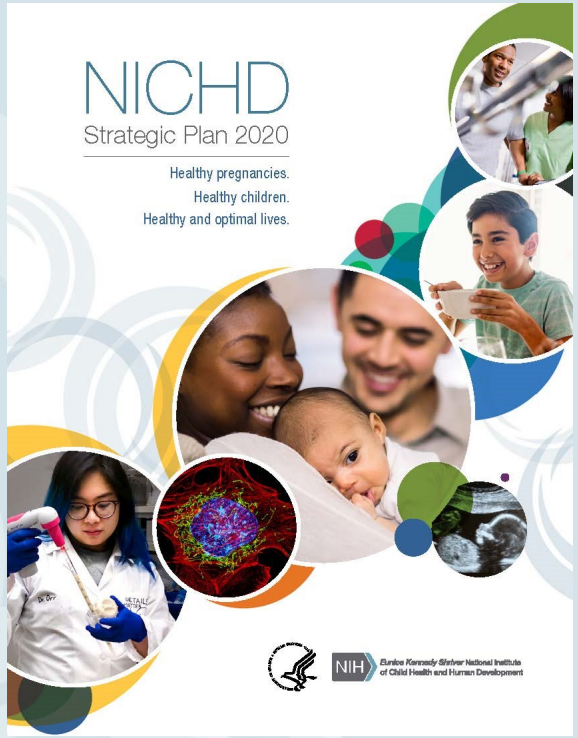
Bridging the Gap

Basic Research, Therapeutic Discovery, Non-clinical Development

Inclusive Product Development

Inspired by talk by Dr. Suzie McCune 11/21/19

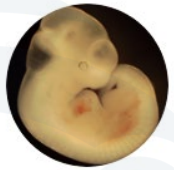
Theme 5: Advancing Safe and Effective Therapeutics and Devices for Pregnant and Lactating Women, Children, and People with Disabilities



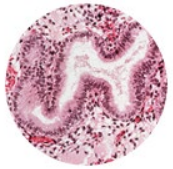
Goal: Lead efforts to develop, test, and evaluate new and existing therapeutics and devices to find safe and effective solutions that **meet the unique needs of pregnant and lactating women, children, and people with intellectual and physical disabilities.**


Child Development and Behavior Branch (CDBB)


Contraception Research Branch (CRB)


Developmental Biology and Structural Variation Branch (DBSVB)


Fertility and Infertility Branch (FIB)


Gynecologic Health and Disease Branch (GHDB)

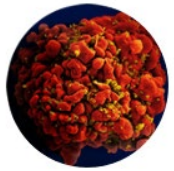

Intellectual and Developmental Disabilities Branch (IDDB)


Pediatric Growth and Nutrition Branch (PGNB)


Pediatric Trauma and Critical Illness Branch (PTCIB)


Population Dynamics Branch (PDB)


Pregnancy and Perinatology Branch (PPB)


Maternal and Pediatric Infectious Disease Branch (MPIDB)


Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB)


National Center for Medical Rehabilitation Research (NCMRR)

NICHD Strategic Plan Aspirational Goals

- Facilitate application of precision medicine

- Train the next generation of scientists

Pharmacology

The branch of medicine concerned with the uses, effects, and modes of action of drugs.

Pharmacokinetics

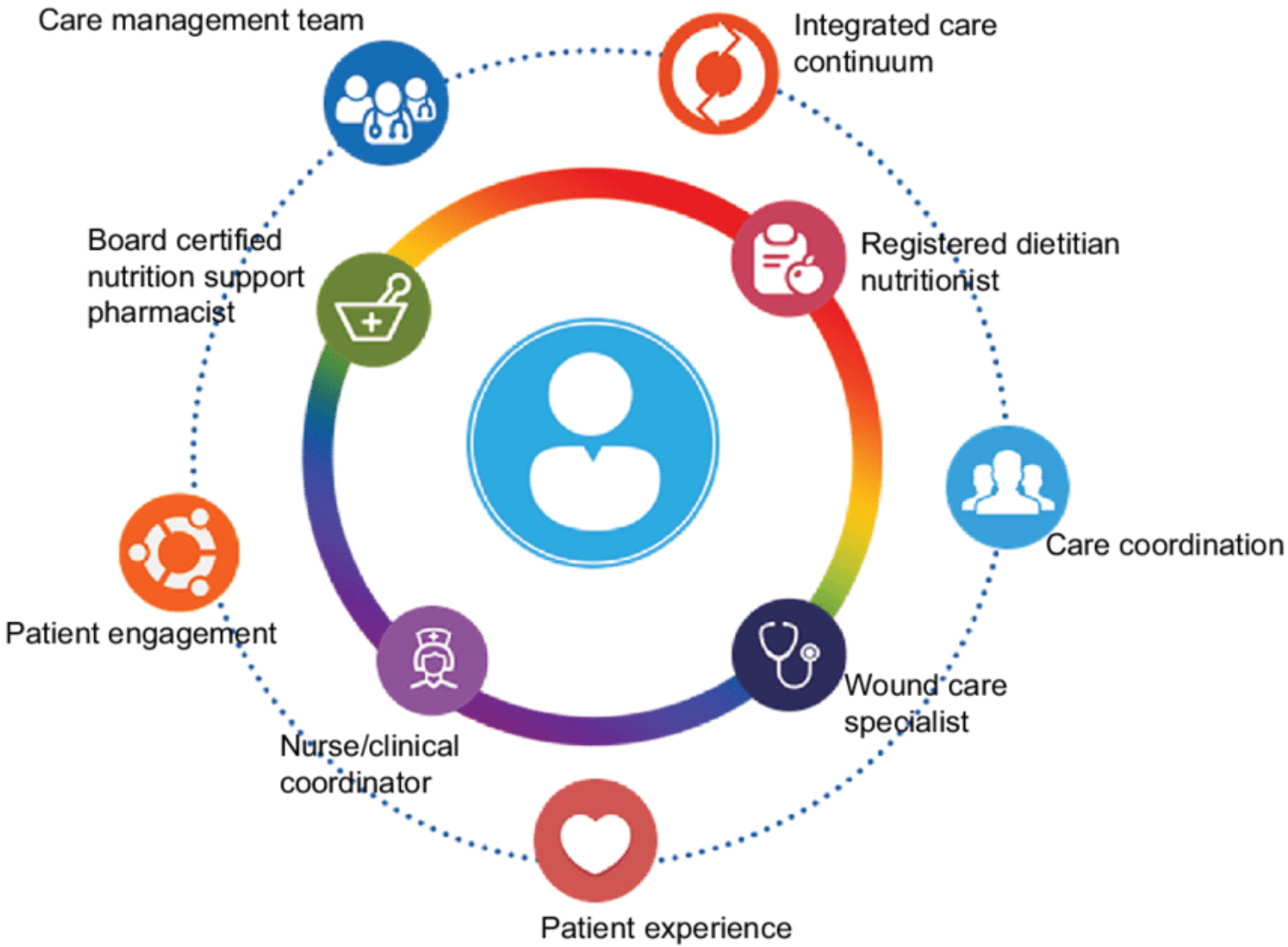
What the body does to the drug.

Pharmacodynamics

What the drug does to the body.

Pharmacogenetics

How genetics affects pharmacokinetics and pharmacodynamics.


Care management team
Integrated care continuum
Board certified nutrition support pharmacist
Registered dietitian nutritionist
Patient engagement
Care coordination
Nurse/clinical coordinator
Wound care specialist
Patient experience

A Big Step Forward: Legislation on Pediatric Drug Trials

Best Pharmaceuticals for Children Act & Pediatric Research Equity Act

FDA (*on-patent)

NIH (*off-patent)

Pharmaceutical Companies' Drug Studies

Pediatrics Division Oversight

Prioritization
Clinical Trials (Sponsor/Submit)
Pharmacology Training
Translational Research

Led to creation of OPPTB in 2004

What the BPCA Clinical program brings to the table… Doing trials BETTER!

Pharmacology expertise

PK/PD modeling, simulation expertise, assay development and validation

Innovative research/trial design

Standard of Care (SOC) and Opportunistic Trial Designs in Pharm

Obesity based dosing

Master protocols

Trailblazing efforts in pediatric REGULATORY research

Interaction and experience with MULTIPLE FDA review divisions (pre-IND meetings)

Cost efficiency

SOC protocols

Junior Investigators

Subsidize site costs

Promoting Investigator Training

T32 Program

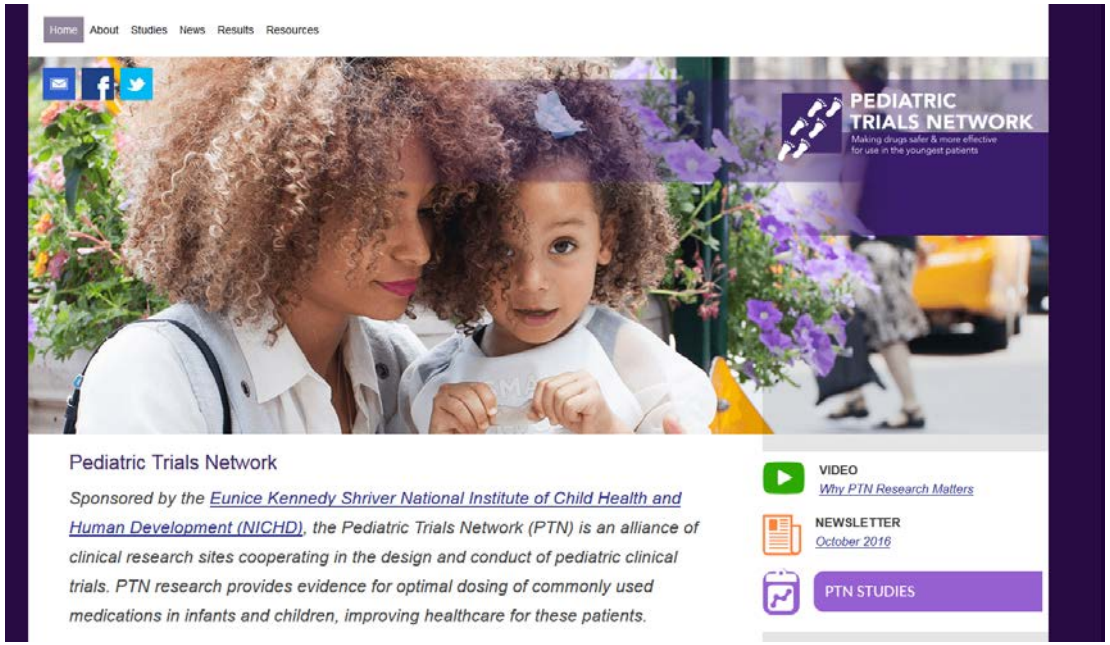
DCRI career development program

Need to bring such expertise to the broader community, expand into maternal populations, address gaps, and continue to build and train the workforce.

One Answer: The Pediatric Trials Network

"Create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health."

- –Sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
- –Success defined by improving dosing, safety information, labeling, and ultimately child health
- –Focus on off-patent therapeutics

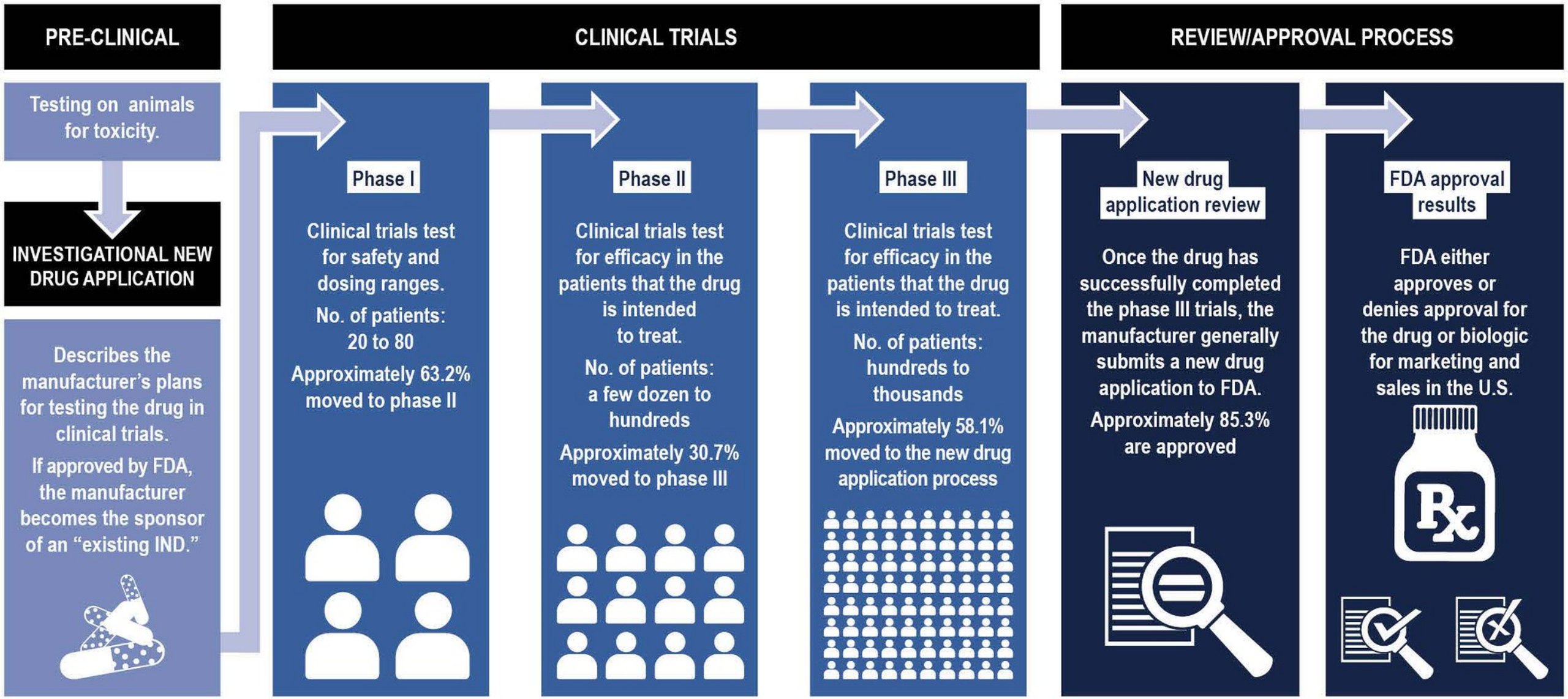


www.Pediatrictrials.org

Dr. Perdita Taylor-Zapata
Ms. Francine Mahase
Dr. Antonello Pileggi
Infinity Conference Group

Emmes

Duke Clinical Research Institute



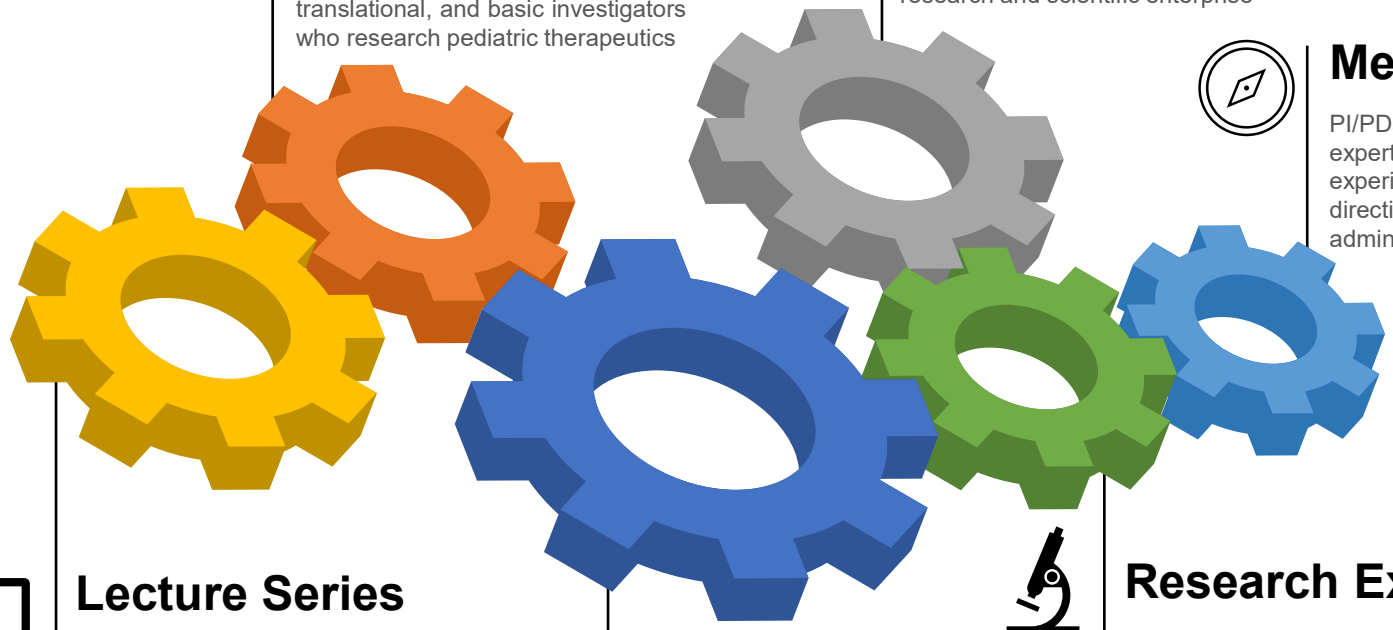
Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion.[a] | GAO-17-564

PK + safety
low $s

PD (efficacy)
mid $$s

PD (efficacy)
high $$$$s

Current T32 Pediatric Clinical Pharmacology Training Program



Collaboration

Network allows interdisciplinary collaboration of clinical, translational, and basic investigators who research pediatric therapeutics

Career Development

Unique training experiences to bridge the gap between scientific discoveries and clinical medicine, fostering career trajectories towards research and scientific enterprise

Mentorship

PI/PDs with scientific background, expertise, and administrative and training experience to provide strong leadership, direction, management, and administration of the proposed research

Lecture Series

Principles of Pediatric Clinical Pharmacology Course with approximately 29 lectures divided into 8 modules including FDA Corner

Virtual Network

Network of institutions linked by a website, fostering cross-institutions interactions and Interdisclipinary collaboration

Research Experiences

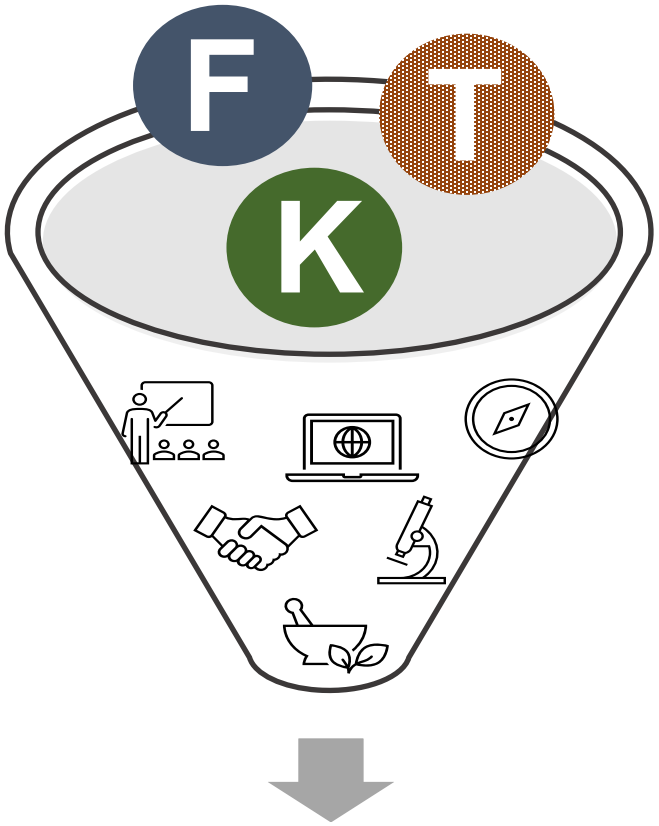
Training and experience in the methods and conduct of basic and clinical drug research in the different phases of pediatric drug development

Dr. George Giacoia
Dr. Lesly Samedy-Bates

Expansion of Training and Career Development Program

Stronger Network

- Combining Training Program (T), Individual Fellowships (F), and Career Development Awards (K)
- Expand to Maternal Clinical Pharmacology



1. Networking of Fellows with Early Career Awardees for a unified program
2. Didactic training and seminar series to strengthen knowledge and foundation
3. Strategic coordination of maternal and pediatric clinical pharmacology training and education

Leverage NICHD networks

Pediatric Trials Network (PTN), MPRINT Hub, Maternal-Fetal Medicine Units (MFMU) Network, Neonatal Research Network (NRN), etc.

Implementation Plan Submitted to the Secretary August 2020, Posted on PRGLAC Website

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

The 21st Century Cures Act established PRGLAC to advise the Secretary of Health and Human Services (HHS) regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. PRGLAC was tasked with identifying these gaps and reporting its findings back to the Secretary.

Federal members include the directors of NIH, NICHD, the Centers for Disease Control and Prevention, the HHS Office on Women's Health, and the Commissioner of Food and Drugs. Non-federal members include representatives from relevant medical societies, non-profit organizations, and industry.

Advisory Groups

Board of Scientific Counselors (BSC)

National Advisory Child Health and Human Development (NACHHD) Council

National Advisory Board on Medical Rehabilitation Research (NABMRR)

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

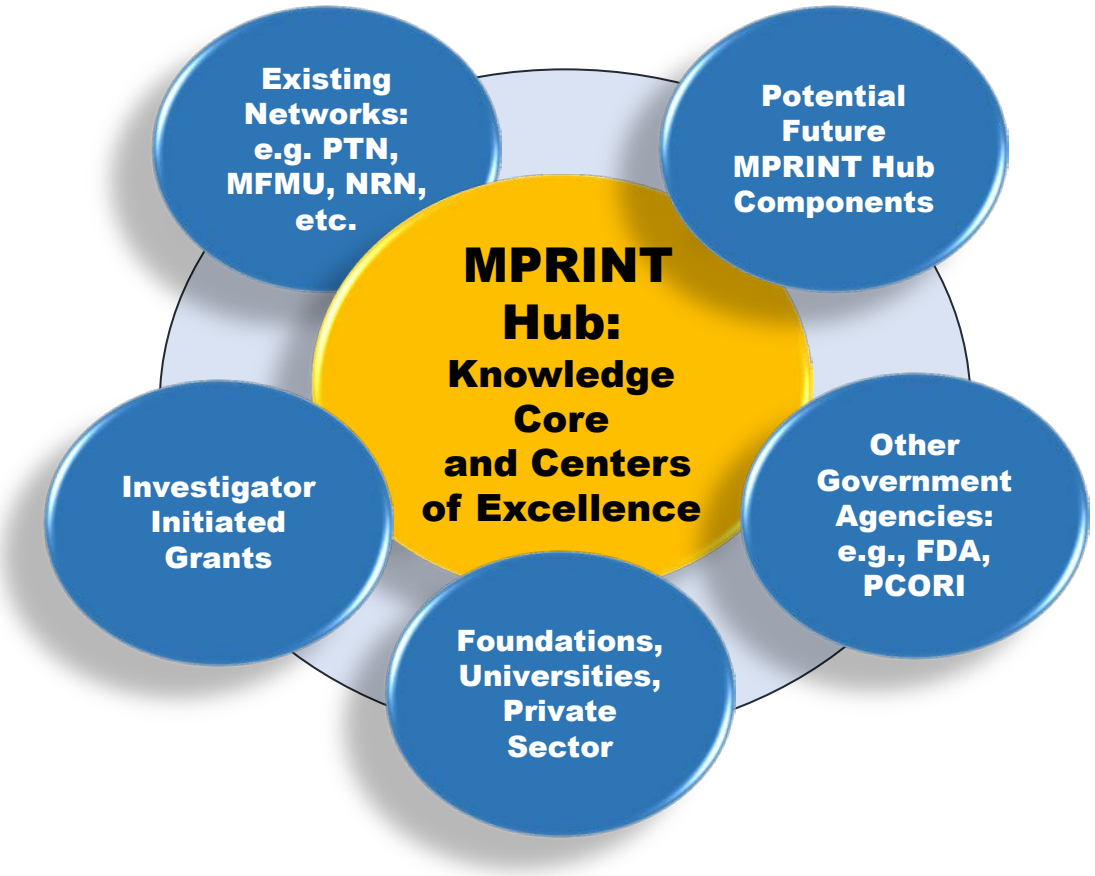
Learn More

https://www.nichd.nih.gov/about/advisory/PRGLAC

Maternal and Pediatric pRecision *in* Therapeutics Hub

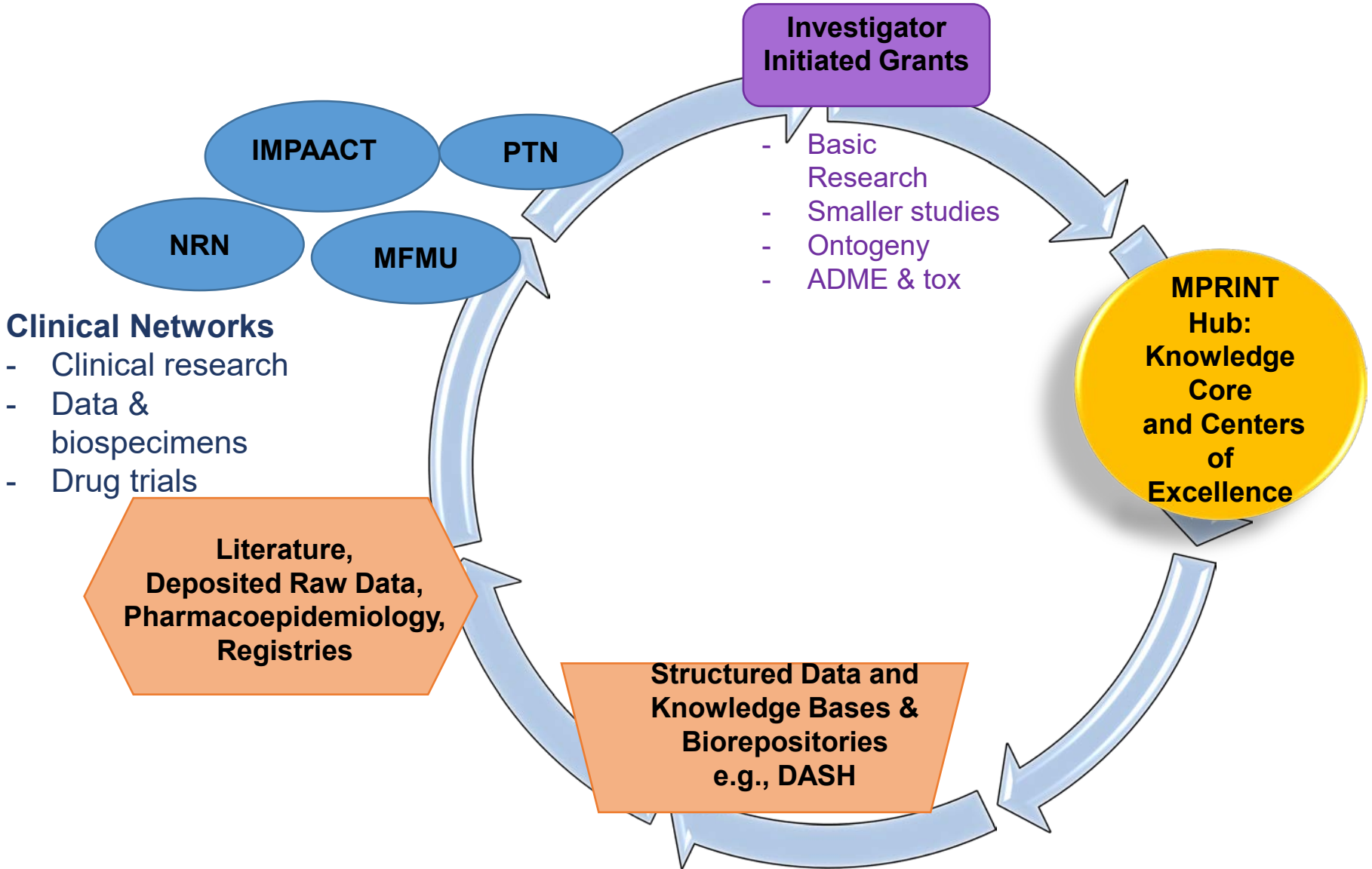
MPRINT Hub is a service center and science catalyst:

- Provide knowledge and expertise to the scientific community
- Catalyze and accelerate maternal and pediatric therapeutics towards precision medicine
- Synergize with other resources and networks
- Build upon prior OPPTB efforts (PTN, OPRCs, RPDPs) and lay groundwork for future efforts



https://www.nichd.nih.gov/about/org/der/branches/opptb/mprint

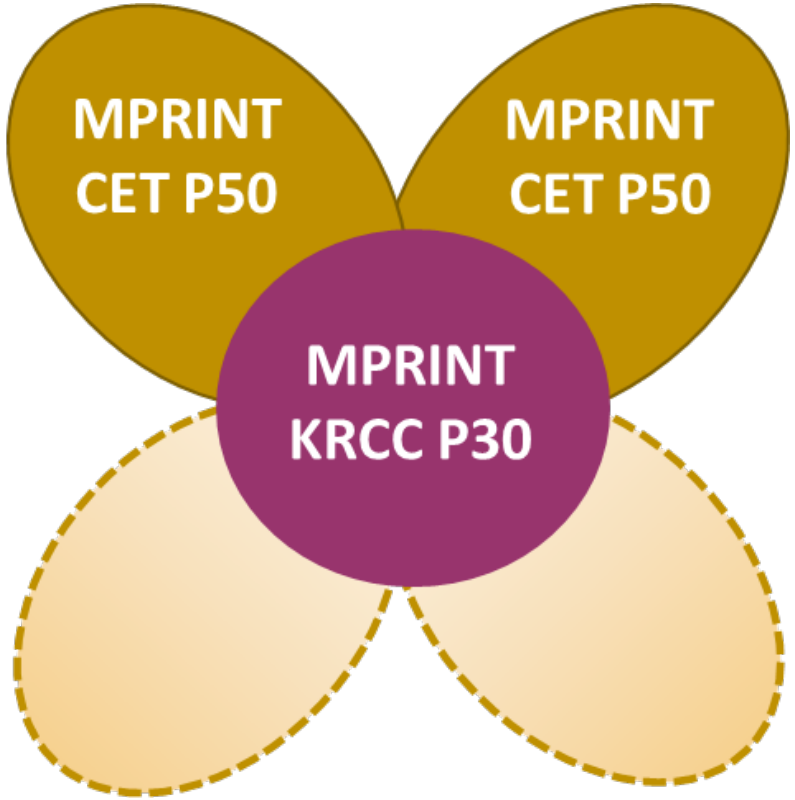
The MPRINT Hub's Place in the Ecosystem



Needs to Catalyze Regulatory Clinical Trials

- Centralized maternal and pediatric pharmacology knowledgebase
  - Common framework
  - ID'd knowledge gaps
- Tools to facilitate drug development in pediatric and maternal pharmacology
  - Biomarkers
  - Clinical outcomes
  - Enhanced modeling
  - Outcome measures
  - Technologies
- Education, training, outreach

MPRINT Hub Components



MPRINT KRCC P30:

- administrative structure
- technical and scientific infrastructure
- responsible for knowledge aggregation and dissemination.

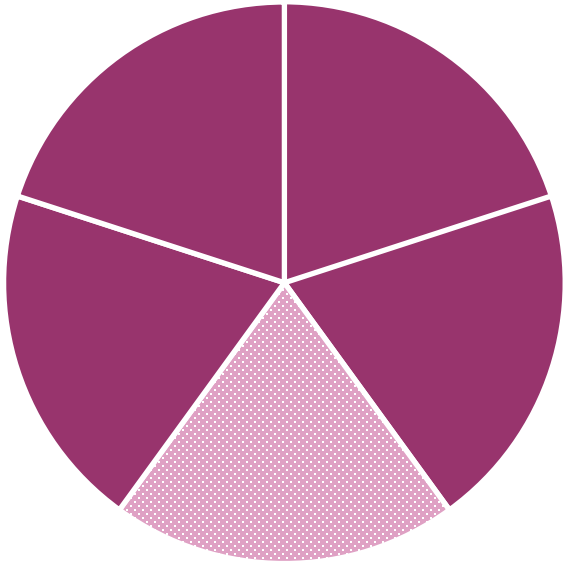
MPRINT CET P50:

- address key knowledge deficits
- conduct/facilitate novel clinical, translational, basic, and/or data sciences research.

Components of the Knowledge and Research Coordination Center

Knowledge Base & Portal
- Primary database, integrator, and analytical platform

Pharmacometrics and Clinical Trial Design Core
- Pharmacometric models and expertise for dose selection in maternal and pediatric clinical trials



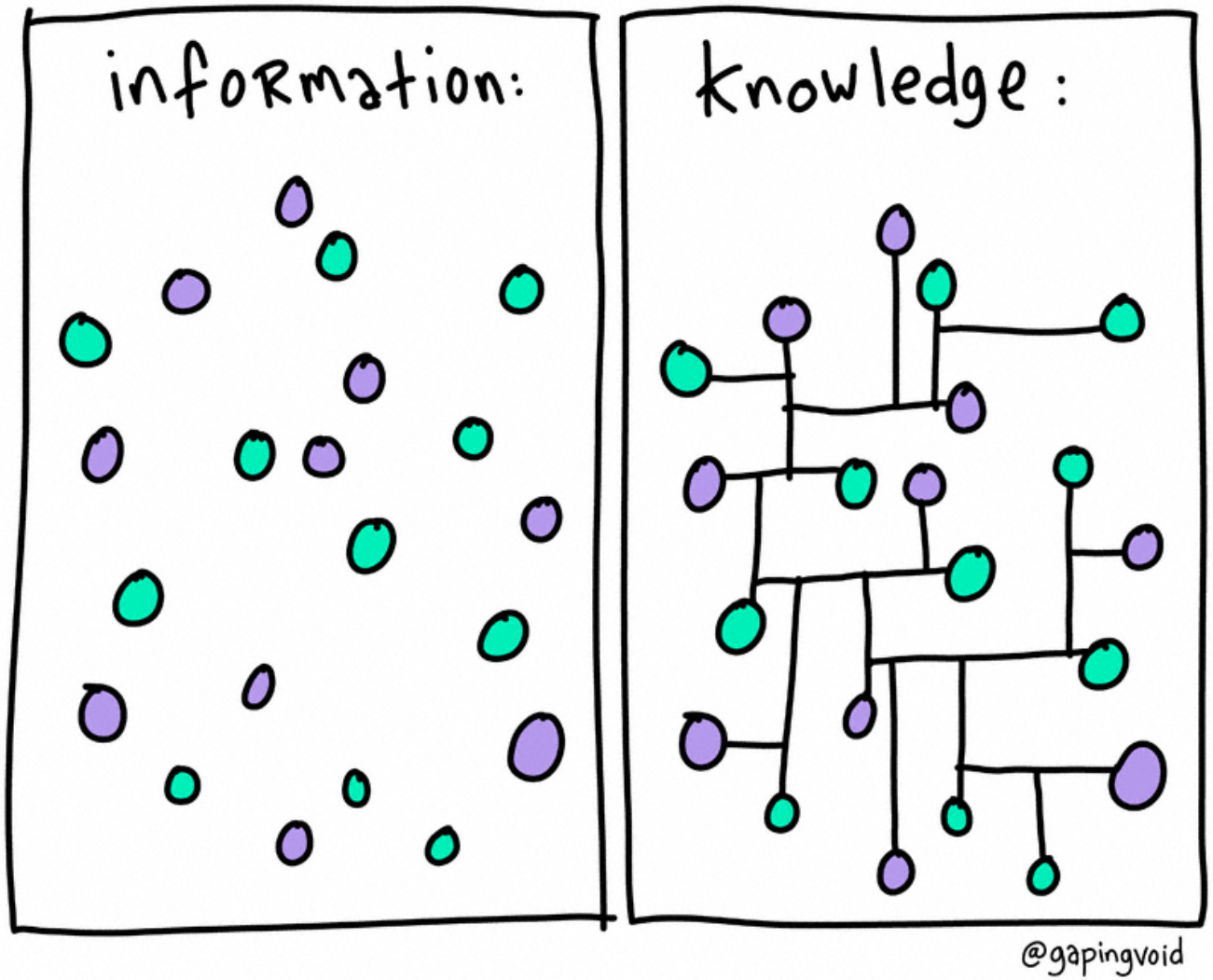
Outreach, Dissemination, and Training Core
- Support of interactions between the MPRINT Hub and the broader scientific community

Logistics Core
- Overall logistic and administrative coordination for KRCC, CETs and future components
- Will oversee use of the Opportunity Pool funds

Optional Core
- Provide support services for other Cores

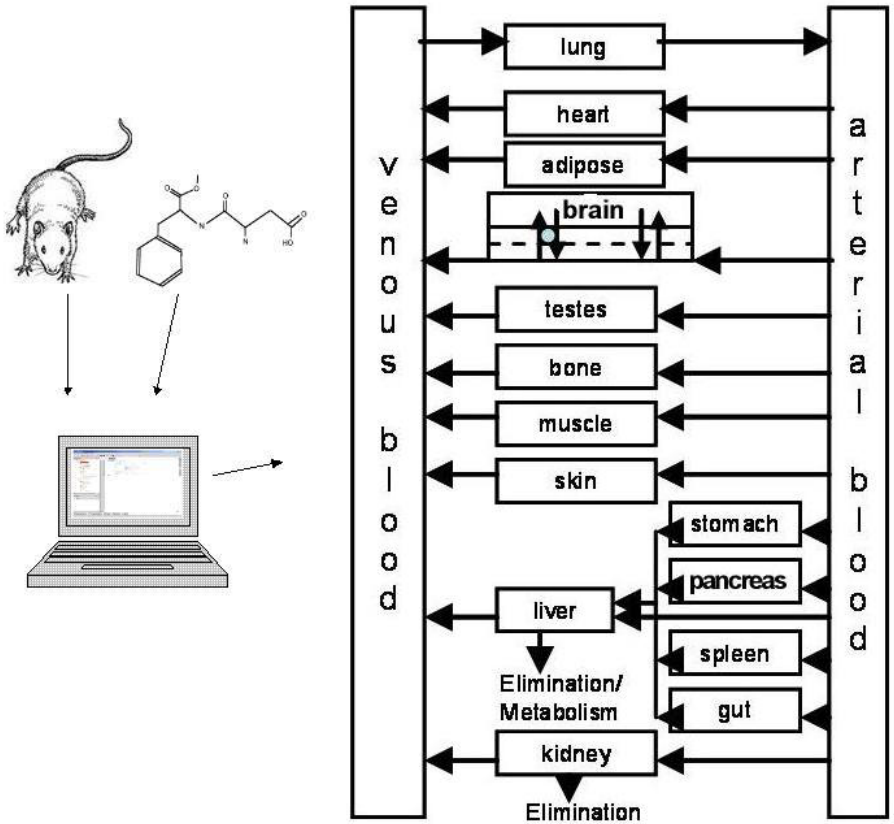
From Data to Knowledge

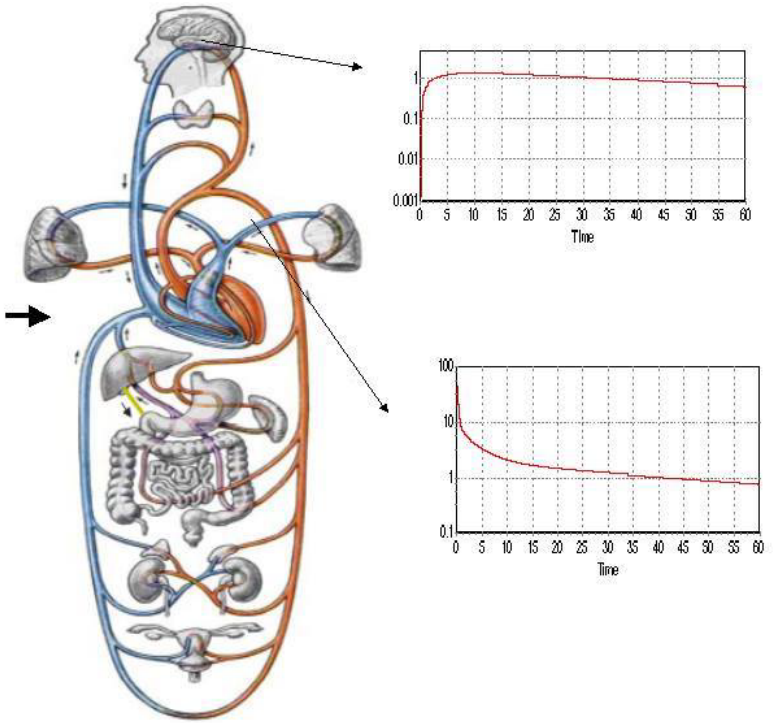
- Comprehensive knowledge repository for pediatric and maternal pharmacology.
- Organize knowledge into a cohesive framework.
- Present knowledge to multiple user types
- Identify gaps in knowledge.



Pharmacometric Modeling

- Goes beyond estimating dose by body size and weight.
- Incorporates detailed understanding of physiological processes.
- Requires high degree of technical expertise.





Goteborg University, online PK module
http://pharmguse.net/pkdm/index.html

PROPOSED PLAN FOR COLLABORATIVE APPROACH TO IMPROVE RIGOROUS APPROACH TO MATERNAL THERAPEUTICS

Goals and approach: leveraging synergistic investments

NIH Programs

Fogarty

The Fogarty Global Health Program for Fellows and Scholars supports U.S. university consortia to provide collaborative, mentored global health research training opportunities in low- and middle-income countries (LMICs).

MPRINT

The MPRINT Hub is a national resource that aims to aggregate, present, and expand the available knowledge, tools, and expertise in maternal and pediatric therapeutics to the broader research, regulatory science, and drug development communities.

Broad dissemination of RFP

Virtual Pregnancy grantees supported to train and collaborate with MPRINT Hub

BMGF Programs

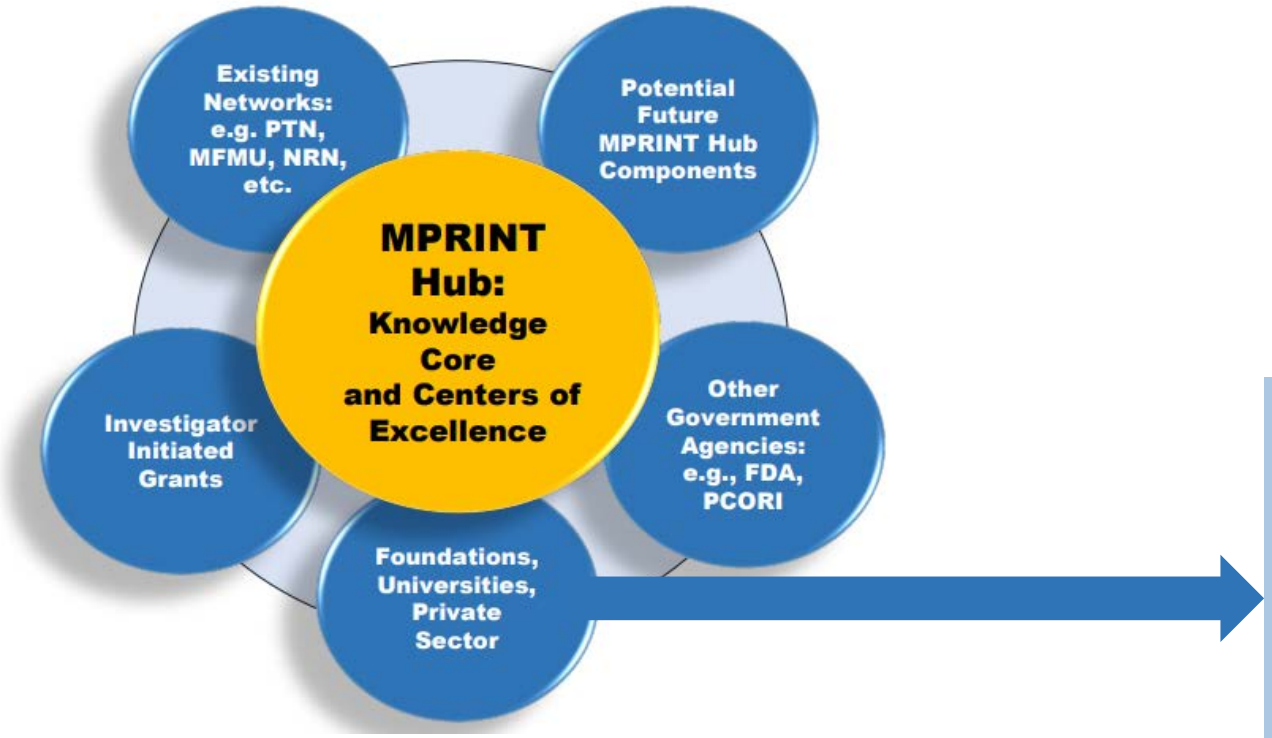
Virtual Pregnancy

The Virtual Pregnancy investment aims to establish an *in silico* resource based upon physiologically-based pharmacokinetic modeling. The technology would be informed by globally comprehensive data regarding placental transfer and maternal adaptation to pregnancy. The platform will support acceleration of development and safe implementation of maternal therapeutics in LMICs.

Overarching goals of this collaboration:

- Accelerate preclinical assessment of potential maternal therapeutics with a view toward global safety and generalizability
- Fill gaps in global pharmacogenomic data
- Support promising LMIC-based investigators

BMGF VIRTUAL PREGNANCY COLLABORATION AS A GLOBAL HEALTH SPOKE IN THE MPRINT HUB



Global health "spoke:"

- Establishment of virtual pregnancy models to inform use of therapeutics in pregnancy globally
- Ensure LMIC representation in pregnancy-focused pharmacometric modelling
- Capacity building for LMIC-based investigators
- Meets NICHD Strategic Plan Cross-Cutting goal in Global Health

Dr. Zhaoxia Ren (NICHD/OPPTB)
Dr. Hilary Gammill (BMGF)
Dr. Ping Zhao (BMGF)

Inclusion of Pediatrics in Existing Pharmacogenomic Resource

Dr. Zhaoxia Ren (NICHD/OPPTB)
Dr. Aaron Pawlyk (NICHD/OPPTB)
Dr. Melissa Parisi (NICHD/IDDB)
Dr. Rongling Li (NHGRI)

Search PharmGKB

PHARMGKB PEDIATRIC

Pediatric PGx Dashboard

Legend: non-pediatric | pediatric | pediatric-only | BPCA

Clinical Annotations

266 with pediatric VA's only
292 with at least one pediatric VA
4,855 clinical annotations

view pediatric clinical annotations

Variant Annotations

2,084 pediatric
24,771 variant annotations

view pediatric variant annotations

Label Annotations

7 pediatric
371 FDA label annotations

view pediatric label annotations

Guideline Annotations

30 pediatric
51 CPIC guideline annotations

view pediatric guideline annotations

Automated Annotations

831 pediatric
20,223 automated annotations

view pediatric automated annotations

Literature

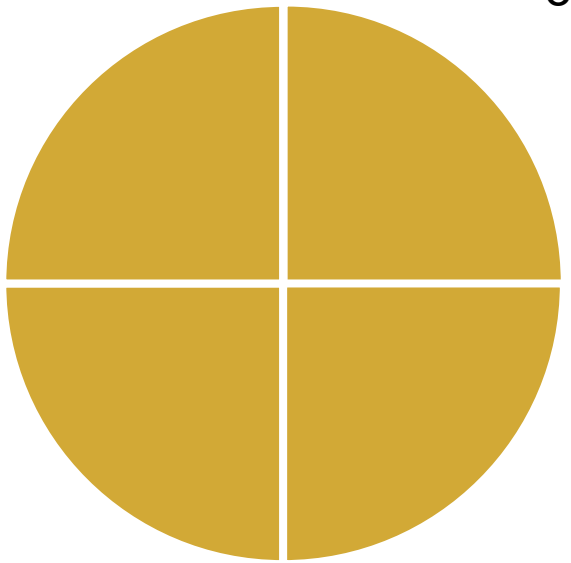
6,970 pediatric
74,046 literature

view pediatric literature

Components of the Centers for Excellence in Therapeutics (CETs)

Research Projects (#1)
- At least one research project must be a clinical research project

Research Projects (#2)
- May be a clinical, basic/translational, or data science project



Administrative Core
- Provide oversight, support and management of Research Projects and Support Cores
- Work and coordinate with the MPRINT KRCC

Support Cores
- Support the Research Projects within the proposed CET

What the MPRINT CETs can Start Doing

- Develop ways to link parent/child EHR data and biosamples
- Assess effects of drugs on composition of breast milk
- Develop new devices and methodologies for precision dosing
- Build new pharmacometric models for predicting safety and efficacy of drugs in children and pregnant persons
- Determine and address causes of health disparities
- Educate and train the workforce, patients, and caregivers

Organization and Management of the MPRINT Hub

- Subject Matter Experts (SMEs) selected by NICHD to review the Hub annually.
- Hub will be governed by a Steering Committee with input from NICHD and SMEs.
- In negotiation with the NICHD, awardees will reprioritize and adjust activities, deliverables, timelines, and milestones on an annual basis.

Innovation in Safety Science

A goal to stimulate innovation in safety sciences that inform risk to pregnant persons, children, and adolescents.

New approaches informed by ADME and toxicodynamic variation due to: life stage, sex, genetics, and environmental factors.

Dr. Alison Harrill

MPRINT Hub

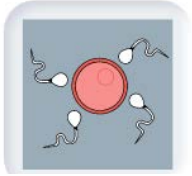
Computational modeling

Clinical trial design, risk communication

Inter-individual variability, social determinants, mixtures

Additional Branch Priorities

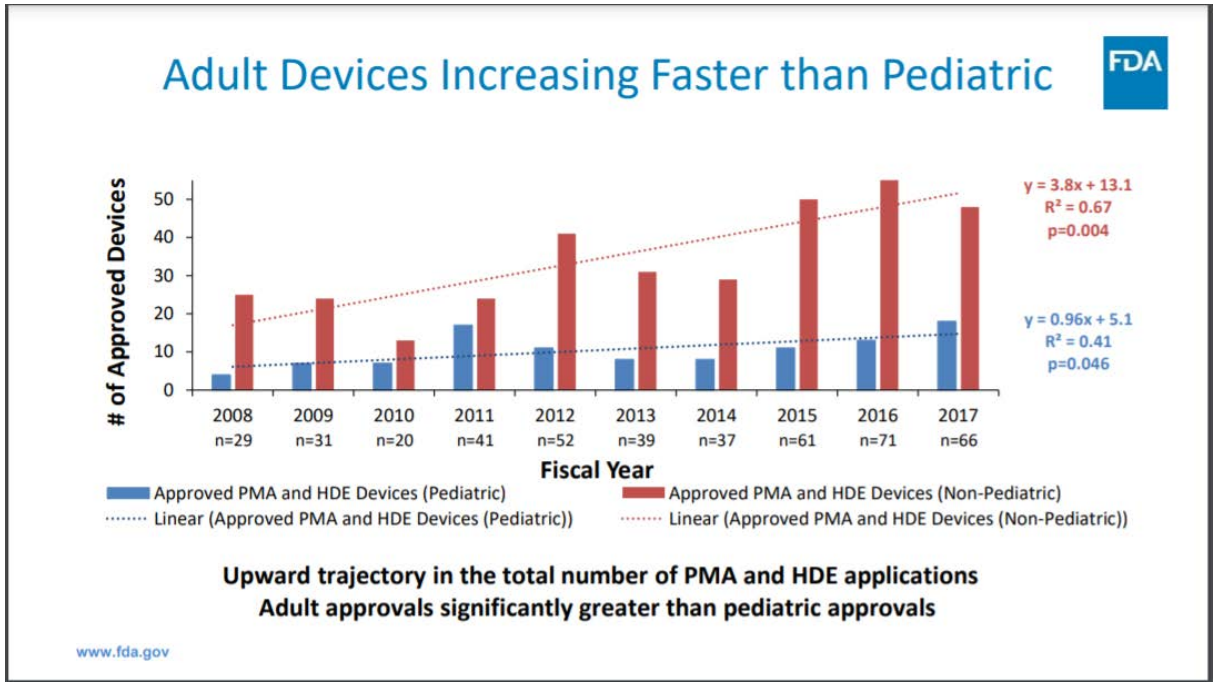
In vitro and adverse outcome pathways

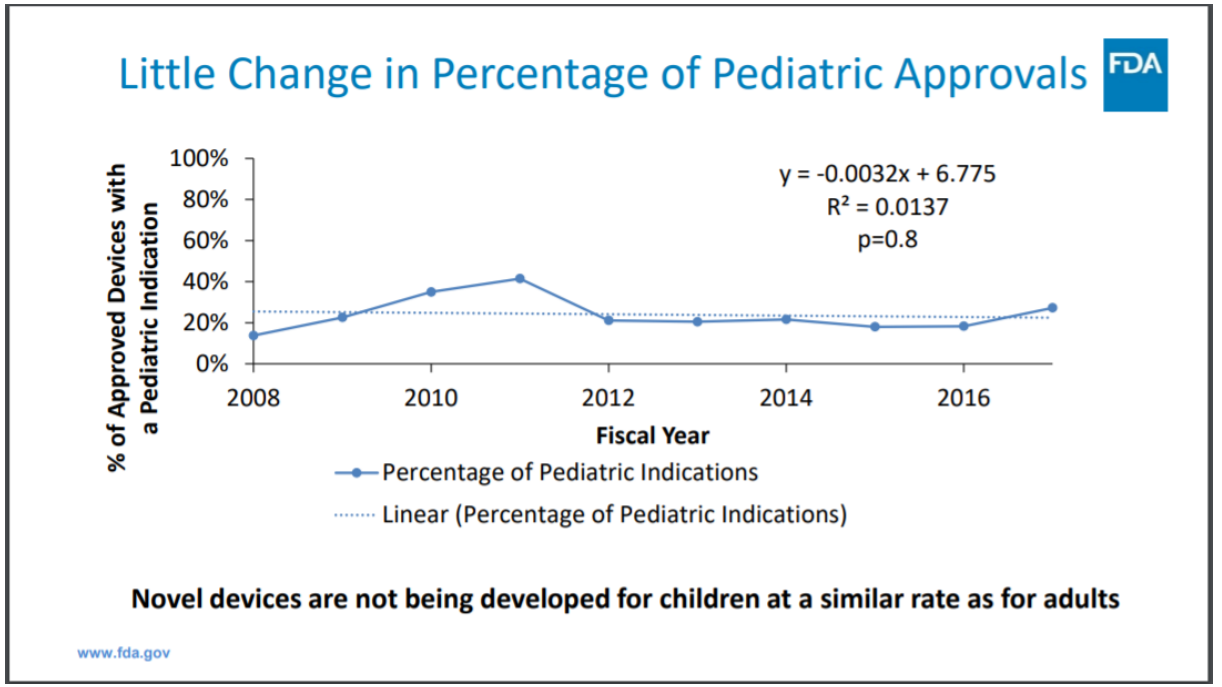


Cellular & organ-on-a-chip models

Animal models for developmental and reproductive toxicology

Challenges of Pediatric Medical Devices





- Medical device development for children continues to lag behind that for adults.
- Some products are designed specifically for children, while others are *borrowed* from adult applications or produced for more general use.

Dr. Antonello Pileggi

Peiris, V. Pediatric Medical Device Development, Public Meeting and Workshop, August 13, 2018

System of Hospitals for Innovation in Pediatrics – Medical Devices

The National Innovation Ecosystem for Pediatric Medical Device Development

Multi-Stakeholder Engagement on FDA's Proposed Novel Framework

Pre-Consortium Organization

Executive Committee

- U.S. FOOD & DRUG ADMINISTRATION
- American Academy of Pediatrics — DEDICATED TO THE HEALTH OF ALL CHILDREN™
- AdvaMed — Advanced Medical Technology Association
- CRITICAL PATH INSTITUTE

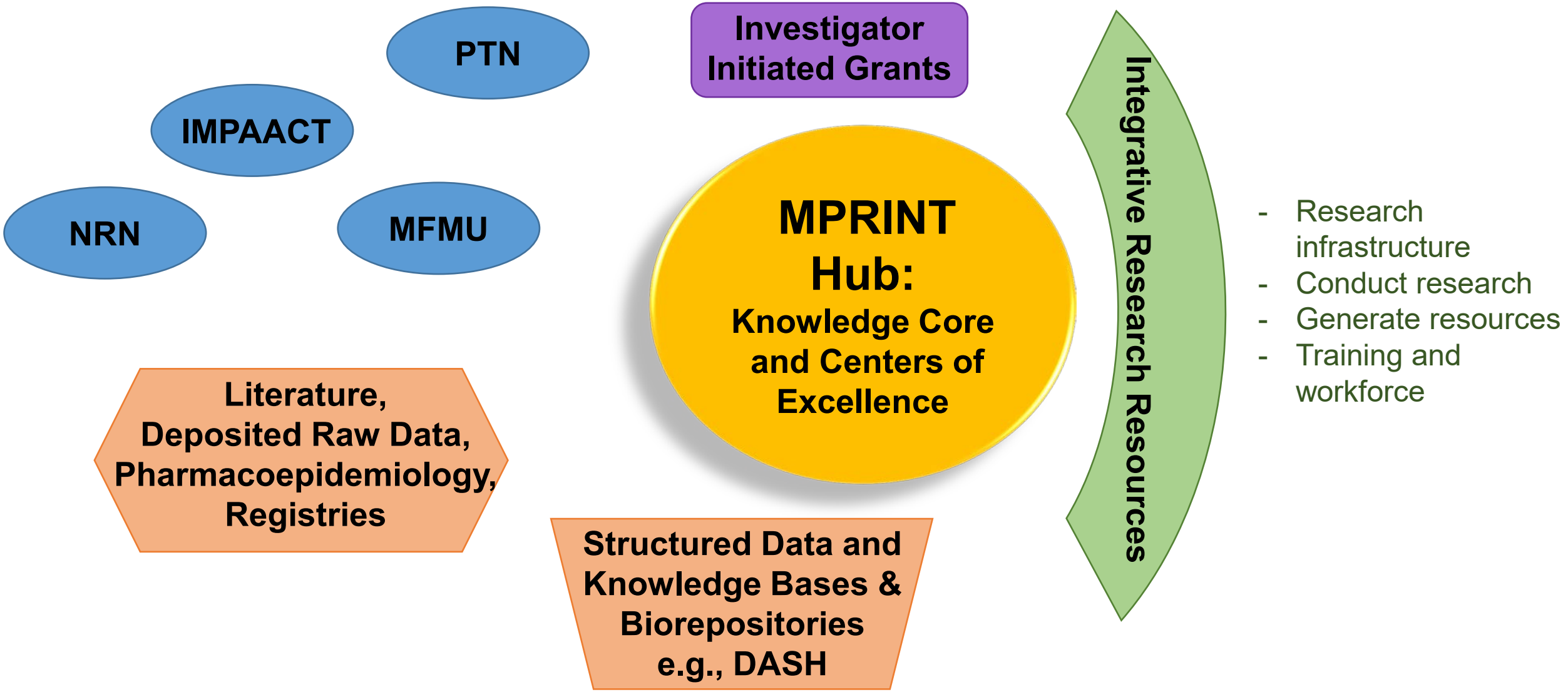
Coordinating Committee

Patient Advocacy
Industry
Children's Hospital Association
Payors
Venture Capitalist
Regulatory
Academia
NIH
C-Path Institute

Virtual Public Meeting & Workshop
February 9th - 11th 2021
Recording available:
https://c-path.org/ship-md/

- Workstream 1 — **SHIP Boarding, Sailing, Exit**
- Workstream 2 — **Criteria for Qualifying Hospitals**
- Workstream 3 — **Reimbursement**
- Workstream 4 — **Finance**
- Workstream 5 — **Regulatory**

Additional Needs in the Research Ecosystem



The MPRINT Hub is something new…

…and we're building the bridge as we cross it!

Questions?