Newborn Screening by Genome Sequencing: Needs, challenges, solutions, and opportunities

Session 2: Discussing Challenges and Opportunities for Building Newborn Screening Research Infrastructure

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Need: Current approach to diagnosis & management of rare disease is inefficient, ineffective, & inequitable

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Burden of Rare Genetic Disease

On average, reaching a diagnosis takes

1 in 20

children have a rare genetic disease

4.8 Years

AND

7.3

Specialists

and some people are never diagnosed

>$1 T

annual US healthcare burden of rare disease with average PPPY cost of $9k–140k

~$1T annual cost of 379 rare diseases (direct and indirect costs, non-medical costs, and healthcare costs not covered by insurance). 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; NIH; ClearView Analysis.

Opportunity: We are at an inflection point in genome-informed pediatric care

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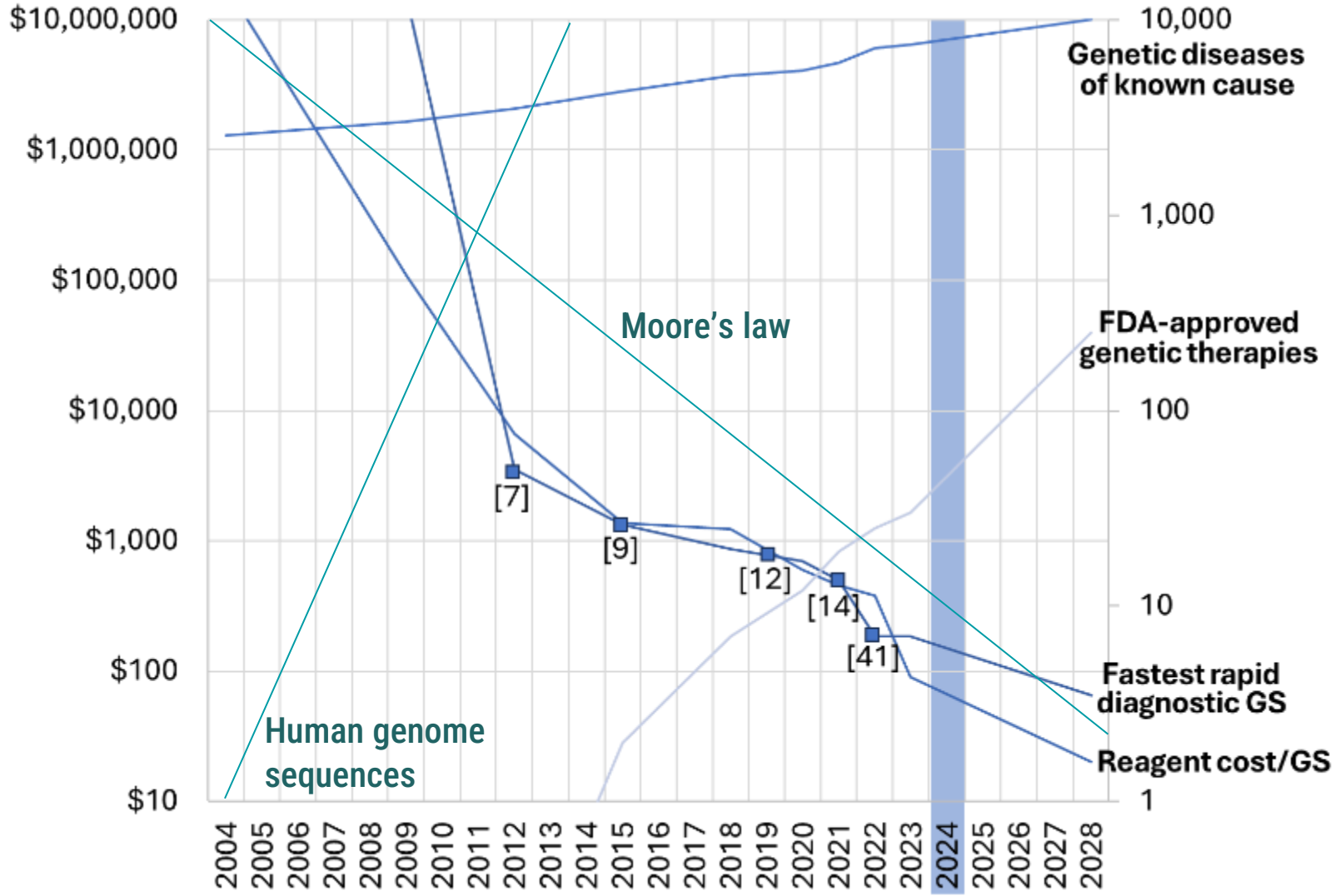

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Need: 61 years of Newborn Screening

36 disorders on RUSP panel

12,500 US infants benefit per year

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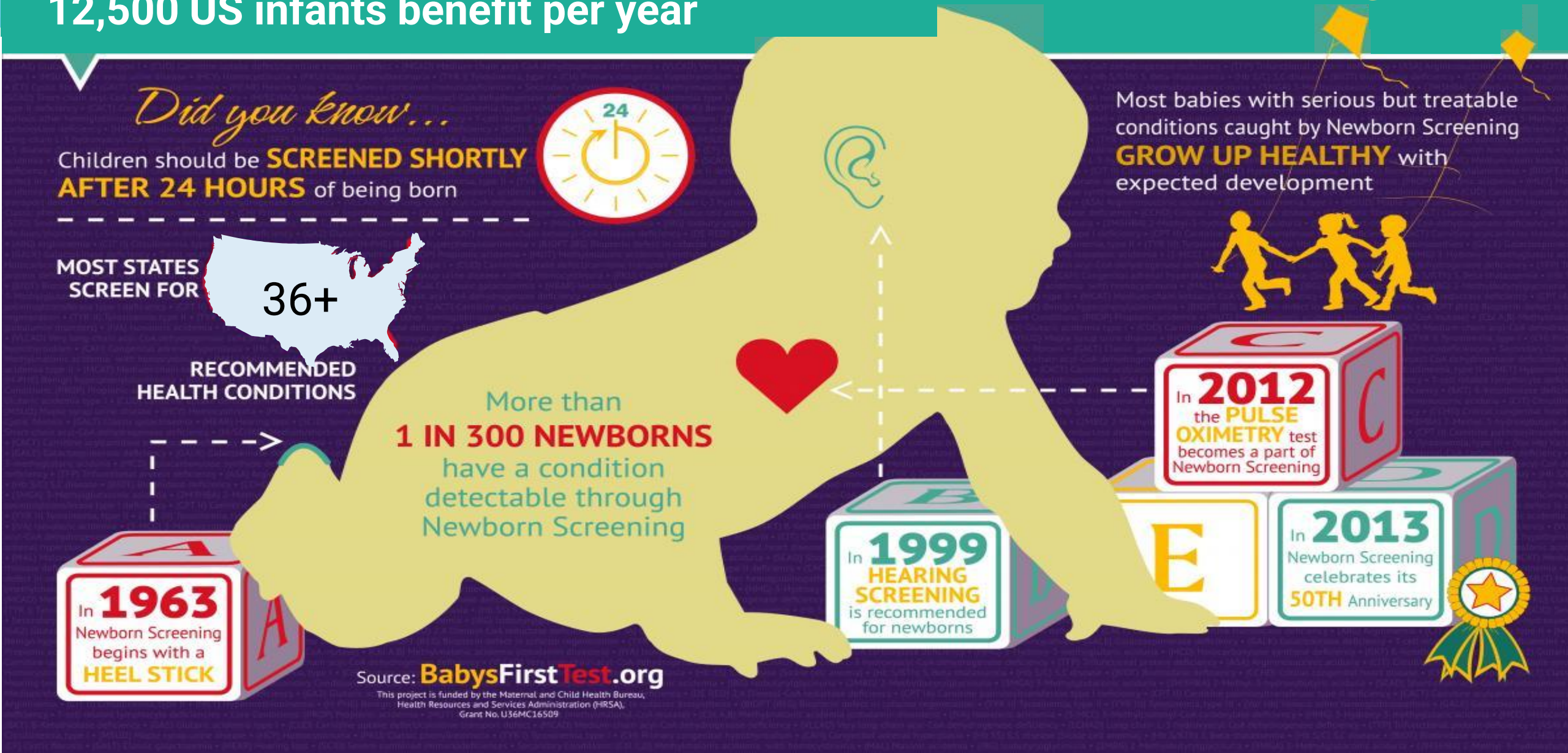

Source: BabysFirstTest.org

This project is funded by the Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA), Grant No. U36MC16509

Opportunity: 66 years of Newborn Screening

1000+ disorder panel

75,000 US infants benefit per year

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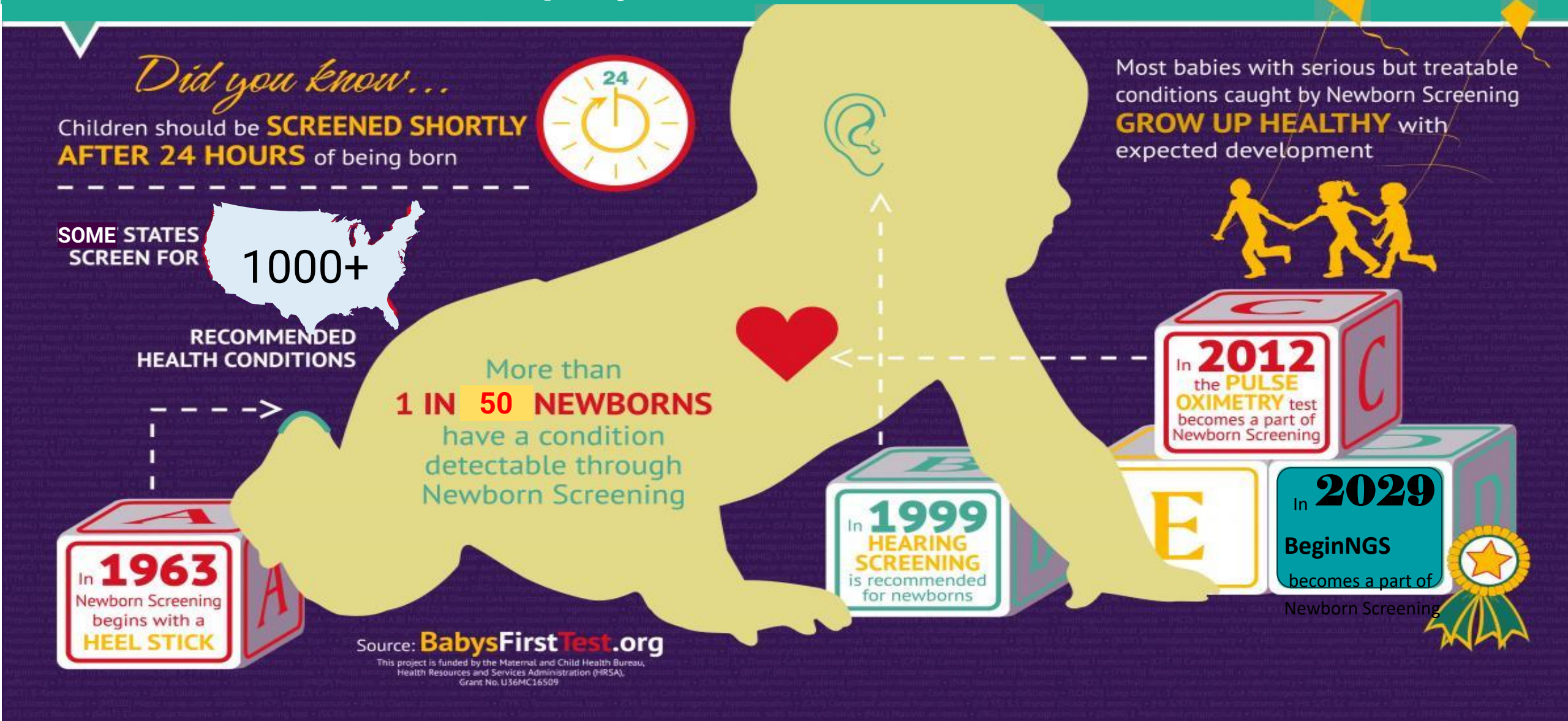
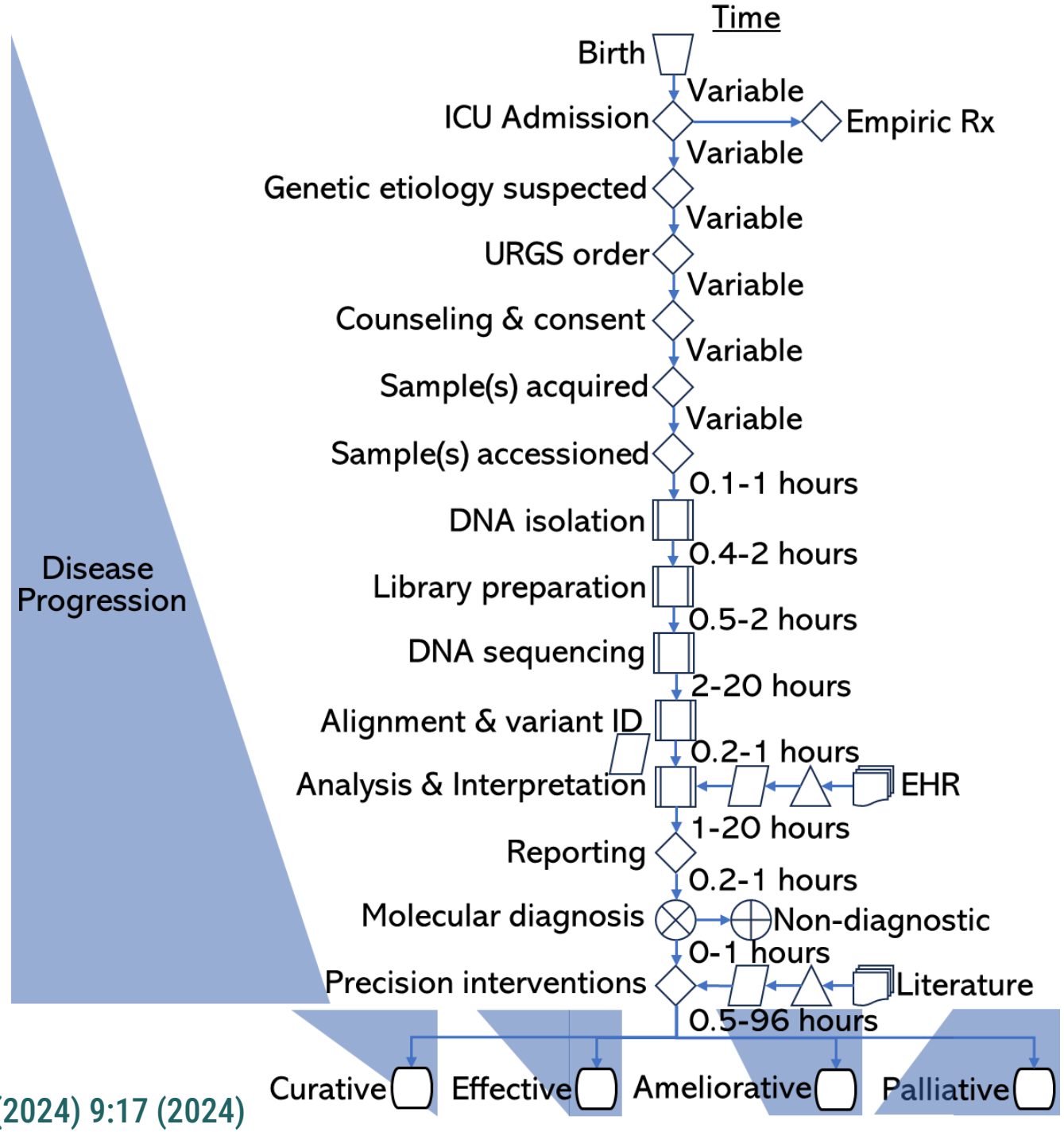


Opportunity: Rapid Diagnostic Genome Sequencing

- Manual operation
- Decision
- Predefined process
- Data
- Extract
- Multidocument
- Summing junction

Or

Terminator



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Opportunity: Learn from Rapid Diagnostic Genome Sequencing for NBS by Genome Sequencing

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Feature	Rapid Diagnostic Genome Sequencing	BeginNGS AI and GS-based NBS
Core technologies	Genome sequencing, artificial intelligence, electronic clinical decision support	
Primary objective	Phenotype-informed molecular diagnosis	Presymptomatic identification, prevention or treatment
Intended indicated use	Hospitalized, acutely ill children with diseases of unknown etiology	All (mainly healthy) infants
Diseases examined	Any childhood genetic disease	Preventable or effectively treatable, severe childhood genetic diseases
Variants reported	P, LP, VUS-S (VUS with disease-subject phenotype concordance)	Prequalified set of P, LP, Conflicting (but with P or LP assertions) variants
Incidental findings	Yes, childhood diseases	None
Pre-test probability of +ve	50%, including VUS	<5%
Upper limit of COGS	$3000 per subject	$300 per subject
Desired recall	100%	>90%
Positive Predictive Value	~80%	>50%
Time to result	1-2 days	2 weeks
Physician receiving results	Primarily neonatologist, intensivist	Primarily primary care pediatrician
Intended scope	Diagnosis, precision medicine guidance, physician education	Screening, confirmatory testing, referral, precision medicine guidance, physician and parent education

Challenges: Ultra-rare disease; Penetrance; Expressivity; Under-representation of non-EUR genomes

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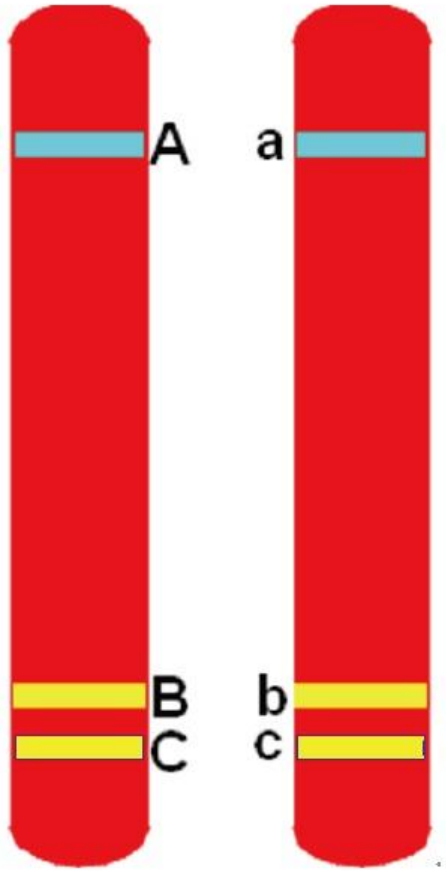
Ultra-rare disease: Prevalence <1 in 50,000

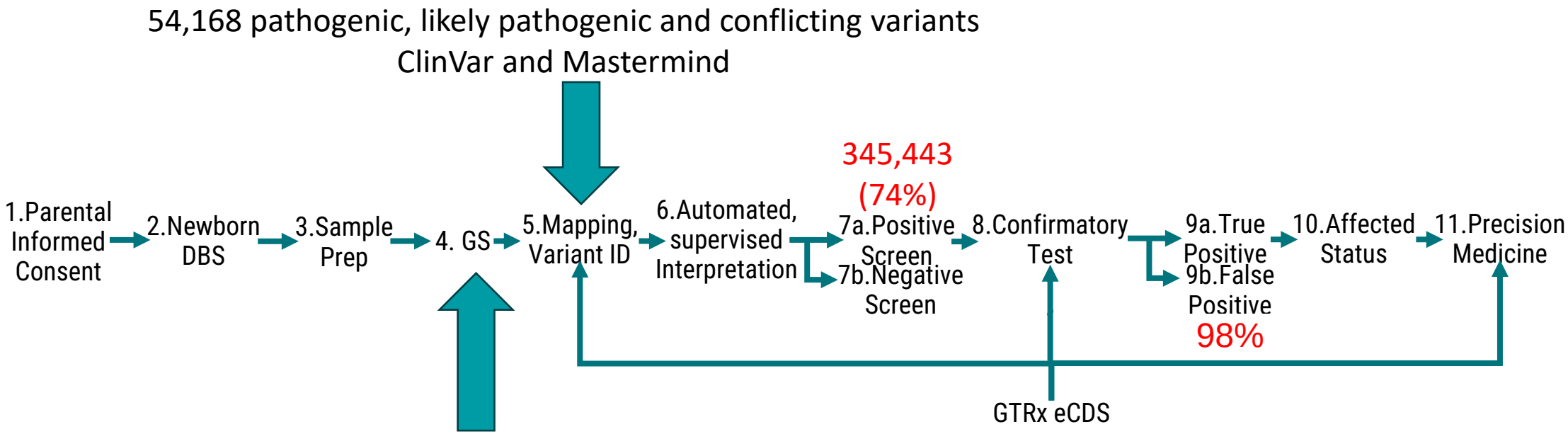
Penetrance: Proportion of children with a pathogenic diplotype that is consistent with the pattern of inheritance who are affected by the disease associated with that gene e.g. 8 genes associated with atypical hemolytic uremic syndrome have childhood penetrance of ~5%

Expressivity: Proportion of children with a pathogenic diplotype that is consistent with the pattern of inheritance who are fully affected by the disease associated with that gene e.g. severe mucopolysaccharidosis II has expressivity of ~7%



Alleles: A, B, C, a, b and c
Genotypes: A/a; B/b and C/c
Haplotypes: ABC and abc
Diplotype: ABC/abc

Retrospective Study: BeginNGS x 470,000 UK adults



469,902 participants
aged 40–69 years
86% white British, 10.1% other European, 1.3% African, East Asian 1.1%

Solution: 1.9% positive rate following federated training in large cohorts

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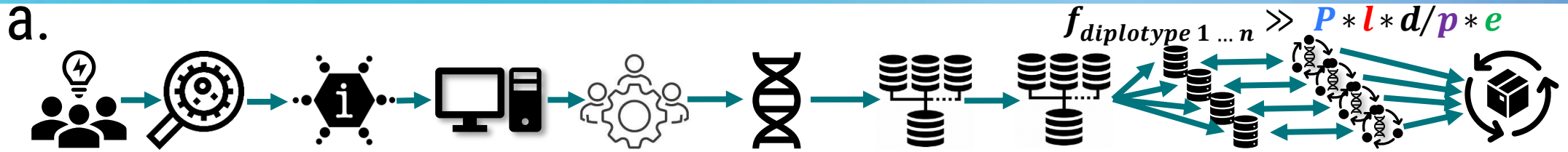
a.



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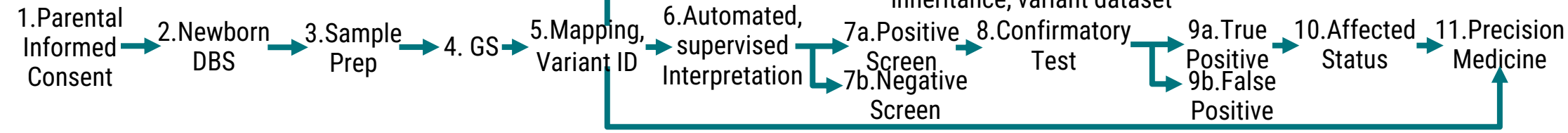

Gene	Inh	Adult UK Disorder Prevalence	Observed UKB470K Genetic Prevalence	Estimated Adult Penetrance	Estimated Adult Expressivity	OMIM Disorders Assoc. With Gene	Genes Assoc. With OMIM Disorder	Est. Locus Hetero-geneity	Corrected Adult UK Genetic Prevalence ($P_{corrected}$)	UKB470K Positive Diplotypes	Diplotype Hetero-geneity	Corrected UK Diplotype frequency ($f_{corrected}$)	BeginNGS .2 Variants Assoc. with Gene	Corrected UKB470K Positive Diplotypes	Corrected UKB470K Genetic Prevalence
		P	O	p	e	x		l	$P*l/p*e$	n	d	$P_{corrected}*d$			$O_{corrected}$
HNF1A	AD	6,400	52,905	0.7	0.7	3	396	0.01	131	46	0.2	26	259	43	69
CYP21A2	AR	10	37,320	0.5	0.5	2	1	1	40	46	0.25	10	101	28	54
CFTR	AR	20	2,349	0.7	0.7	1	4	0.95	39	160	0.6	23	1261	74	56
GALT	AR	4	1,043	0.6	0.6	1	4	0.9	10	34	0.25	3	250	6	1
FGG	AD	15	955	0.5	0.5	2	3	0.33	20	9	0.2	4	21	7	6

Summary

- Newborn screening by genome sequencing has the potential to improve outcomes for ~1,000 severe, single locus disorders with early childhood onset and effective treatments by early identification and intervention.
- Fully automated interpretation is possible by prequalification of diseases, genes, inheritance modes, variants, and therapeutic interventions
- Federated training in large, diverse cohorts decreased the positive rate in UK adults from 73% to 1.9%.
- Phase 3 of development includes expansion to all treatable and preventable rare diseases of early childhood, federated training, and a large adaptive clinical trial

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Dedicated to the memory of Gunter Scharer. *A Deo lumen, ab amicis auxilium*