The Future of Genomic Newborn Screening is starting now: BeginNGS

BeginNGS™
NEWBORN GENOMIC SEQUENCING
to end the diagnostic odyssey

skingsmore@rchsd.org

June 9th 2023, 14:00

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Good: Diagnose a critically ill baby in 2 days
Best: Identify + treat before symptoms

Presenting complaint: 1 month old female with hemiparesis

Phenotypes of illness: Cephalohematoma; Enlarged fontanelles

Laboratory workup: Intracranial hemorrhage; Lactic acidosis; Reduced factor 13 activity

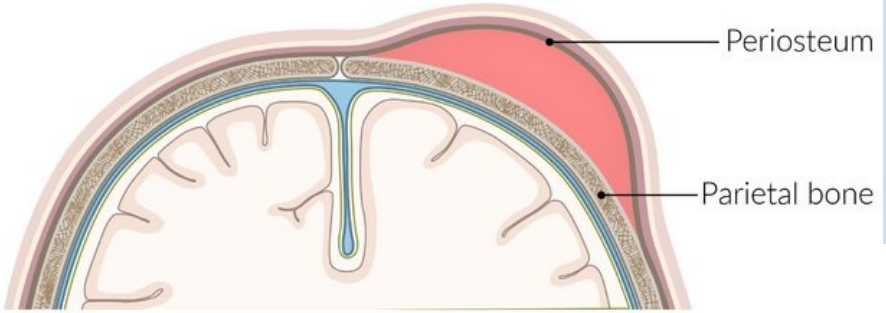
rWGS ordered: Genomic Medicine for Ill Neonates and Infants (GEMINI) Study

Diagnosis: Clotting factor 13A1, *F13A1* pathogenic homozygous c.27del p.Phe9fs

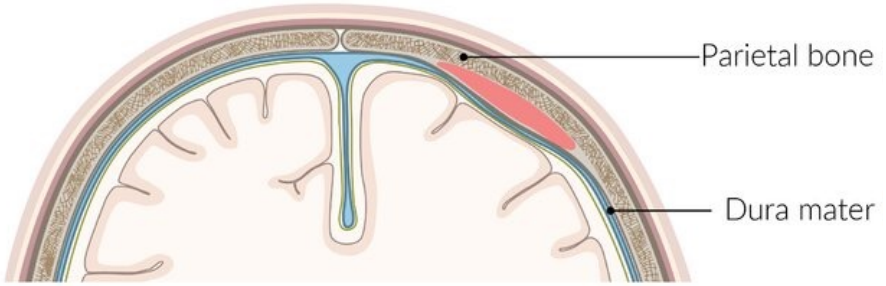
Autosomal recessive Factor 13A deficiency

Treatment:

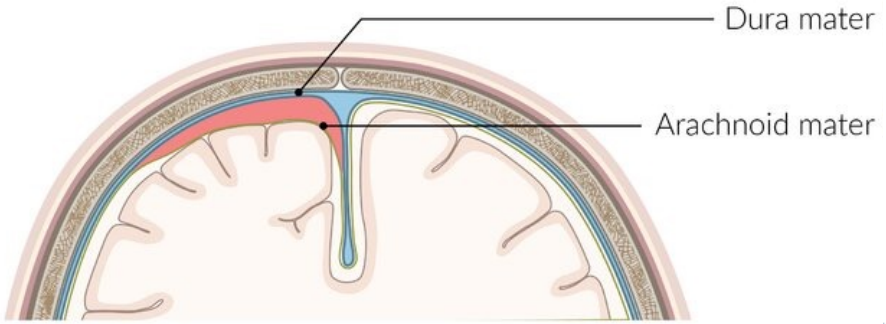
- Fresh frozen plasma or cryoprecipitate;
- FXIII or Catridecacog



Cephalohematoma



Epidural hemorrhage



Subdural hemorrhage

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Cold Spring Harb Mol Case Stud. 2018 Dec 17;4(6):a003525.

The approach to diagnosing + managing rare genetic disease is unacceptably inefficient + inequitable

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Burden of Rare Genetic Disease

1 in 20

children have a rare genetic disease[1]

On average, reaching a diagnosis takes

4.8 Years

AND

7.3

Specialists

and some children never get diagnosed

>$1 T

annual burden of rare disease on U.S. healthcare system[2] with an average PPPY cost between ~$9 – 140 K[3]

Management of rare disease patients is a **global issue** that needs to be addressed by integrated healthcare systems

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[1] Estimates of number of rare diseases are 5000 – 8000, and U.S. rare disease prevalence are 1 in 10, where children are about half. [2] ~$1 T annual cost of subset of 379 rare diseases, comprised of direct and indirect costs, non-medical costs, and healthcare costs not covered by insurance. [3] Range from rare diseases diagnostic / treatment costs, compared to <$6 K annual cost for non-rare disease pts. PPPY: Per patient per year.
Source: Bavisetty. *Rare Dis.* 2013; Marwaha. *Genome Medicine.* 2022; Tisdale et al. *Orphanet Journ. Rare Disease.* 2021; Yang et al. *Orphanet Journ. Rare Disease.* 2019; RCIGM Prior Materials; NIH; ClearView Analysis.

BeginNGS is informed by 11 years experience delivering rapid diagnostic genome sequencing for critically ill children

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2003 Human Genome Project

2004 Next Generation Sequencing
Solexa
454

2009 Nic Volker
First Diagnostic Sequencing Case

2012 1st Ultra-rapid diagnostic genome
at Children's Mercy Hospital

2013 NBS-by-NGS
NCNexus
NSIGHT1
BabySeq
NBSeq

2014 RCIGM
Founded

2015 NSIGHT2
at Rady Children's Hospital

2018 Project Baby Bear
State of California

2019 Project Baby Manatee
State of Florida
GEMINI

2020 SOMID
Rady Children's & UCSD

2021 Project Baby Deer
State of Michigan

2021 Genome-To-Treatment
GTRx

2022 BeginNGS Retrospective Study 1

2022 1st Automated ultra-rapid diagnostic genome

2022 ICONS
founded

2023 BeginNGS Prospective Study 1

2023 BeginNGS Retrospective Study 2

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Future Trends in Genomic Medicine

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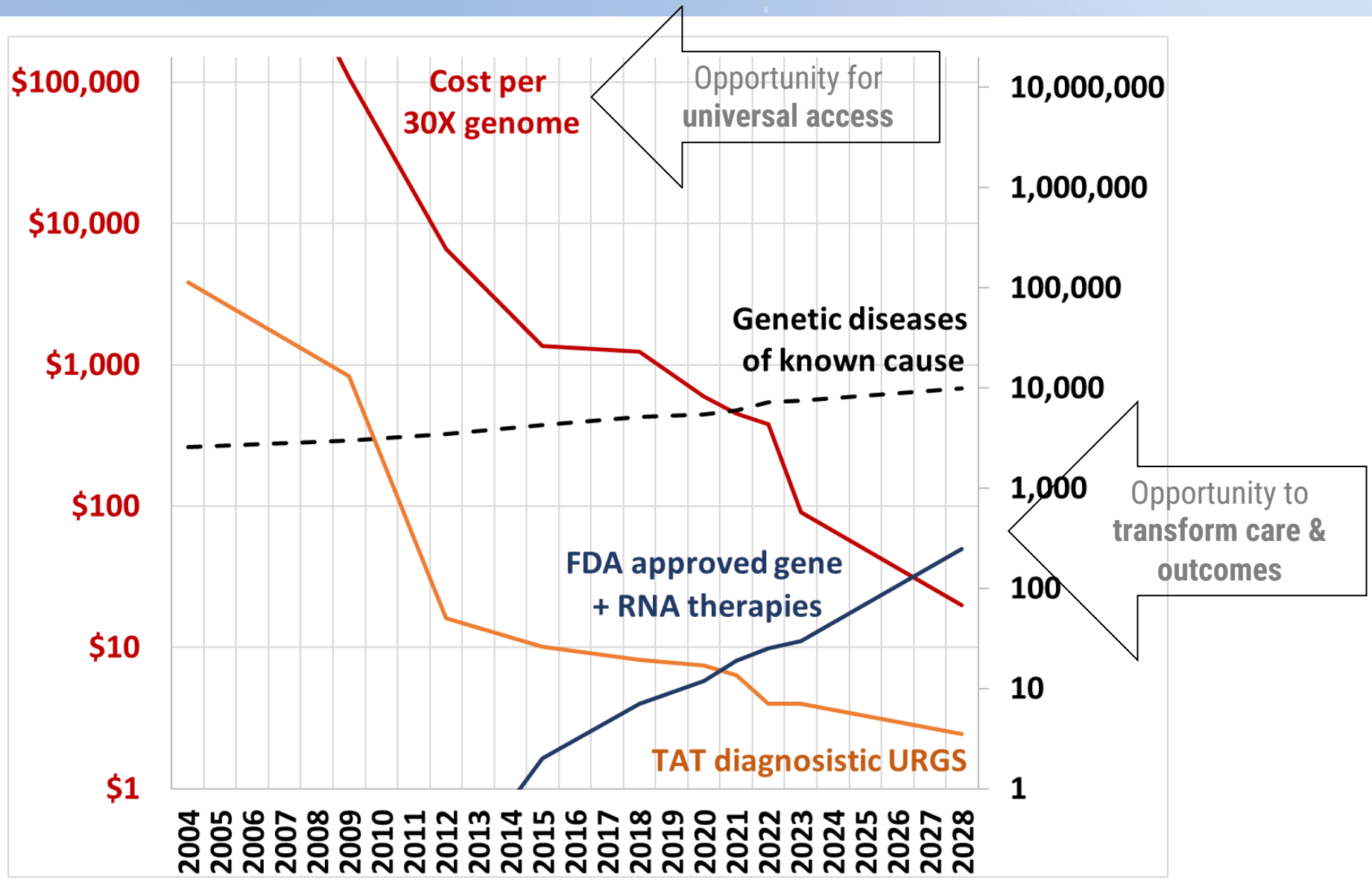

What if we could decode all babies' genomes in the 1st week of life?

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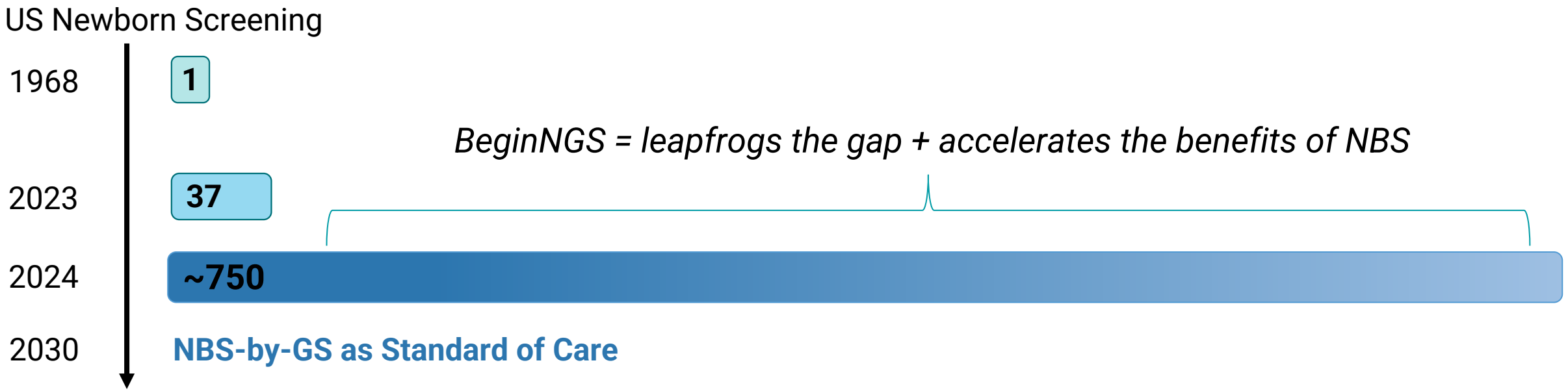
~750 genetic diseases affect newborns that could be screened by genome sequencing for which somewhat effective therapeutic interventions currently exist.



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BeginNGS Founding Partners

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Rare Disease Pharma

ALEXION
AstraZeneca Rare Disease

TRAVERE™ THERAPEUTICS

inozyme pharma

ultragenyx

SAREPTA THERAPEUTICS

SENTYNL THERAPEUTICS, INC.

Orchard therapeutics

sanofi

HORIZON

rocket pharma

MAHZI therapeutics

Advocacy/Health Systems

Rady Children's Hospital San Diego

LeBonheur Children's Hospital

EVERYLIFE FOUNDATION FOR RARE DISEASES

Global Genes®
Allies in Rare Disease

COMBINED

NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

Indiana Hemophilia & Thrombosis Center

Technology

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ALEXION
AstraZeneca Rare Disease

illumina

[tile]DB

FABRIC GENOMICS

GENOMENON

plumcare

luna DNA

BeginNGS will eliminate the diagnostic odyssey + provide equitable access to optimal precision care

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Challenges of Genetic Disease Care

Lengthy diagnostic odyssey prevents effective management of genetic disease

Specialist expertise + treatment access for genetic disease is **limited to centers of excellence**

Difficulty identifying rare disease patients creates challenges for drug development

BeginNGS

digital healthcare delivery system for genetic disease families + their healthcare providers

Population genome sequencing to identify genetic disease at/before symptoms in newborns in an acceptable manner to families + physicians

Treatment guidance + referral platform to support non-expert physicians + provide equitable access to optimal treatment

Aggregated genomic database accelerates therapeutic innovation + approval + increases access for patients

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Source: ClearView Analysis.

gtrx.radygenomiclab.com: 341 genes x 410 disorders x 1,654 effective therapies

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Indication Contraindication Timing Efficacy Evidence for efficacy Adverse effects

ClinGen	HGNC	Medscape	NCBI Gene	OMIM
DrugBank	Inxight:Drugs	Orphanet	NORD Rare Disease	MedGen
GeneReviews	MedlinePlus GHR	NCATS GARD		PubMed

Disease-Gene list development:
Inclusion Criteria
1. Severe, childhood-onset disease
2. Effective therapeutic intervention available

Phase 4
AI & expert curation of treatment literature

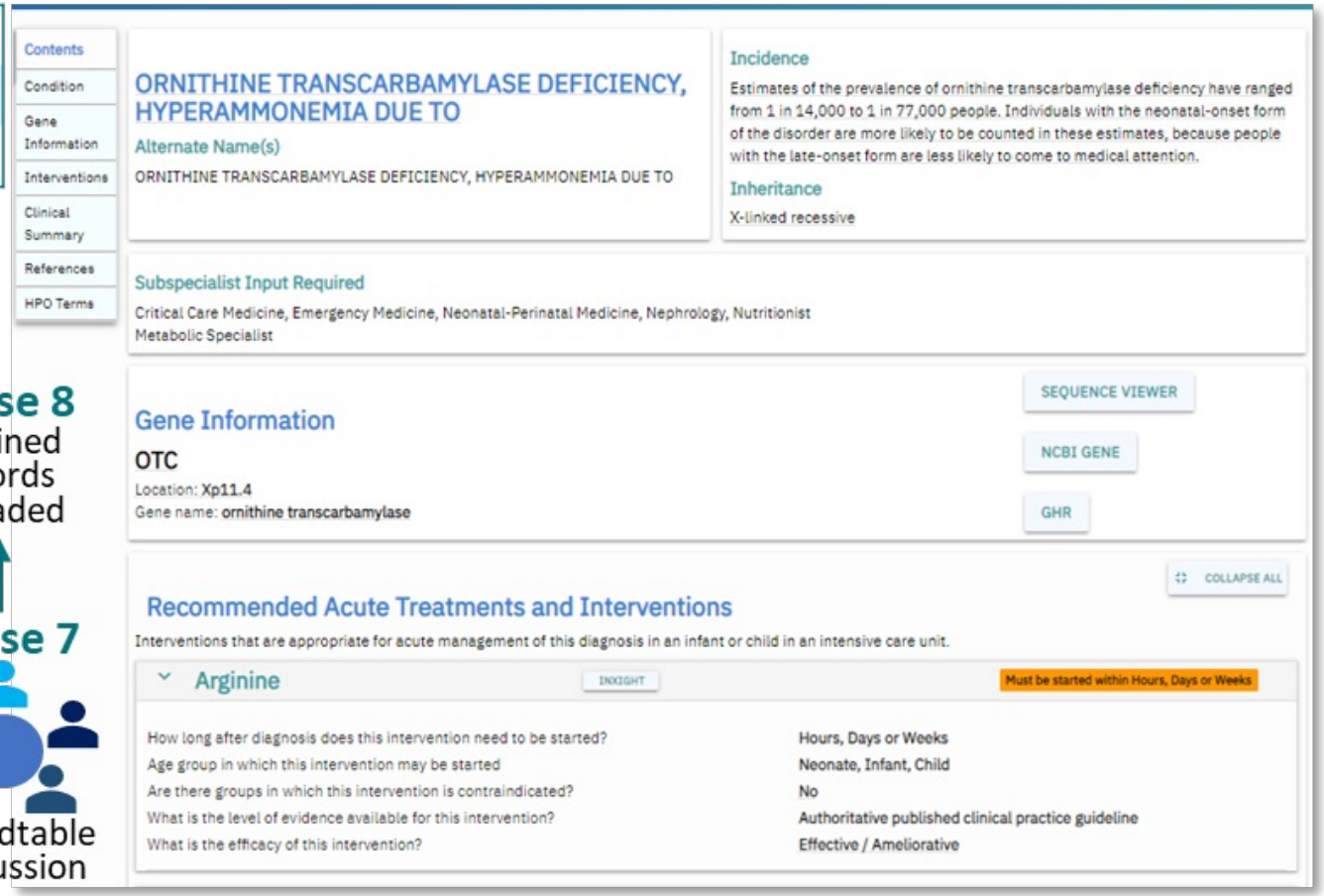
REDCap
Development of structured curation system
Phase 5

Phase 6a
Independent review by 5 experts

Phase 6b
Primary expert review
Secondary expert review

Curated records with consensus → **Phase 8** Retained Records uploaded

Curated records lacking consensus → **Phase 7** Roundtable Discussion



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Nat Commun. 2022 Jul 13:4057.

gtrx.radygenomiclab.com: 341 genes x 410 disorders x 1,654 effective therapies

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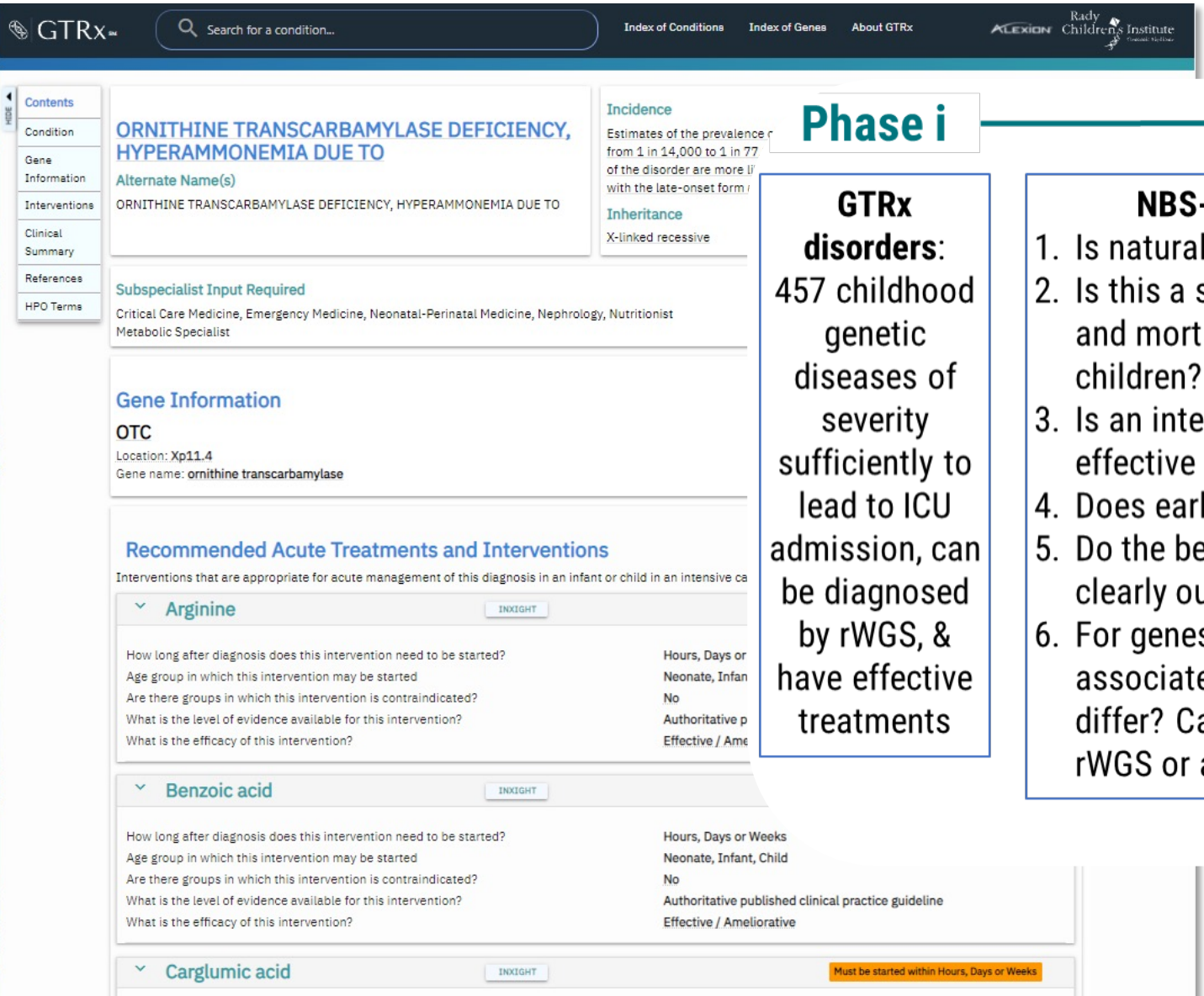

Phase i → **Phase ii** → **Phase iii** → **Phase iv** → **Phase v** → **Phase vi**

GTRx disorders: 457 childhood genetic diseases of severity sufficiently to lead to ICU admission, can be diagnosed by rWGS, & have effective treatments

NBS-rWGS list development:

1. Is natural history well-understood?
2. Is this a significant risk for morbidity and mortality in infants or young children?
3. Is an intervention available that is effective and accepted?
4. Does early treatment improve outcome?
5. Do the benefits of early intervention clearly outweigh the risks?
6. For genes with more than one associated disorder, do treatments differ? Can they be distinguished by rWGS or another test?

Development of structured curation system

Review by 5 experts

15% Rejected
64% Retained, Group A
21% Retained, Group B

Roundtable Discussion

Am J Hum Genet. 2022 109:1605-1619.

Final Selection of Disorders, Genes, Inheritance Patterns, Variants for BeginNGS

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Problems & Solutions:

1. One gene → several disorders
    - Retain disorders with strong gene-disorder association
    - Lump disorders that are a spectrum
2. One disorder → several patterns of inheritance
    - Retain patterns of inheritance with strong evidence
    - Add female carriers for X-linked disorders with Lyonization
3. Review ability of short-read genome sequencing to identify causative variants
    - 410 disorders, 341 genes
4. ~50,0000 ClinVar & Genomenon semi-structured “pathogenic” + “likely pathogenic variants”
    - Extract, transform, load to TileDB; Python queries
    - Train with true positive + true negative population genome sets

BeginNGS Workflow

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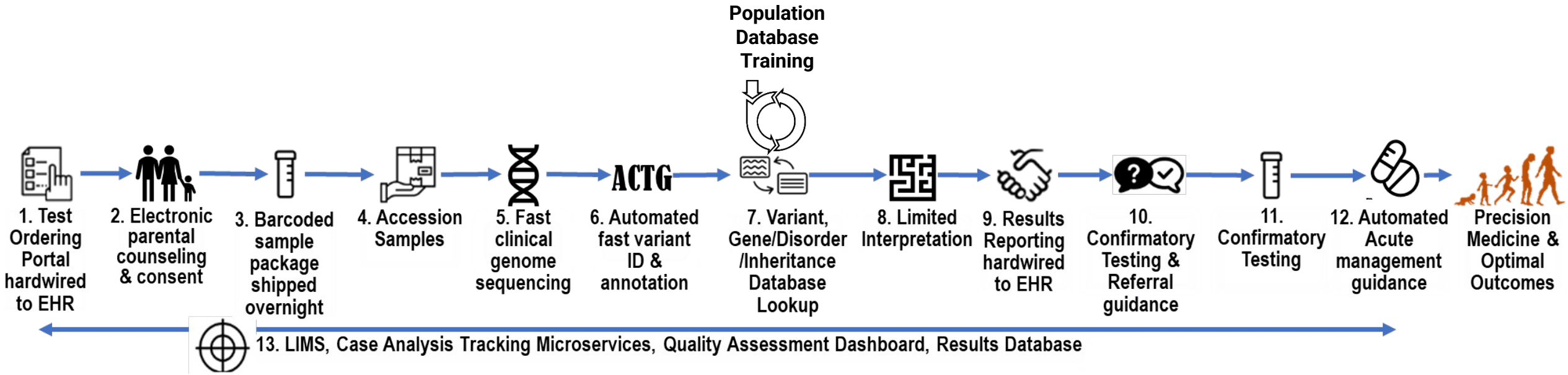
ClinVar + Genomenon pathogenic + likely pathogenic variants
Transformer artificial intelligence software for novel LOF variants



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Am J Hum Genet. 2022 109:1605

GTRx empowers non-COEs to use BeginNGS, navigate genome results + optimally treat rare disease

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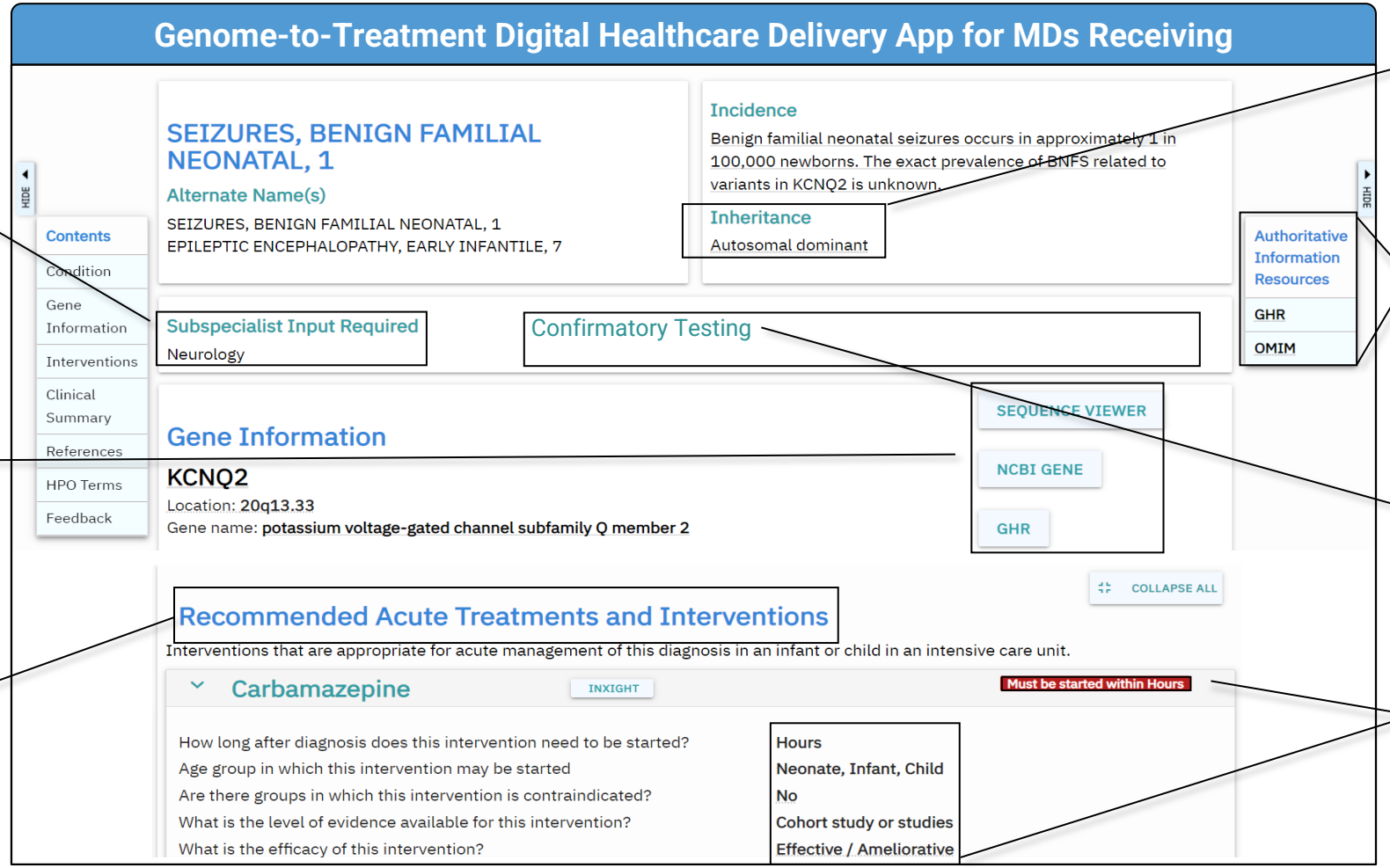
Help front-line physicians **refer screen-positive patients to local subspecialists**

Information about genetic **variants** can **be predictive of disease severity**

In future, rare disease pharma may be able to link-out to **clinical trials of investigational drugs**



Help guide front-line physicians regarding **recurrence risk and need for testing 1st degree relatives**

Direct links to clinical information enable physicians to **understand rare disease** presentation, progression, prognosis

Help guide front-line physicians regarding **confirmatory testing while awaiting subspecialist referral**

Physicians in **non-COE** settings have **COE-level resources for treatment guidance** to provide immediate management

https://gtrx.radygenomiclab.com

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Phased Consortium Activities to Make Genome Based Screening a Reimbursed Reality

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Research

	Phase 1: Completed	Phase 2: In Progress	Phase 3: Clinical test	Phase 4: Demonstrate clinical utility	Phase 5: Early commercial-ization	Phase 6: Early Standard of Care
Phase						
Scope + Goals	• Consortium announced • Prototype: 388 disorders, 29,875 variants • Retrospective study 1: Sensitivity 89%, False positive rate 2.7/1,000					
End	August 2022					
Scalab-ility	4,376 retrospective cases & 454,000 controls					

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Retrospective clinical trial of BeginNGS

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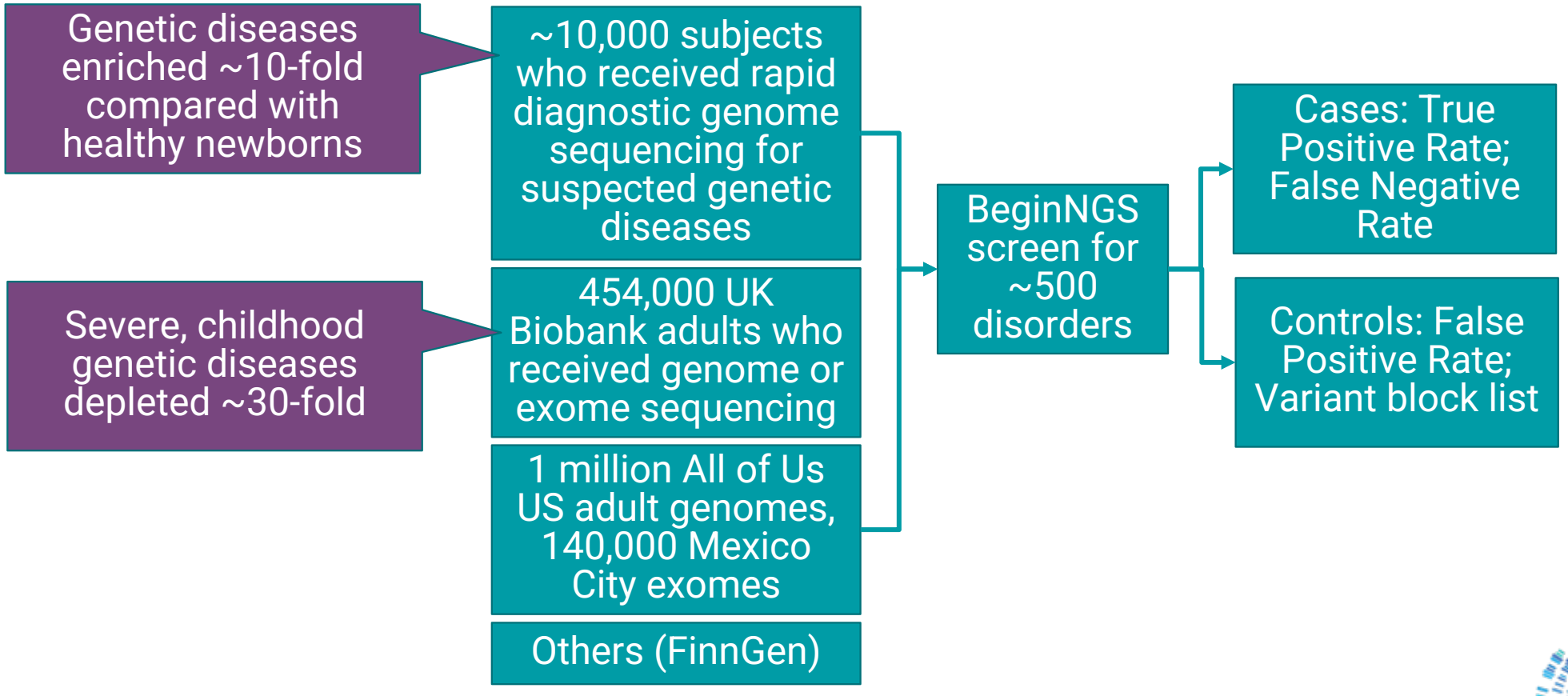
Goals

1. Train + test BeginNGS in 2 million DIVERSE cases + controls
2. Forces scaling of informatics to millions of genomes



Retrospective study 1 demonstrated excellent sensitivity and specificity

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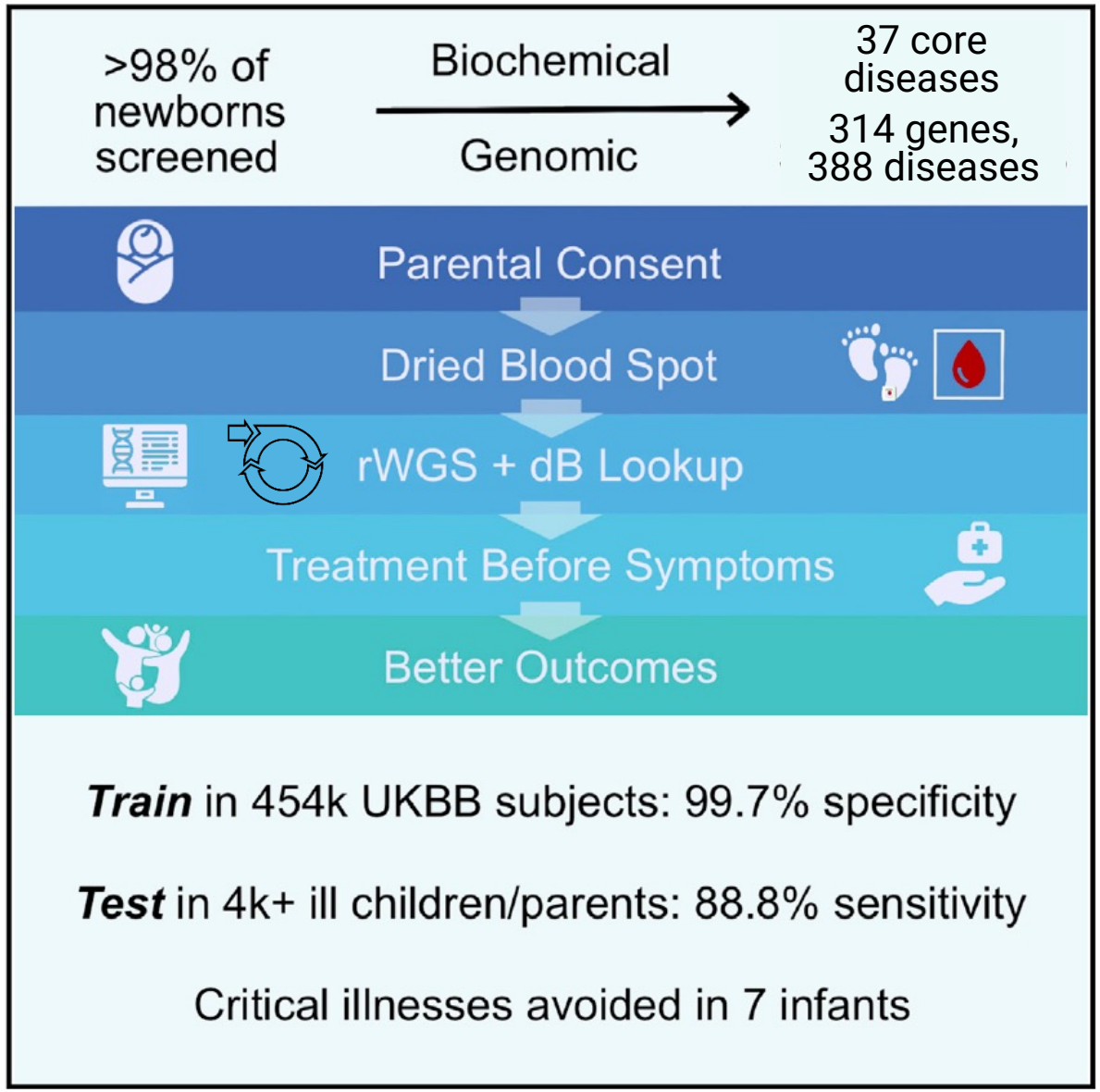
Retrospective testing of BeginNGS in 458,000 genomes
Am J Hum Genet. 2022 109:1605.



Simulated BeginNGS testing

3 false positives/1000 screens

Compared with rapid diagnostic genome sequencing

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Research

Phase	Phase 1: Completed	Phase 2: In Progress	Phase 3: Clinical test	Phase 4: Demonstrate clinical utility	Phase 5: Early commercial-ization	Phase 6: Early Standard of Care
Scope + Goals	• Consortium announced • Prototype: 388 disorders, 29,875 variants • Retrospective study 1: Sensitivity 89%, False positive rate 2.7/1,000	• 412 disorders, 40,783 variants • Sensitivity of 91% • Prospective pilot clinical trial 1				
End	August 2022	August 2023				
Scalab-ility	4,376 retrospective cases & 454,000 controls	7,575 retrospective & 50 prospective cases; 454,000 controls				

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Pilot prospective clinical trials of BeginNGS

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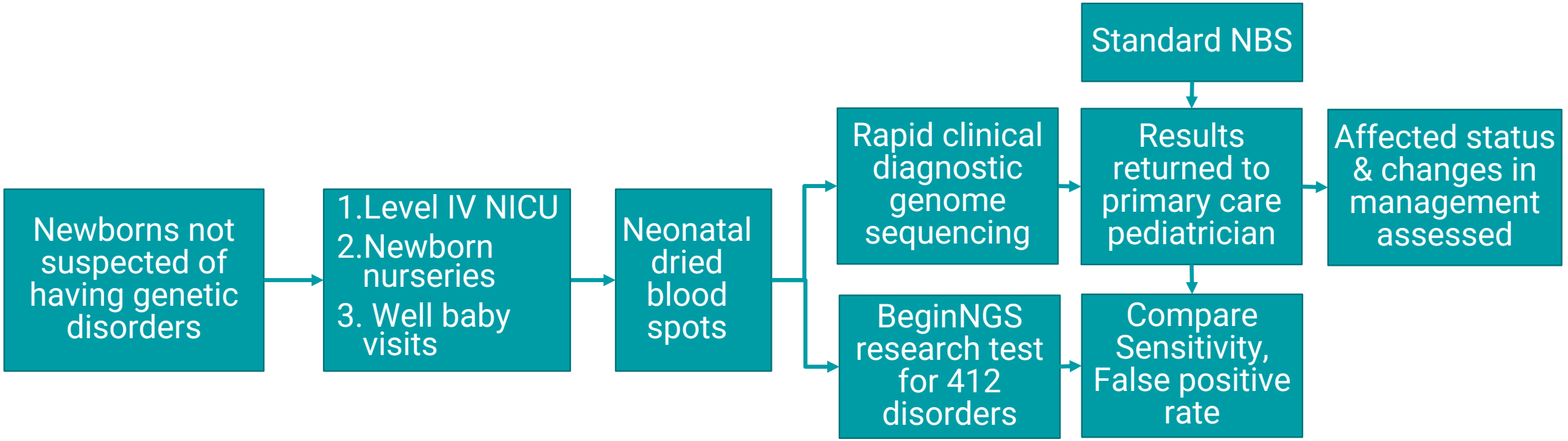
Goals:

1. Assess safety, timing, potential adverse effects of BeginNGS
2. Inform optimal design & size of clinical utility/cost effectiveness study



Status: 24 newborns enrolled; 1 NBS screen positive; 5/20 rapid diagnostic genome sequencing positives

Phased Consortium Activities to Make Genome Based Screening a Reimbursed Reality

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Research | Lock down | Clinical service

Phase	Phase 1: Completed	Phase 2: In Progress	Phase 3: Clinical test	Phase 4: Demonstrate clinical utility	Phase 5: Early commercial-ization	Phase 6: Early Standard of Care
Scope + Goals	• Consortium announced • Prototype: 388 disorders, 29,875 variants • Retrospective study 1: Sensitivity 89%, False positive rate 2.7/1,000	• 412 disorders + 40,783 variants • Sensitivity of 91% • Prospective pilot clinical trial 1	• CLIA validated BeginNGS test • ~500 disorders • 3rd retrospective study with HEOR • Prospective pilot clinical trials 2 & 3	• Automation & EHR integration • ~750 disorders • 4th retrospective study • Large, adaptive clinical utility/cost effectiveness trial	• Start reimbursed BeginNGS services • Scale to 100k newborns • ?1000 disorders	• Sustainable, population screening that is comprehensive, well accepted and improving outcomes
End	August 2022	August 2023	Mid 2024	Late 2025	End 2026	2027+
Scalab-ility	4,376 retrospective cases & 454,000 controls	7,575 retrospective & 50 prospective cases; 454,000 controls	~10,000 retrospective & 600 prospective cases; ~1 million controls	~20,000 newborns, 2 million controls	100,000 newborns	1 million newborns

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Comparison of specification of BeginNGS with other diagnostic + screening tests for genetic diseases

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	Microarray + Karyotype	Gene Panel Test	Diagnostic Rapid Genome Sequencing	BeginNGS	California Newborn Screening of DBS
Population tested	Children in ICUs with suspected genetic diseases			Primary Use: All newborns Multiple secondary uses	
Genetic disorders evaluated	~1,000	~2,000	~7,000	~750	80
Cost per newborn	$1,887	$4,500	$7,000	$500	$211
Average diagnostic rate	14%	28%	38%	5%	0.18%
Average cost per newborn diagnosis	$13,978	$16,071	$18,421	$10,000	$118,688
Median net savings per newborn tested	n.d.	n.d.	$14,265	?	n.d.

Meet Fitz: NBS + Diagnostic Genome Sequencing + Gene Therapy Success Story

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- Appeared healthy at birth
- Screen positive for Severe Combined Immunodeficiency (SCID)
- Rapid diagnostic genome sequencing identified Athabascan (Artemis) SCID in 1st week of life
- Precise diagnosis allowed Fitz to qualify for an *ex-vivo* gene therapy clinical trial during infancy
- Lentivirus/*DELRE1C* phase 1 transduction of autologous $CD34^+$ cells successful
- Read his story in USA Today here: Baby Fitz was born without an immune system. His treatment offers hope for curing rare diseases. (yahoo.com)

USA TODAY

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Summary

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1. BeginNGS is a a **digital healthcare delivery system for genetic disease families + their healthcare providers** that **starts at birth + extends across the lifespan**
2. Screening goal: 750 diseases, $500 per screen
3. BeginNGS is being undertaken by an international consortium
4. Phase 1 studies indicated false positive rate of 3/1,000 and sensitivity of 91% for 388 diseases
5. Phase 2 retrospective and prospective studies underway x 410 diseases
6. Like rapid diagnostic genome sequencing, this is a 10-year journey
    - De-risk and amortize effort by collaboration with genomic NBS efforts world-wide

Acknowledgements

Thank you to 150 people at Rady Children's Institute, Alexion, illumina, Fabric, TileDB, Genomenon, Plumcare, and Rady Children's Hospital who are undertaking this.

Thank you sponsors - Ernest and Evelyn Rady, the Marriott Foundation, the Conrad Prebys Foundation, NICHD, NCATS, NHGRI, our philanthropic donors, and sponsoring pharmaceutical companies.

A Deo lumen, ab amicis auxilium