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Rapid whole genome sequencing (rWGS)™ in neonatal and pediatric acute care: Keys to successful implementation

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Disclosures

- None.

Learning Objectives

- Identify the key components of new technology adoption in healthcare settings
- Discuss different pathways to implementation of rWGS in neonatal and pediatric inpatient settings
- Assess facilitators and barriers to rapid whole genome sequencing adoption in your settings

Before we begin…Where are we now?

- Have you heard of genomic testing in newborns?
- Is it being done in your setting?
- Do you understand the technology?
- Are you enthusiastic about its potential?
- Are you worried about unintended consequences?

https://bioinformatics.csiro.au/blog/new-research-finds-genomic-professionals-support-patient-genomic-data-ownership-in-australia/

Some definitions:

- Next Generation (Next Gen) Sequencing:
  - A high-throughput method used to determine a portion of the nucleotide sequence of an individual's genome (22,000 genes)
  - Utilizes DNA sequencing technologies that are capable of processing multiple DNA sequences in parallel
  - Also called massively parallel sequencing and NGS

https://www.cancer.gov/publications/dictionaries/genetics-dictionary/

Some definitions:

- Whole exome sequencing (WES or WXS)

  - WES selectively looks at only the **protein-coding** gene regions (i.e., exons) of a genome (about 1-2% of the genome)

  - Because most known disease-causing variations occur in exons, exome sequencing can be an efficient way to identify such variations

https://www.cancer.gov/publications/dictionaries/genetics-dictionary/

Some definitions:

- Whole genome sequencing (WGS or GS)
  - Analyzes up to 90% of the genome - **coding and non-coding regions** - to determine the order of the nucleotides in an individual's DNA, and to identify variations
  - WGS detects complex variations such as translocations and rearrangements, copy number variations (CNVs), small insertions and deletions, and single nucleotide variations (SNVs)
  - A typical whole genome has 4.1-5 million single-nucleotide and insertion-deletion variants per sample
  - Not all variants affect health (but we know them all) – new genome-based disorders discovered daily

https://www.cancer.gov/publications/dictionaries/genetics-dictionary/

What's all the fuss about?

- Thousands of genes can be screened at once
- Vast libraries of genetic disorders can be searched instantly
- Turn-around time is now hours to days (rWGS)

Photo credit: Enan Liang

"23 and Baby", Scientific American, Lewis T, Jan 2020
https://www.scientificamerican.com/article/23-and-baby/

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New Technology Adoption

Step 1: Efficacy

Does it work?

Rapid Whole Genome Sequencing (rWGS)™ Efficacy

Dimmock et al, Am J Human Genetics 2020;107, 942–952

Ref.	Date	Study Type	Seq Type	Neonatal and Pediatric Intensive Care Unit (NICU, PICU) Enrollment Criteria	Size	Dx Rate	Change in Management	Change in Outcome	TAT (d)
11	2012	Cases	urWGS	NICU infants with suspected genetic disease	4	75%	n.d.	n.d.	2
12,13	2015	Cohort	rWGS	<4 mo of age; Suspected actionable genetic disease	35	57%	31%	29%	23
14	2017	Cohort	rWES	<100 days of life; Suspected genetic disease	63	51%	37%	19%	13
15	2018	RCT	rWGS	<4 mo of age; Suspected genetic disease	32	41%	31%	n.d.	13
16	2018	Cohort	rWGS	infants; Suspected genetic disease	42	43%	31%	26%	23
17	2018	Cohort	rWES	Acutely ill children with suspected genetic diseases	40	53%	30%	8%	16
18	2018	Cohort	rWGS	Children; PICU and Cardiovascular ICU	24	42%	13%	n.d.	9
19	2019	Cohort	rWGS	4 months-18 years; PICU; Suspected genetic diseases	38	48%	39%	8%	14
7	2019	Cohort	rWGS	Suspected genetic disease	195	21%	13%	n.d.	21
20	2019	Cases	urWGS	Infants; Suspected genetic disease	7	43%	43%	n.d.	0.8
21	2019	Cohort	rWES	<4 mo of age; ICU; hypotonia, seizures, metabolic, multiple congenital anomalies	50	54%	48%	n.d.	5
22	2020	Cohort	rWES	NICU & PICU; complex	130	48%	23%	n.d.	3.8
23	2020	Cohort	rWES	PICU; < 6 years; new metabolic/neurologic disease	10	50%	30%	n.d.	9.8
6, here	**2019**	**RCT**	**rWGS**	**Infants; disease of unknown etiology; within 96 hours of admission**	**94**	**19%**	**24%**	**10%**	**11**
			rWES		**95**	**20%**	**20%**	**16%**	**11**
			urWGS		**24**	**46%**	**63%**	**25%**	**4.6**
Weighted Average, urWGS					**35**	**49%**	**58%**	**25%**	**3.6**
Weighted Average, rWGS or rWES					**894**	**37%**	**38%**	**16%**	**15**

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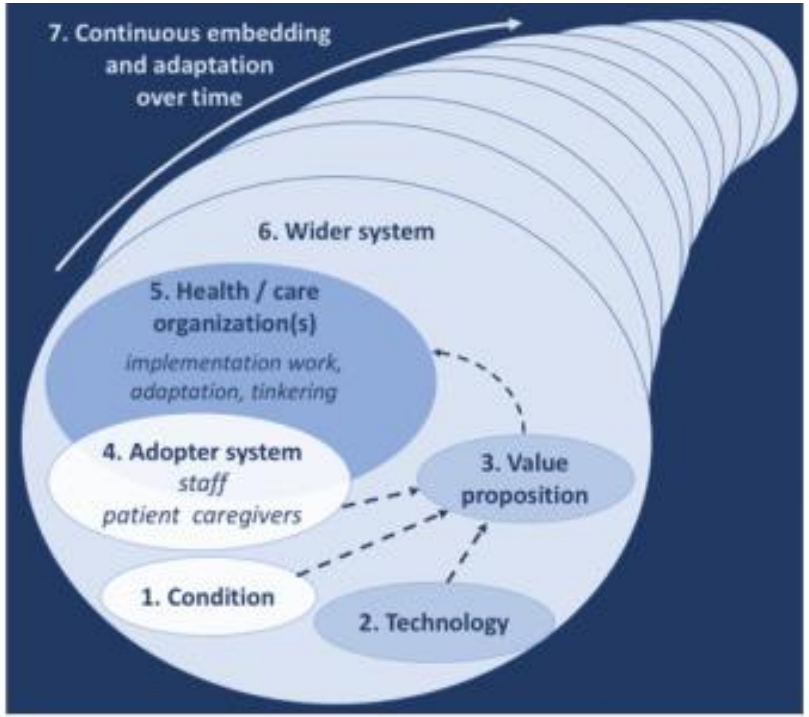
New Technology Adoption Step 2:

Implementation

Does it work in the Real World?

Factors beyond technology influence adoption

- End-user knowledge and attitudes
- Organizational characteristics
- Resource allocation
- Policy and politics



Greenlagh et al 2017 doi: 10.2196/jmir.8775: 10.2196/jmir.8775

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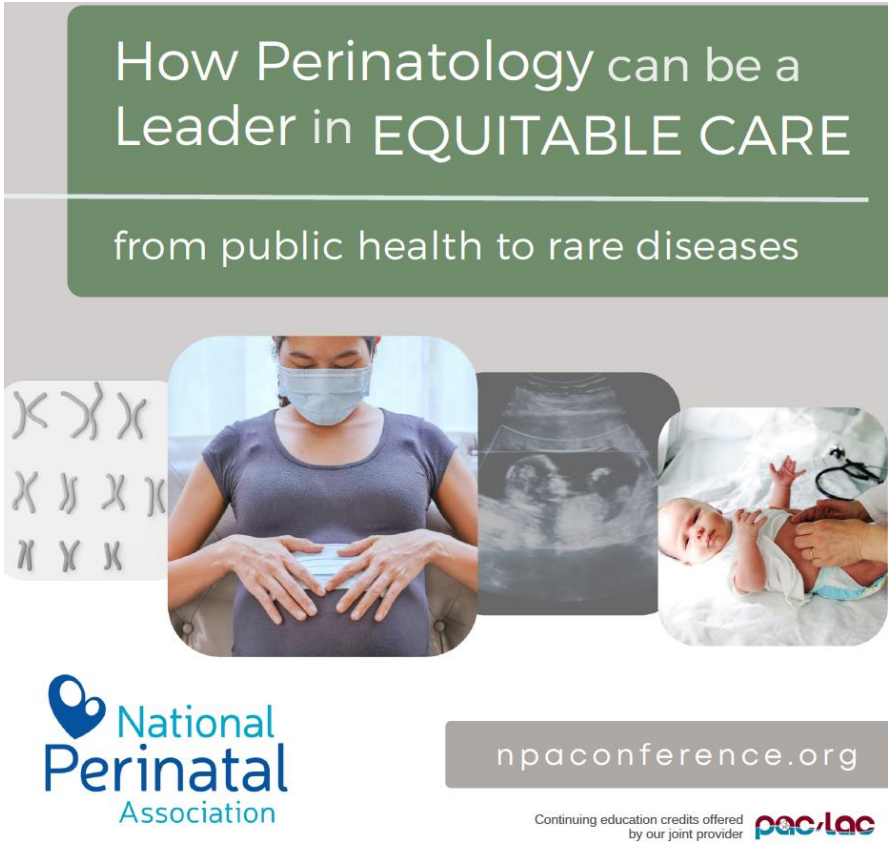
Adoption of next gen sequencing in neonatal/pediatric settings

- rWGS has a higher diagnostic sensitivity compared to standard genetic tests
- Fast turn around time of 2-5 days = early and meaningful impact on clinical decisions and facilitates family counseling

And yet, not widely implemented…

- Concerns about cost because of limited coverage by insurance
- Lack of guidance on how to implement
- What to do when Variants of Unknown Significance (VUS)?

Can new genomic technology be implemented equitably?



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From Research to Practice – Early Adopters

- **California's Project Baby Bear (PBB)** (2018-2020)

- **Michigan's Project Baby Deer (PBD)** (2020-2021)

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rWGS implementation: Project Baby Bear

Legislatively funded 5-hospital pilot project for **publicly-insured** babies in ICUs

- 178 babies received rWGS over 23 months
- Provided diagnoses for 76 babies (43%)
    - Diagnosed 35 rare conditions (< 1 in 1 mil)
- 3-day turnaround time for provisional results
- Change in the management for 55 babies (31%)
- Clinical utility:
    - Fewer hospital days | fewer procedures/new therapies | reduced costs

http://analyses.chbrp.com/document/view.php?id=1545/

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Project Baby Bear Implementation

- Interviews with 24 key informants | 2-7 from each site

Sample			
Neonatologist	4	Social Worker	3
NICU or PICU Division Chief/Medical Director	2	Lab Director	2
Geneticist	4	Project Coordinator	4
Genetic Counselor	2	Hospital Administrator	2
Hospitalist	1		

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PBB Implementation Themes

Who made it happen?

- Project champions – essential to getting started
- Designated staff - to identify patients and get the test ordered
- Collaborators – so all the steps of the procedures happened correctly

"You have to have a champion who believes it's important and be willing to invest their time in it."

PBB Implementation

How did they negotiate roles and responsibilities?

- Agreed eligibility criteria (to start with)
- Cautious use at first – treated as a precious resource
- With experience/actionable results, more comfort, some expansion of use
- Intensivist (NICU or PICU)-led OR geneticist-led process
    - Approach to case selection and ordering; often collaborative
    - Contact with parents (pre- and post-testing)

"At some level, genetics involvement is critical... I don't mind if the test is sent by other people, so long as we're around when the results are there."

PBB Implementation Themes

Workflow / work-arounds

- Availability of genetics consults when needed
    - New genetics team workflow for inpatient coverage
- Parent testing procedures
- Turn-around time/lab logistics
- Approvals for tests outside of pre-specified criteria
- Differentiating usual care from research

"Sometimes providers can think, 'It's going to be so hard to order. This test is really complicated' - and so making it as easy as possible is important."

PBB Implementation

How they felt about rWGS as a first-tier test

Fears/anxieties

- Primary providers not feeling competent
- Genetics experts as gatekeepers
- How to assess/provide families the right information
- Potential future negative implications for patients and families
- Overuse of an “expensive” test
- Who will pay for it?

PBB Implementation

How they felt about rWGS as a first-tier test

Good value

- “Aha moment”
- Giving answers earlier – shortening the “diagnostic odyssey”
- Improving outcomes; avoiding futile treatments
- Saving resources
- Supporting parent decision-making; providing answers

New collaborations

- Closer relations between intensive care, lab and genetics services, administration, RCIGM, other project sites
- Figuring out telehealth solutions
- Opportunities to engage with policy-makers

PBB Implementation

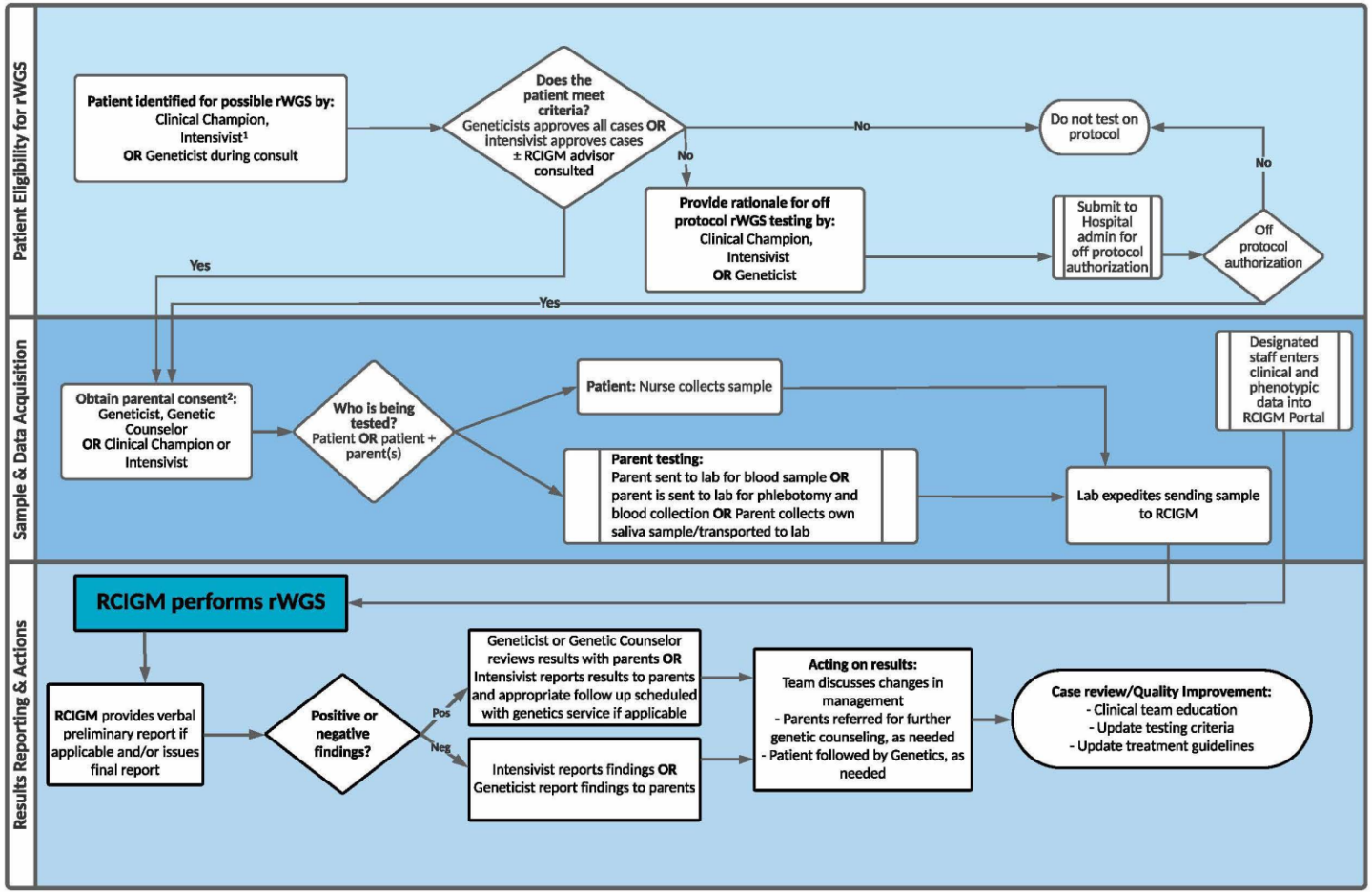
How they felt about rWGS as a first-tier test

Pride

- Being on the cutting edge, early adopters
- **Caring for underserved patients – first instead of last access to new technology**

"We can't say that our mission is to improve the health of our kids - and investment in technology is part of the ways in which we do that - and then not find ways to be able to promote that when there's clear scientific evidence that it provides clinical value…."

PBB Workflow



J Pediatr. 2021 Oct;237:237-243.e2. Https://10.1016/j.jpeds.2021.05.045

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Implementing Rapid Whole-Genome Sequencing in Critical Care: A Qualitative Study of Facilitators and Barriers to New Technology Adoption

Linda S. Franck, RN, PhD[1], Rebecca M. Kriz, RN, MS[2], Seema Rego, PhD[3], Karen Garman, EdD, MAPP, BCC[3], Charlotte Hobbs, MD, PhD[3,4], and David Dimmock, MD, FACMG DABP[3,4]

Objective To characterize the views of members of the multi-disciplinary team regarding the implementation of rapid whole-genome sequencing (rWGS) as a first-tier test for critically ill children in diverse children's hospital settings.

Study design Qualitative interviews informed by implementation science theory were conducted with the multi-disciplinary patient care teams and hospital leaders at each of the 5 tertiary care children's hospitals involved in a statewide rWGS implementation project.

Results Our analysis revealed 5 key themes regarding the implementation process across the sites: the need for rWGS champions, educational needs and strategies, negotiating decision-making roles and processes, workflows and workarounds, and perceptions about rWGS. From the findings a composite clinical workflow diagram was developed to summarize all of the processes involved in the implementation of the test, and the key areas where implementation practices differed.

Conclusions These findings provide insights for design of interventions to support adoption, scale-up, and sustainability of rWGS and other novel technologies in neonatal and pediatric critical care settings. *(J Pediatr 2021;237:237-43)*.

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What did we learn from PBB?

- Policy advocacy is essential
- Engagement of ALL stakeholders is key
- Several different ways to enter – need keys to doors #1,2,3…
- Need to unlock many gates along the way for smooth processes

rWGS implementation: Project Baby Deer

8-hospital clinical implementation for any infant or child meeting criteria in ICUs or acute care units

Clinical impact:

- 89 infants and children received rWGS over 18m
- Provided diagnoses for 35 patients (39%)
- Change in the management for 24 patients (27%)
- Estimated hospital cost savings = $4,155 per patient

rWGS implementation: Project Baby Deer

- Family impact:
  - Some families expressed the wish that rWGS had been done sooner in the hospital stay
  - Many families felt that all children should have access to quick answers and early prevention
- Policy Impact:
  - **Michigan rWGS Medicaid Policy** went live on September 1, 2021, making Michigan the first state in the nation to have a carve-out payment for inpatient rWGS

Health Professional Attitudes about rWGS

A 44-item survey exploring views on rWGS implementation was created - adapted from existing scales:

- Demographics
- Experience with rWGS in practice
- Genomics education/knowledge
- rWGS resource access
- General and future use of rWGS
- rWGS implementation experience

A link to the voluntary online anonymous survey distributed by the rWGS clinical champion at each site (March – June 2021)

Health Professional Attitudes about rWGS

Respondents from 8 sites (N=305)	% (n)
Primary position	
Physician - attending	26% (80)
Physician - resident	9% (26)
Nurse practitioner	6% (19)
Genetic counselor	4% (13)
Nurse (direct patient care)	42% (130)
Pharmacist/ Therapist/ Social Worker/Parent liaison	4% (12)
Laboratory director	1% (3)
Laboratory staff	2% (6)
Hospital administrator	3% (8)
Nursing director/Nurse manager/CNS/Case manager	3% (10)

Children 2022, 9, 357. https://doi.org/10.3390/children9030357

Health Professional Attitudes about rWGS

Respondents from 8 sites	% (n)
Unit (n=304)	
NICU	46% (141)
Multiple units/hospital wide	19% (58)
PICU	12% (37)
Medical surgical	9% (21)
Outpatient clinic	7% (27)
Non-clinical	5% (14)
Laboratory	1% (3)
Emergency Room	1% (3)

Children 2022, 9, 357. https://doi.org/10.3390/children9030357

PBD Staff Survey Results

Experience with rWGS

- 52% had been involved in the care of an inpatient infant or child for whom rWGS was ordered
- 24% had direct conversations with families about rWGS testing or diagnosed disorders

rWGS self-rated knowledge

- “a little” = 34%; “none” = 29%
- 64% of geneticists and genetic counselors reported “a lot” or “expert”
- 98% of providers reported genetics education
- 53% of direct care nurses reported any genetics education

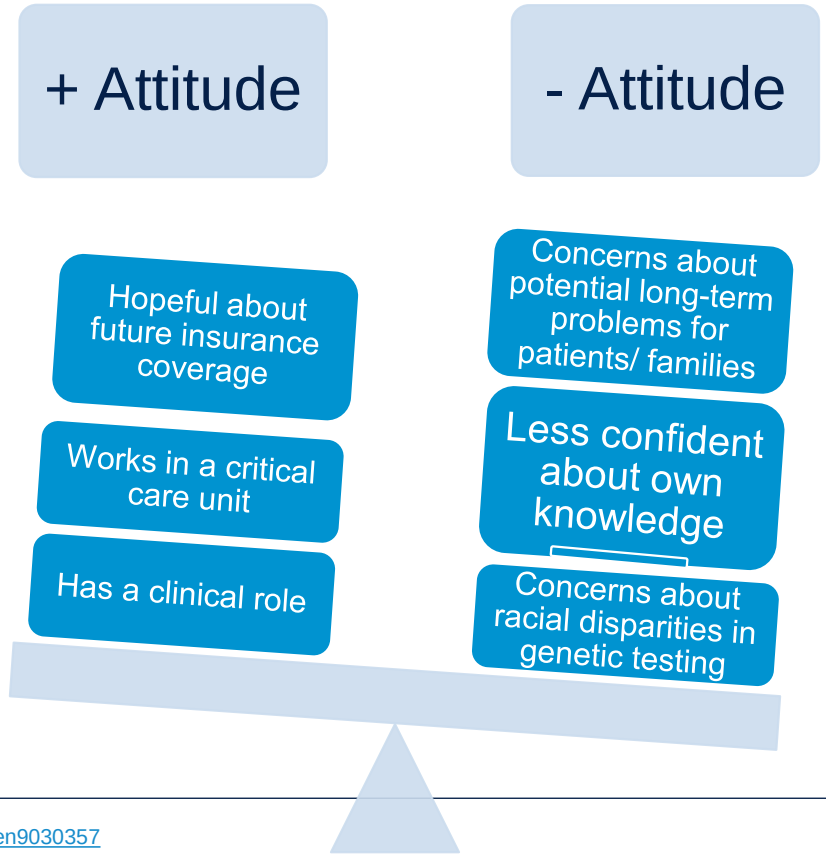
Children 2022, 9, 357. https://doi.org/10.3390/children9030357

Genetics or genomic education of respondents

	% (n)
On-the-job training	53% (164)
Genetics course in initial professional training	42% (130)
Hospital supported training	37% (112)
Self-directed education (journal articles etc)	32% (97)
CME/CEU courses in genetics	26% (79)
Genetics course in grad school	20% (62)
Seminar / workshops in genetics	14% (44)
Genetics specific conferences	12% (37)
Advanced training in genetics	7% (20)
No specific training	25% (76)

Children 2022, 9, 357. https://doi.org/10.3390/children9030357

Factors influencing rWGS attitudes



Children 2022, 9, 357. https://doi.org/10.3390/children9030357

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Article

Breaking Barriers to Rapid Whole Genome Sequencing in Pediatrics: Michigan's Project Baby Deer

Caleb P. Bupp,[1,2*] Elizabeth G. Ames,[3] Madison K. Arenchild,[4] Sara Caylor,[4] David P. Dimmock,[4] Joseph D. Fakhoury,[5,6] Padmani Karna,[7] April Lehman,[8] Cris I. Meghea,[7] Vinod Misra,[8] Danielle A. Nolan,[9] Jessica O'Shea,[3] Aditi Sharangpani,[7] Linda S. Franck,[10‡] Andrea Scheurer-Monaghan[6,11‡]

- Bupp et al https://pubmed.ncbi.nlm.nih.gov/36670656/

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MDPI

Article

Healthcare Professionals' Attitudes toward Rapid Whole Genome Sequencing in Pediatric Acute Care

Linda S. Franck [1,*], Andrea Scheurer-Monaghan [2,3], Caleb P. Bupp [4,5], Joseph D. Fakhoury [3,6], Thomas J. Hoffmann [7], Manasi Deshpandey [1], Madison Arenchild [8] and David P. Dimmock [8]

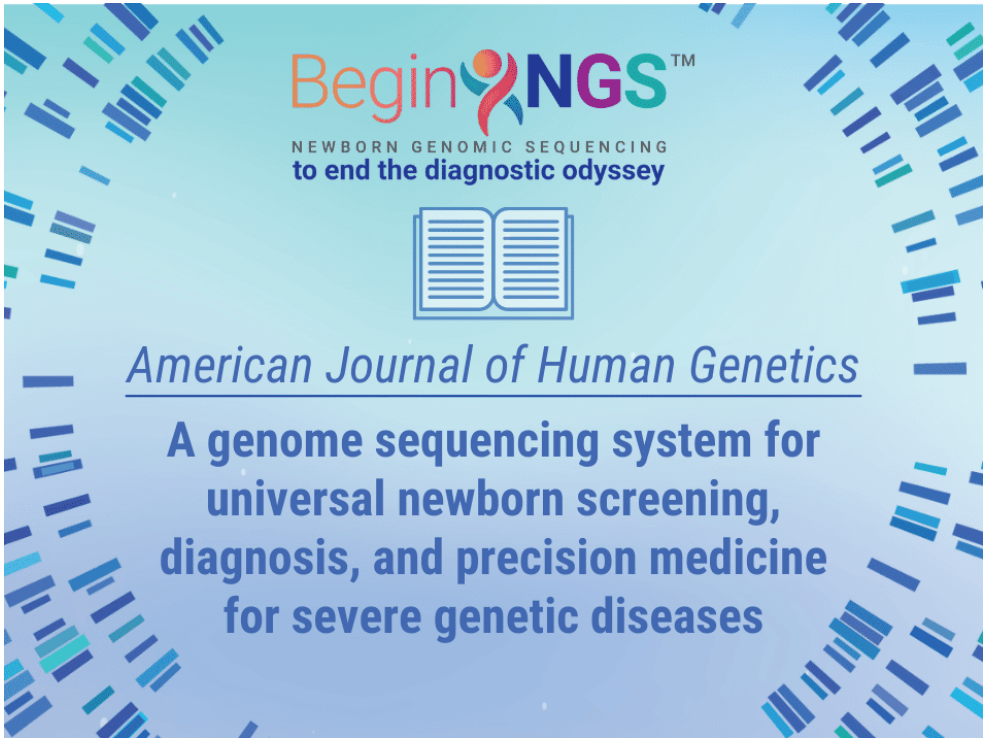
- Franck et al https://pubmed.ncbi.nlm.nih.gov/35327729/

What did we learn from PBD?

- Advocacy is key
- Clinical champions are key
- Education is key
- Exposure is key
- Correcting myths and mis-perceptions is key
- Keeping up with new evidence is key

Coming soon to a NICU/PICU near you!

Nicklaus Children's Hospital | Project Baby Manatee



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Are you ready?

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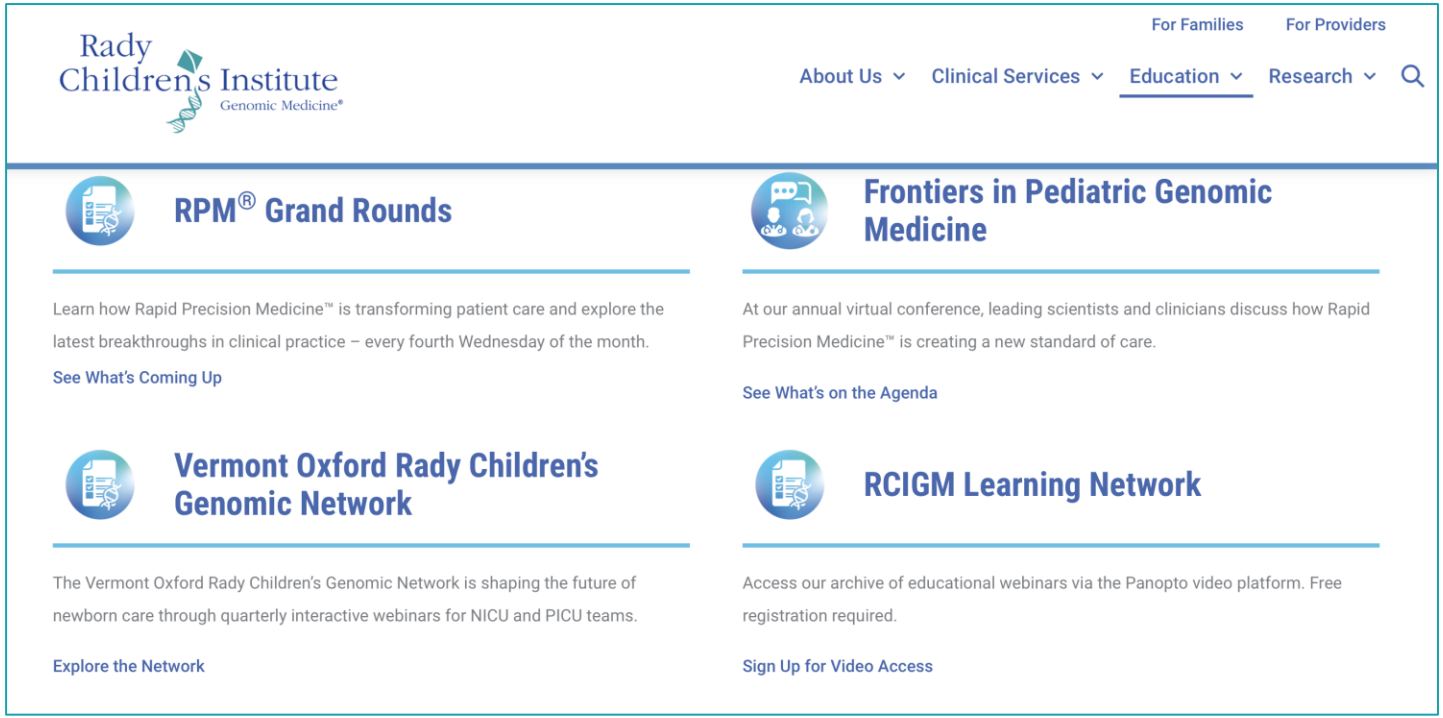
Genomic Sequencing Resources

https://radygenomics.org



Genomic Sequencing Resources

https://www.mha.org/issues-advocacy/project-baby-deer/

+ **Project Baby Deer Media**
+ **Educational Resources**
+ **Genomics 101**
+ **Policies**

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Mind the Gap

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“Key” Points

- ***You got this*** **–** good implementation habits pay off
  - ***We are the champions*** – implementation needs champions
  - ***It takes a village*** – engage all stakeholders
- ***Get into the weeds*** **–** get very familiar with all the ‘deets’ of all the processes involved

Key processes for successful – and equitable - genomic sequencing implementation

1. Learn together
2. Engage in advocacy
3. Assess your current interdepartmental relationships
4. Assess your unit's style/culture
5. Develop a process map

“Key” Points

- ***See one, do one, teach one*** – spread knowledge, competence, comfort
- ***What gets measured, gets done*** – define metrics for success and monitor
- ***Rinse and repeat*** – adjust, recommit, keep implementing

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Thank You!

Collaborators:
Rebecca Kriz
Charlotte Hobbs
Seema Rego
Karen Garman
David Dimmock
Andrea Scheurer-Monaghan
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Joseph D Fakhoury
Manasi Deshpandey
Madison Arenchild