

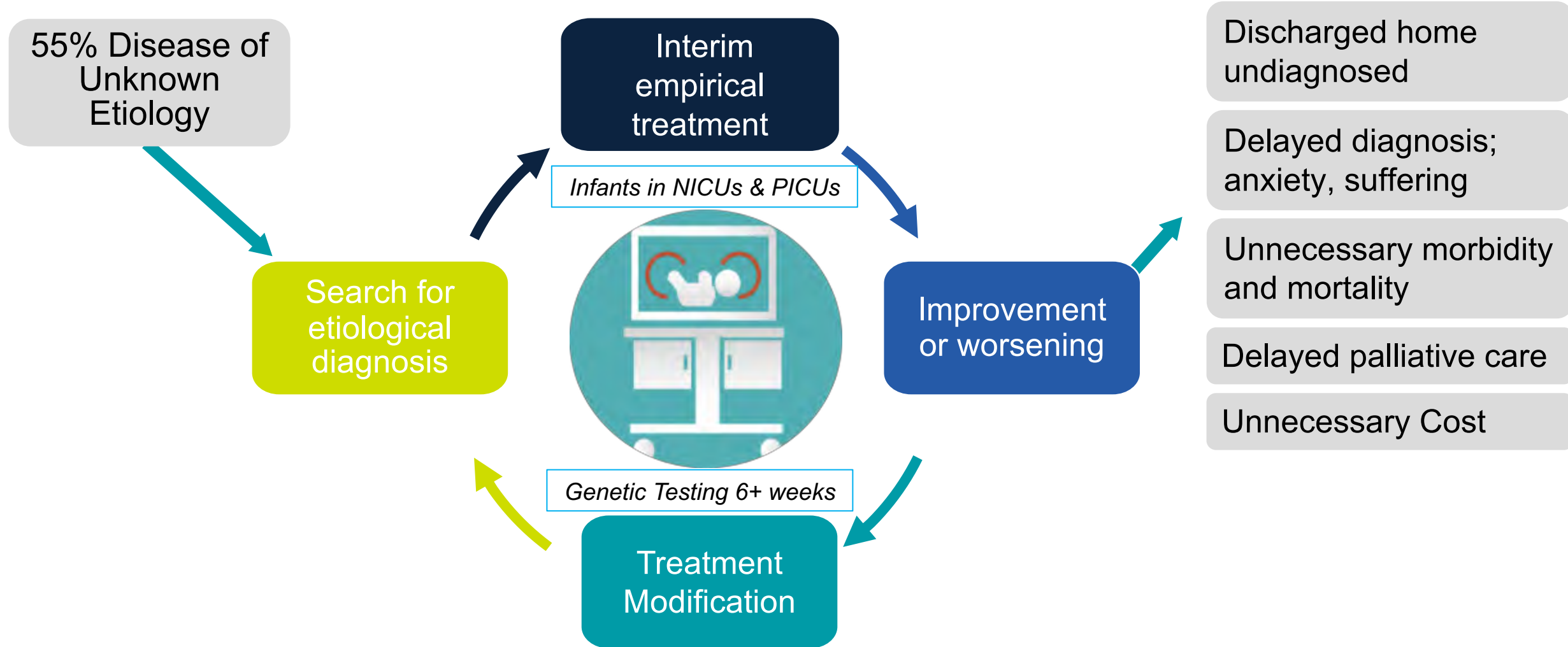
# *Genome- & AI-Informed Individualized Care of infants in ICUs*

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Stephen Kingsmore, MD DSc

**I do not have a conflict of interest with regard to this presentation**



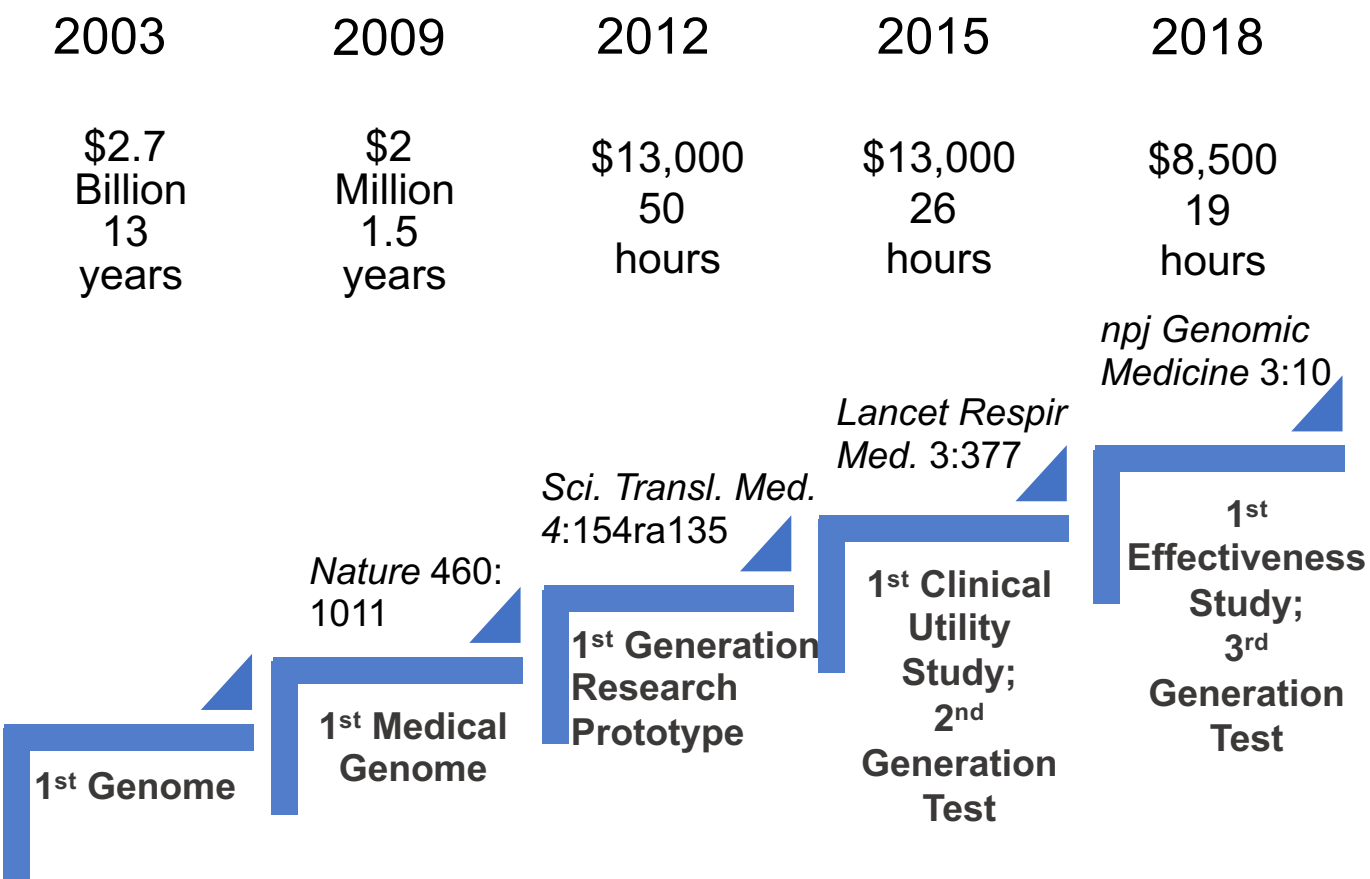


- 15% of 250,000 US NICU and PICU infants have 1 of 14,000 genetic diseases
- 60% go undiagnosed and ∴ are mistreated; leading cause of death



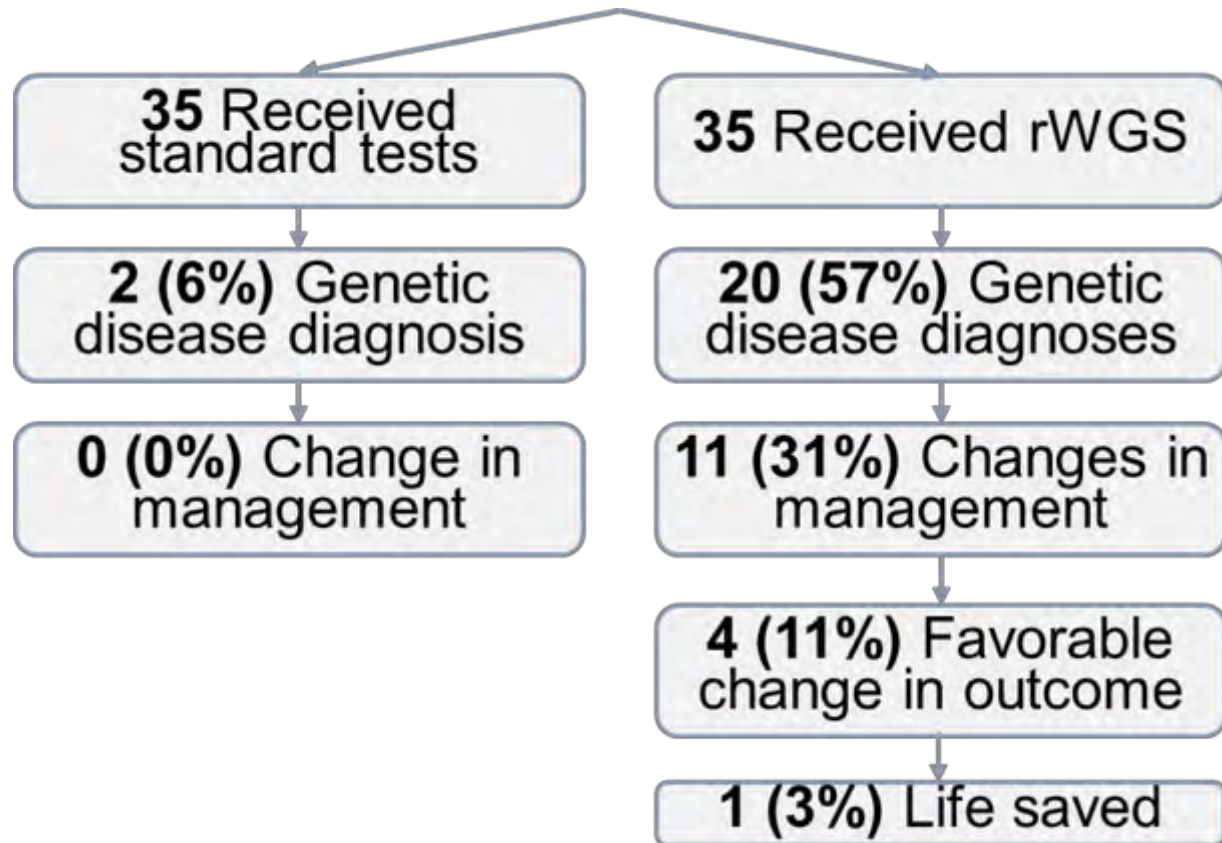


# Evolution of Individualized Medicine in Children's ICUs

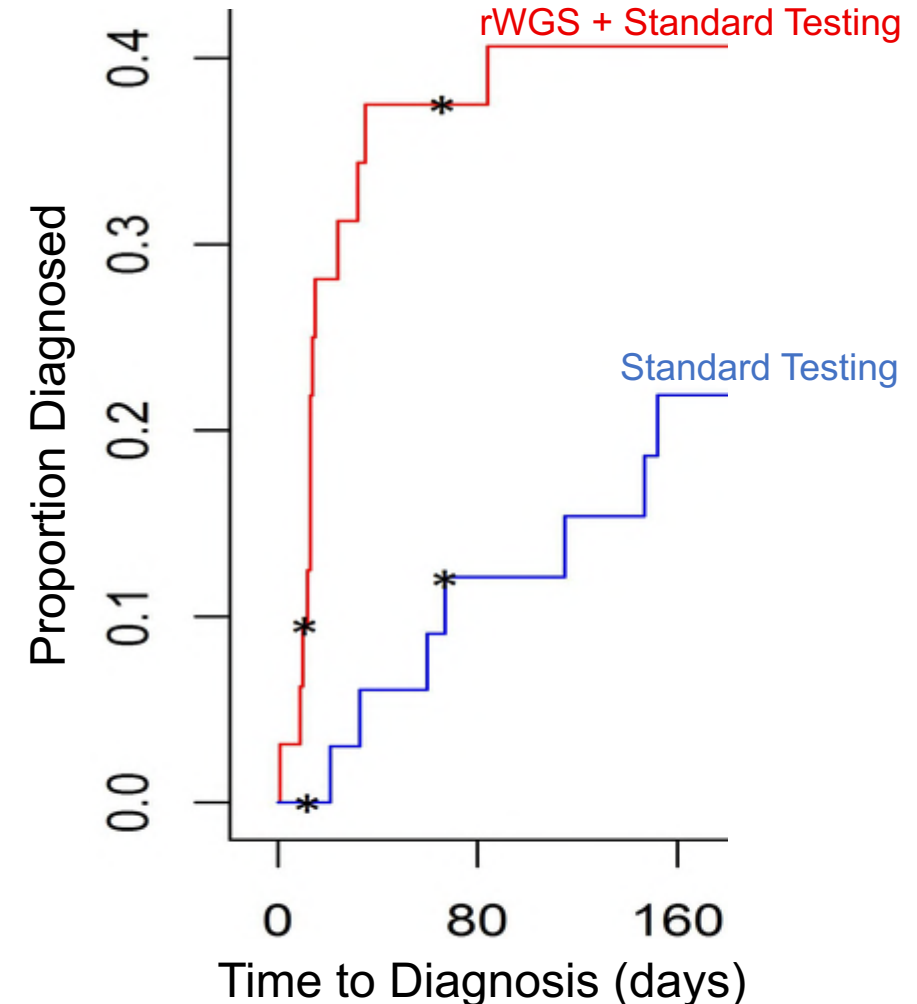




# Two Early Studies of Clinical Utility of rWGS-based Individualized Medicine



(before individualized medicine mentoring)



# Two Recent Studies of Effectiveness of rWGS-based Individualized Medicine

48 Eligible: Inpatient, <1 year of age, no etiologic diagnosis, possible genetic disease

42 Consented, received standard of care and rWGS

4 (10%) Genetic disease diagnosis by standard test

18 (43%) Genetic disease diagnoses by rWGS

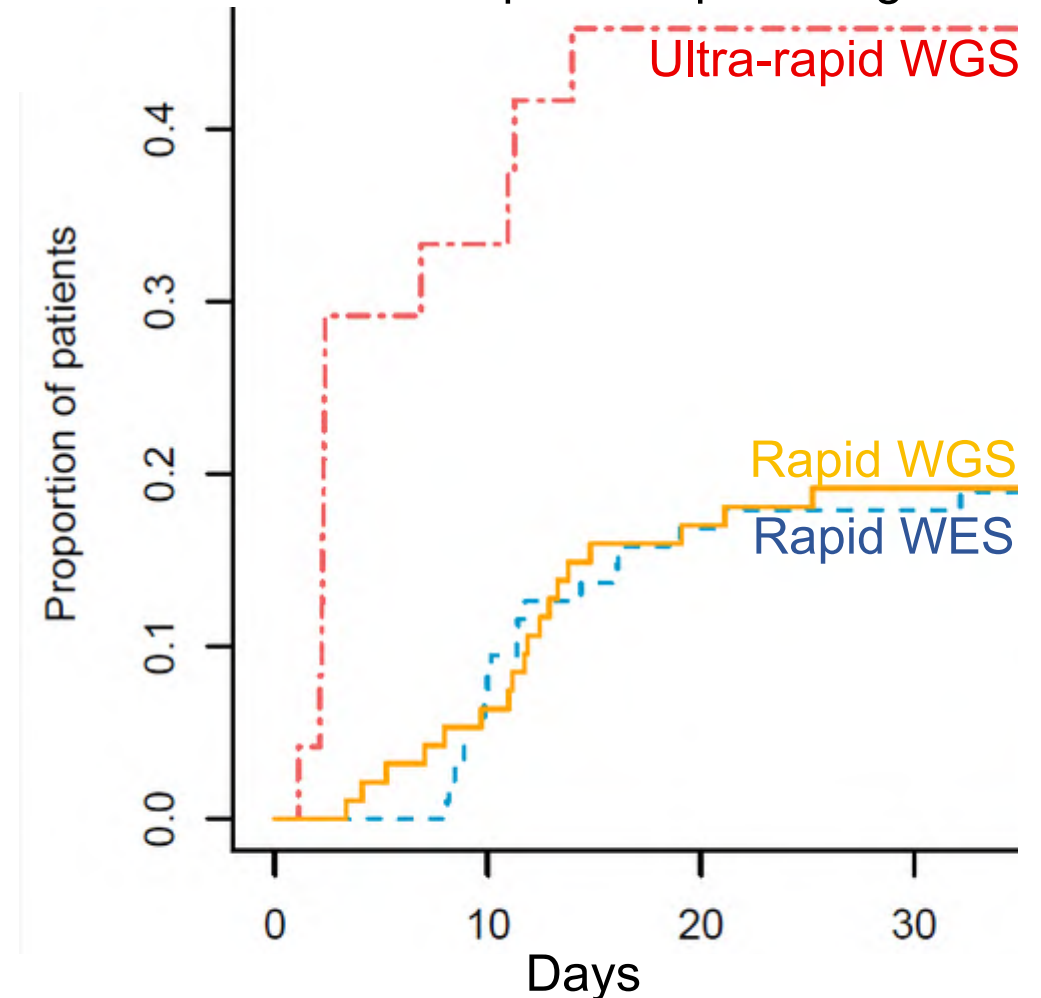
1 (2%) Change in management

13 (31%) Changes in management

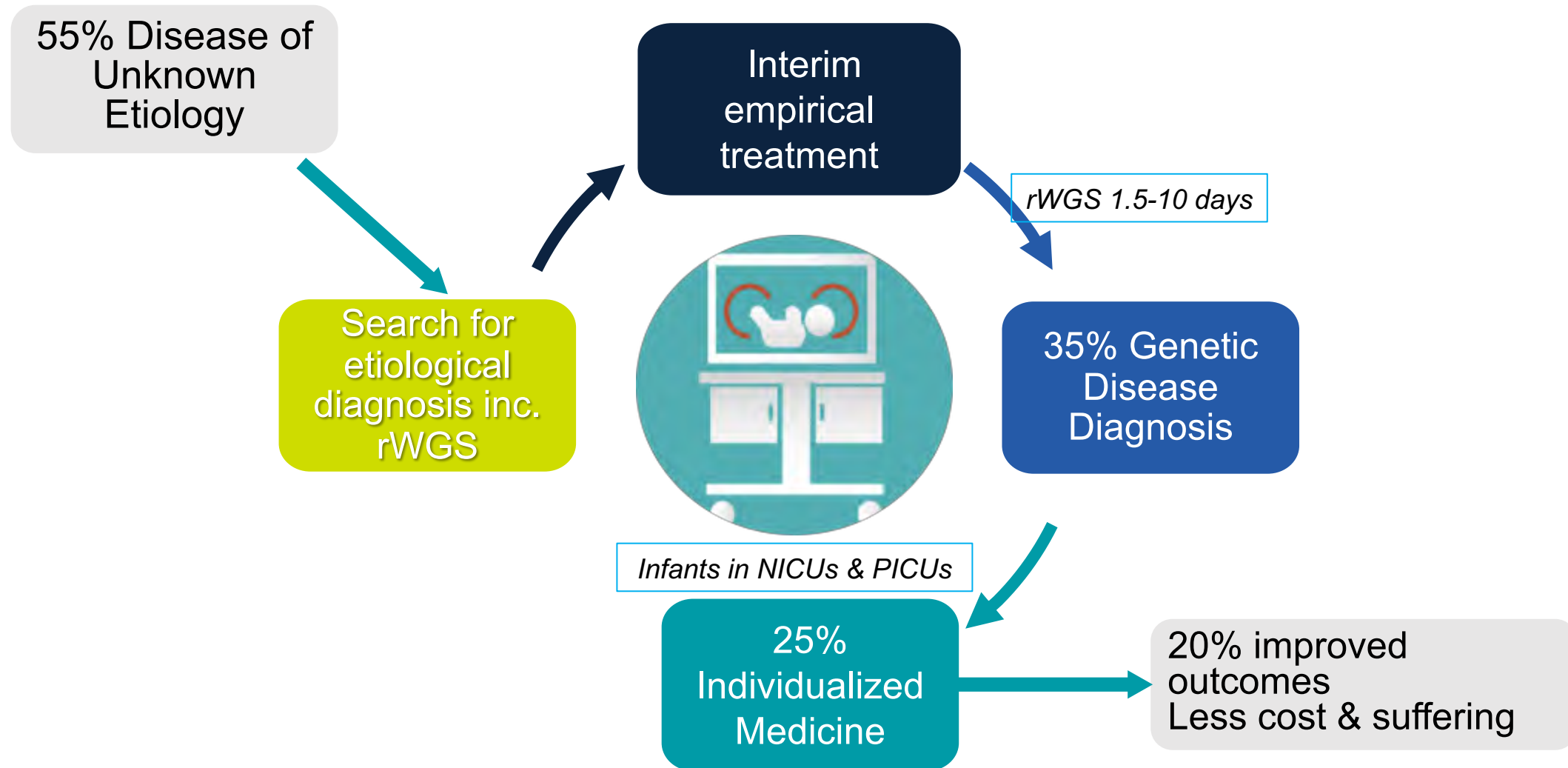
0 (0%) Change in outcome

11 (26%) Changes in outcome

Time from blood sample receipt to diagnosis

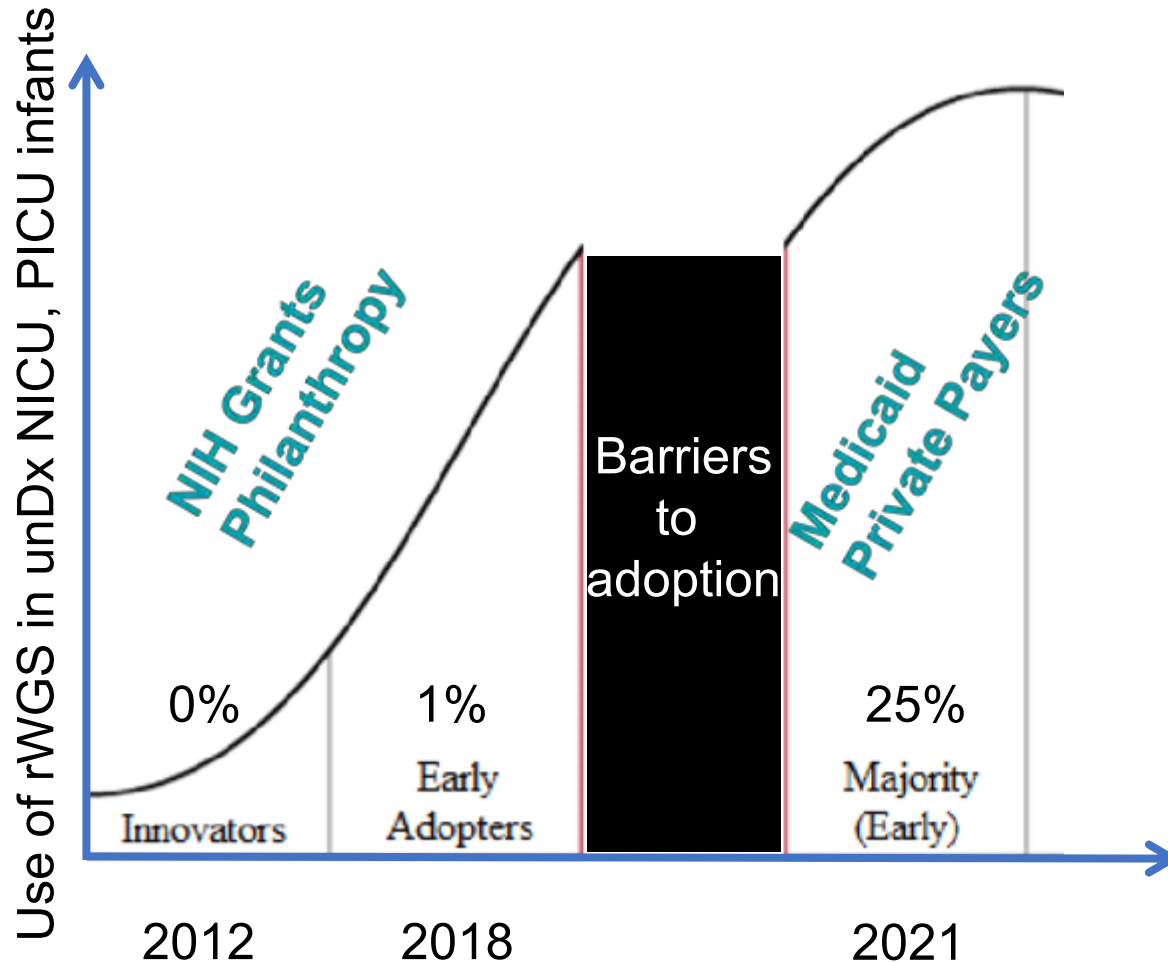


# 2019 status of rWGS-based individualized medicine for NICU and PICU Infants



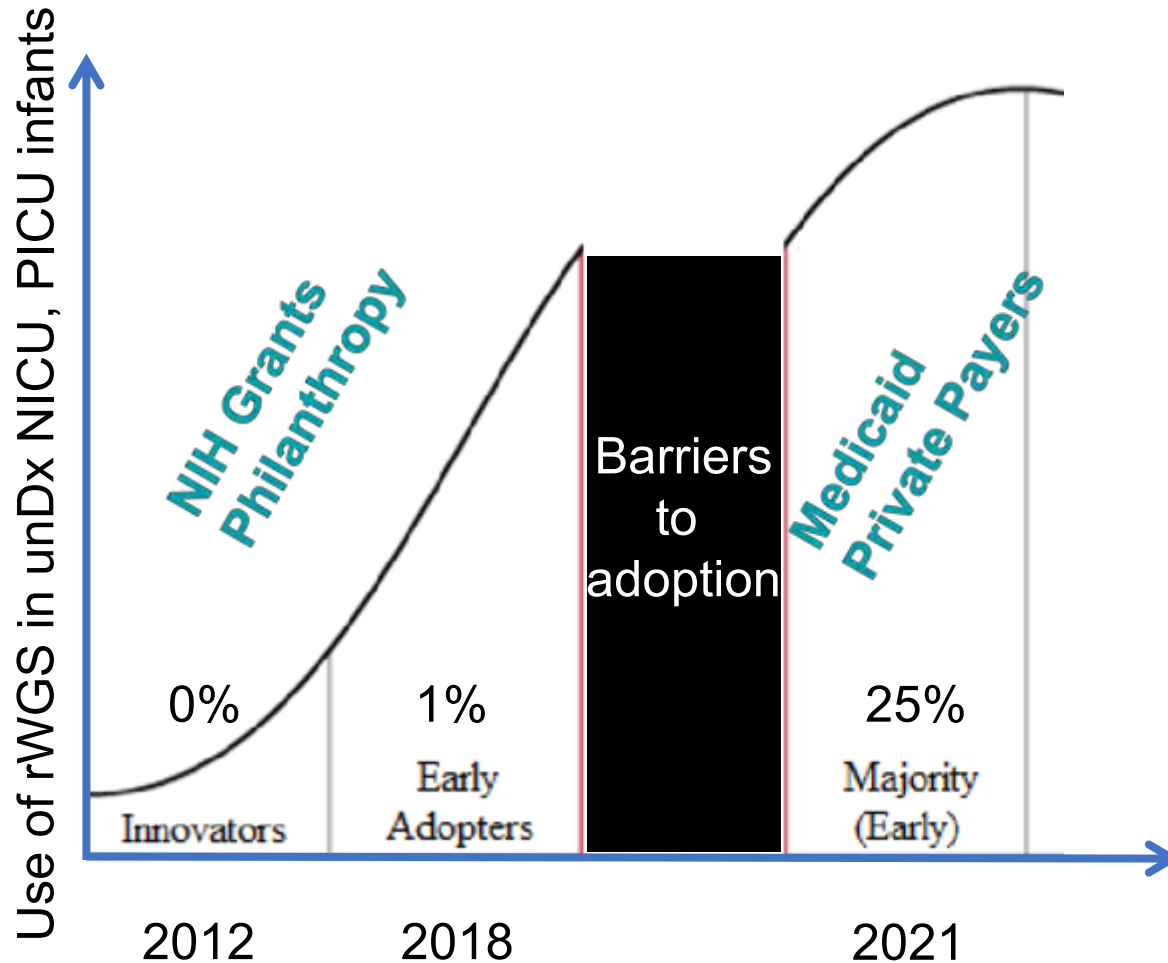


# Barriers to Adoption of rWGS-based individualized medicine for NICU and PICU infants



- Capital & labor intensity of individualized medicine
  - rWGS and rWES methods are too slow to guide NICU and PICU management
  - rWGS and rWES methods not scalable
  - Shortage of expert medical geneticists, laboratory directors, genetic counselors
- Lack of clinician familiarity with individualized medicine
  - Shortage of expert medical geneticists, genetic counselors
- Insufficient evidence of efficacy
  - Absence of reimbursement
- Many genetic diseases lack effective Rx
  - Most treatments lack adequate evidence

# Barriers to Adoption of rWGS-based individualized medicine for NICU and PICU infants



- ~~Capital & labor intensity of individualized medicine~~
  - ~~rWGS and rWES methods are too slow to guide NICU and PICU management~~
  - ~~rWGS and rWES methods not scalable~~
  - ~~Shortage of expert medical geneticists, laboratory directors, genetic counselors~~
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# 3<sup>rd</sup> generation whole genome sequencing with automated genetic disease diagnosis



Median time to result 20 hours; In Press

**17 month old boy with fever ( $T_{\max}$  103°F) x 3 days, vomiting, diarrhea, abdominal pain, labored breathing, skin lesions x 1 day**





# Rady Emergency Department Work Up


- Blood tests:
    - Metabolic panel: metabolic acidosis
    - C-reactive protein: markedly elevated
    - Complete blood count: low white cell count
  - Abdominal ultrasound & computed tomography: No intussusception, possible mild colitis
  - Lumbar puncture
    - Cardiovascular decompensation = hypovolemic shock → intravenous fluids
    - $\text{SiO}_2$  88% on  $\text{FiO}_2$  21% → Continuous Positive Airway Pressure ventilation
    - Sepsis suspected → intravenous vancomycin + ceftriaxone
    - Admitted to PICU → switched to intravenous meropenem
-

# Hospital Day 2

- Blood culture: *Pseudomonas aeruginosa*
- Skin rash diagnosed as *ecthyma gangrenosum*
- Rapid genome sequencing ordered



# Step 1: Order in Epic Electronic Health Record

LAB000796RCIGM Rapid Whole Genome Test - Proband

Counseling Provided and Consent Obtained?

Yes

No

Select Test Type

Proband

Trio

Other

Opt Out of Additional Use?

No

Yes

Include Incidental Findings?

Yes

No


Briefly Provide Clinical Description

Pseudomonal sepsis, leukopenia

Are Family Member Samples Expected?

Yes

No


 Name and DOB of Expected Family Member Sample

Mother

Father

Sibling

Other

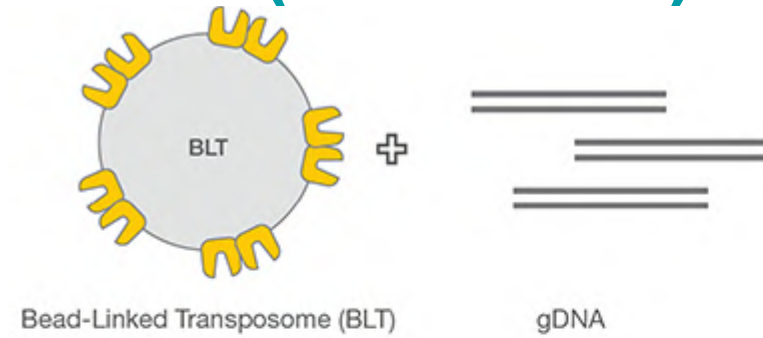
 Ultra-Rapid Processing?

No

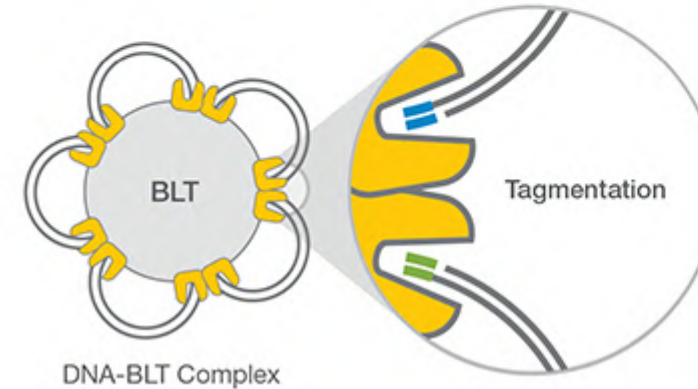
Yes

## Step 2: Genome library preparation (2.5 hours)

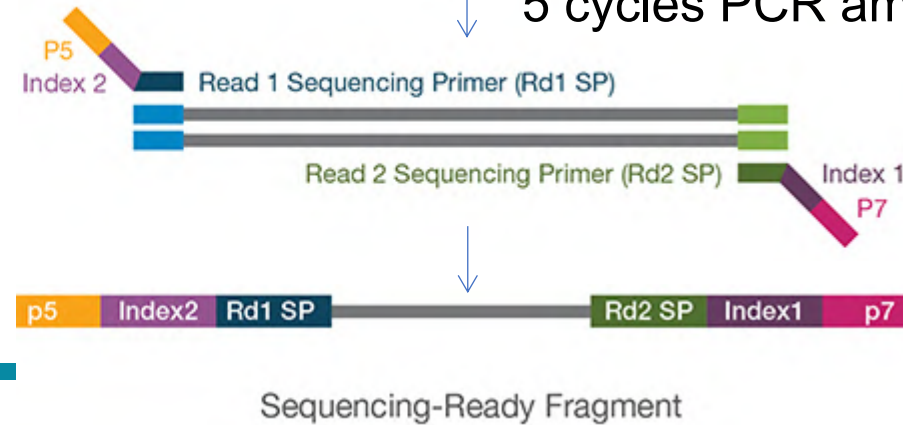
- 0.5 ml blood, dried blood spot
- Illumina Nextera Flex



Fragmentation



5 cycles PCR amplification





## Step 3: Genome Sequencing (15.5 hours)

- 2 x 100 nucleotide paired sequences
- Illumina NovaSeq 6000 instrument
- S1 flowcell
- Trio or 2 Probands per flowcell
- 40X proband; 30X parents

### RADY CHILDREN'S INSTITUTE SETS DNA SEQUENCE WORLD RECORD

Step toward faster diagnoses of puzzling, threatening illness

BY PAUL SISSON

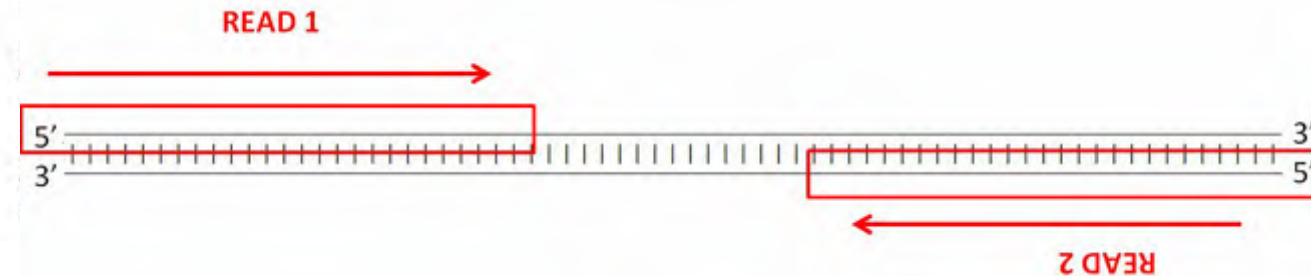
It took 13 years to build the first full set of genetic blueprints for the human race by sequencing the DNA inside our cells that governs everything from eye color to risk of debilitating disease.

But a team at Rady Children's Institute for Genomic Medicine, working closely with homegrown sequencing sensation Illumina Inc., just proved it's possible to get the job done



EDUARDO CONTRERAS U-T

Clinical laboratory scientist Sarah White pulls a flow cell from a new genetic sequencer at Rady Children's Institute for Genomic Medicine.



## Step 4: Identify all disease-causing variants in child's genome: 45 min

125 billion nucleotides sequenced

2.8 billion genomic nucleotides  
assigned

4.9 million variants  
identified & genotyped

*Glossary: Nucleotide – a single DNA letter (base); Adenine, Cytosine, Guanine or Thymidine*

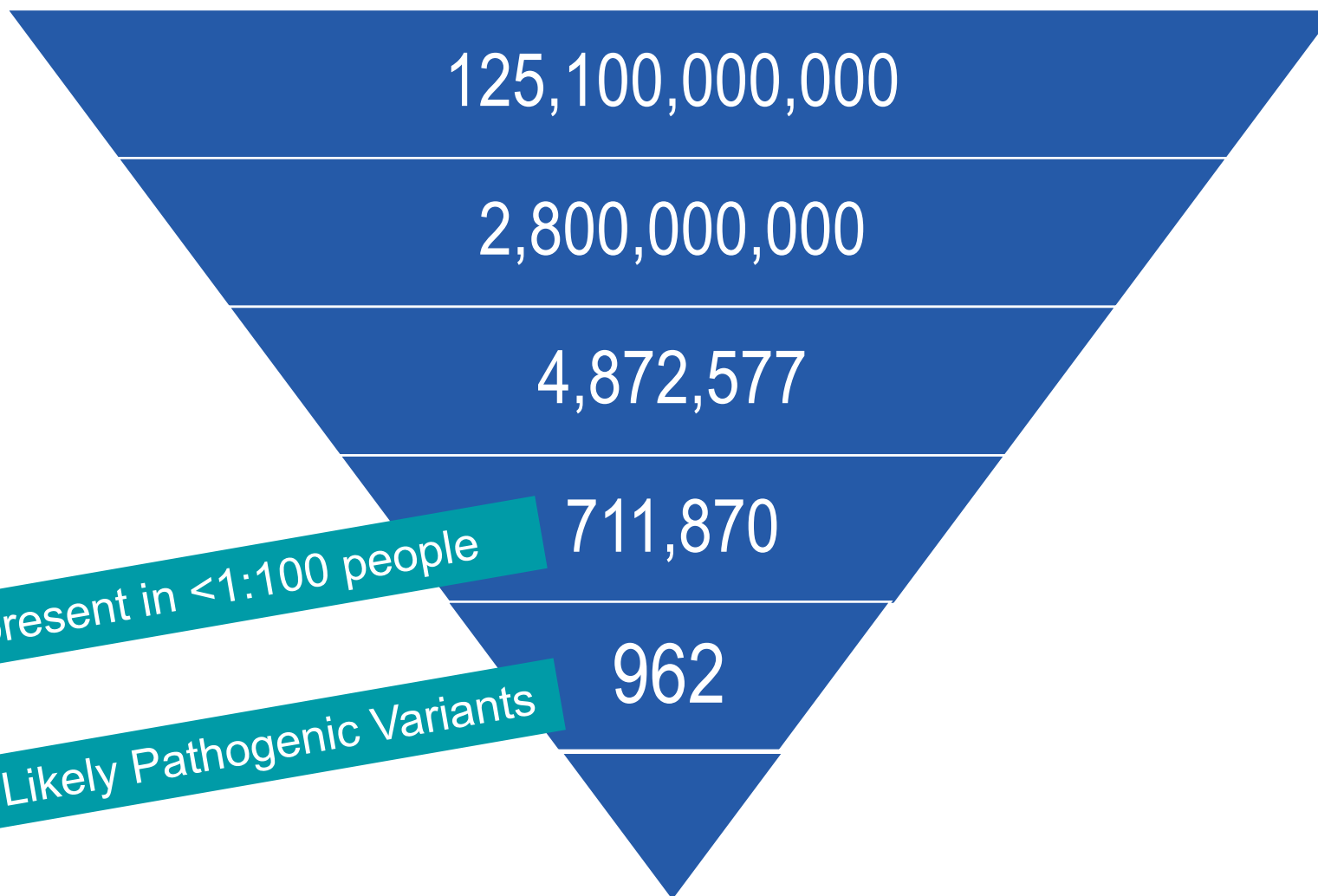
*Variant – a DNA change from the (normal) reference genome sequence*

## Step 5: Variant pathogenicity scoring

Variant Category	Criteria
Pathogenic (P): 99% disease causing	1 VS + (1S or 2M/Sup) 2S 1S + (3M or 2M+2Supp)
Likely Pathogenic (LP): 90% disease causing	1 VS/S + 1 M 1 S + (1 M or 2 Supp) 3 M 2 M + 2 Supp 1 M + 4 Supp
Variant of Uncertain Significance (VUS): 10% disease causing	

<b>Very Strong (VS)</b>	Null variant (nonsense, frameshift, $\pm 1$ or 2 splice site position, initiation codon, exon deletion) in gene where LOF known to cause disease
<b>Strong (S)</b>	<ul style="list-style-type: none"> <li>Same amino acid change as previously established pathogenic variant</li> <li>De novo in a patient with the disease and no family history</li> <li>Functional studies show damaging effect on the gene</li> <li>Prevalence in affected individuals significantly greater than controls</li> </ul>
<b>Moderate (M)</b>	<ul style="list-style-type: none"> <li>Located in mutational hot spot/functional domain without benign variation</li> <li>Extremely low frequency in Gnomad</li> <li>Recessive disorders, detected in trans with a pathogenic variant</li> <li>Protein length changed by in-frame indel in nonrepeat region or stop-loss</li> <li>Novel missense at amino acid where different missense known to be pathogenic</li> <li>Assumed de novo, but without confirmation of paternity and maternity</li> </ul>
<b>Supporting (Supp)</b>	<ul style="list-style-type: none"> <li>Cosegregation with disease in multiple affected family members in gene known to cause disease</li> <li>Missense variant in gene with low rate of benign missense variants and where missense variants commonly cause disease</li> <li>Multiple computational tools call deleterious</li> <li>Phenotype highly specific for disease with single genetic etiology</li> <li>Reputable source reports as pathogenic, but unpublished</li> </ul>

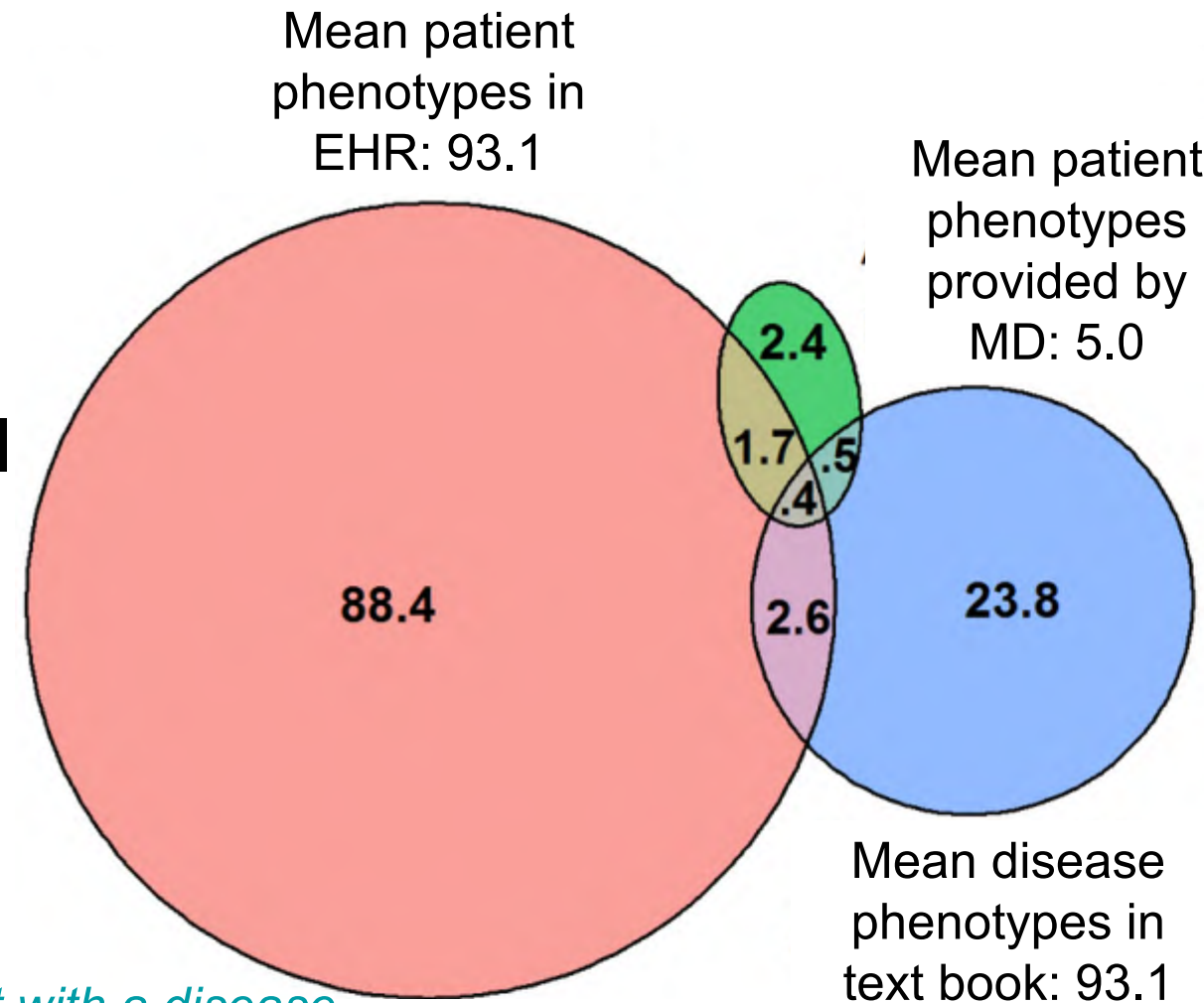
## Step 5: Variant Pathogenicity Scoring: 2 mins





# Why collect a deep phenotype

- The clinical features of NICU infants do NOT correspond well with classical descriptions of their disease
- The ability to make a diagnosis is critically dependent on a full clinical description



Glossary: Phenotype – the clinical features of a patient with a disease



# Step 6: Deep Phenotyping by Natural Language Processing of Epic EMR: 20 sec

The screenshot displays the CLiXENRICH web application. The interface includes a sidebar with navigation options: Home, Import Records, Manage Filters, Run Jobs, View Results, Interactive Testpad, View Status, Manage API Keys, and Logout. The main content area is divided into two panels. The left panel lists various medical conditions with their associated HP codes and confidence scores (all 100%). The right panel displays a detailed text view of a medical record, with specific terms highlighted in orange boxes.

**CLiXENRICH** Welcome back mclark3@rchsd.org (rchsd Administrator)

**Left Panel (Conditions):**

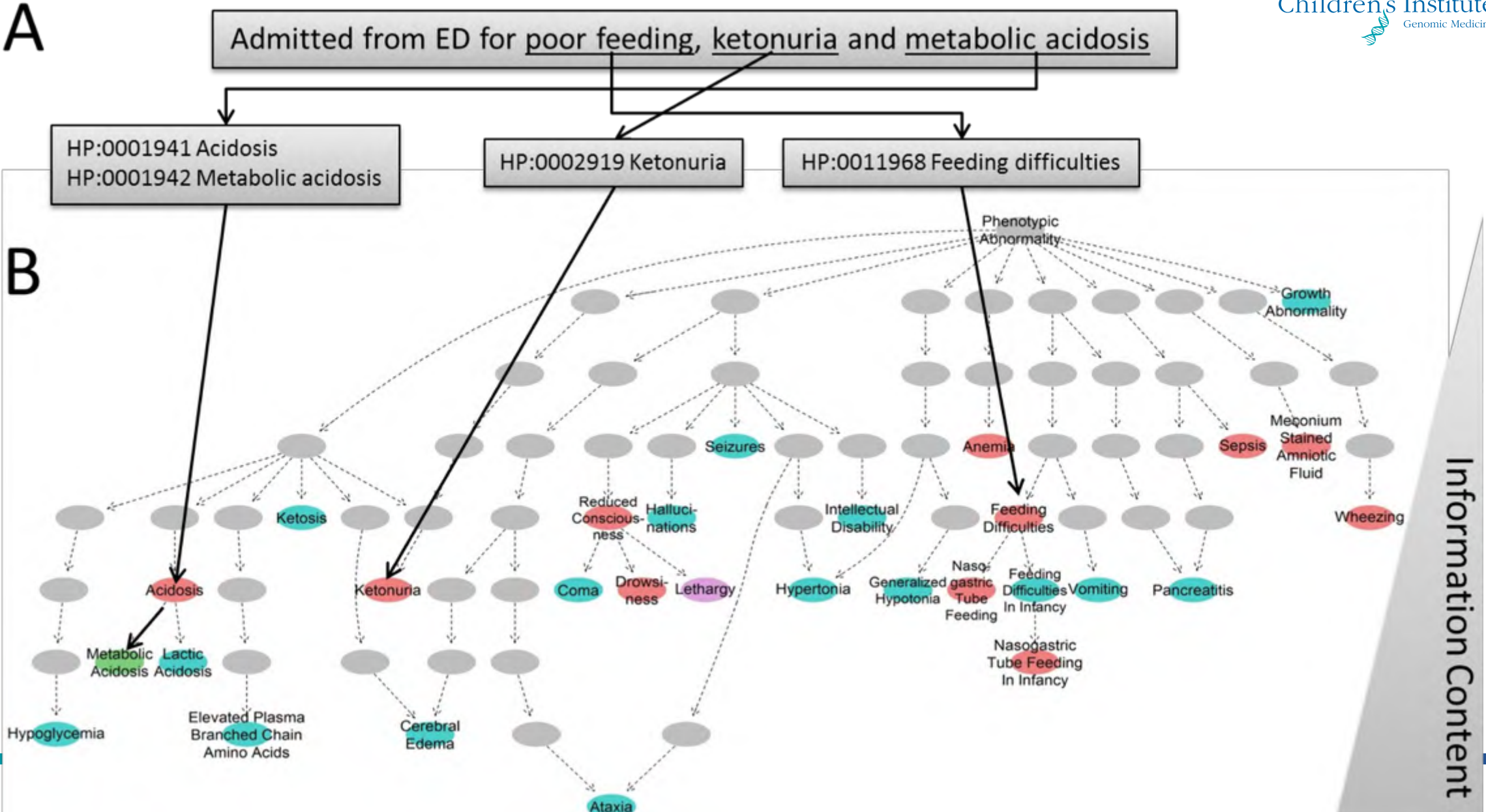
- nervous system (100%)
- HP0001041 Facial erythema (100%)
- HP0001250 Seizures (100%)
- HP0001298 Encephalopathy (100%)
- HP0001336 Myoclonus (100%)
- HP0001438 Abnormality of abdomen morphology (100%)
- HP0001941 Acidosis (100%)
- HP0001942 Metabolic acidosis (100%)
- HP0002011 Morphological abnormality of the central nervous system (100%)
- HP0002060 Abnormality of the cerebrum (100%)
- HP0002329 Drowsiness (100%)
- HP0002353 EEG abnormality (100%)
- HP0002373 Febrile seizures (100%)
- HP0002521 Hypsarrhythmia (100%)
- HP0002527 Falls (100%)
- HP0002790 Neonatal breathing dysregulation (100%)
- HP0002928 Decreased activity of the pyruvate dehydrogenase complex (100%)
- HP0003128 Lactic acidosis (100%)
- HP0004305 Involuntary movements

**Right Panel (Text View):**

10 mg TID depending on kidney functionStep 3: Reload levetiracetam 20 mg/kg and then maintenance of 45 mg/kg divided BID or 15 mg TID depending on kidney functionStep 6 Reload Dilantin 20 mg/kg and start IV maintenance 5 mg/kg/day divided BID for a goal level of 10Step 7: Initiate a midazolam dripStep 8: Consider topiramate or lacosamide2) Metabolic testing:Urine organic acidsSerum amino acidsPlasma acylcarnitine profileAmmonia, lactateFrom a metabolic standpoint, there are a number of time-dependent, treatable conditions that need to be addressed including:1) Vitamin dependent epilepsies including Pyridoxine-dependent seizures, Pyridoxal 5 phosphate dependent seizures and biotinidase deficiency.--Children with these conditions and others need specific vitamin supplementation as soon as possible to prevent permanent brain injury (for example, pyridoxine, PSP, biotin)2) Transporter disorders including GLUT1 deficiency and cerebral folate deficiency--Children with GLUT1 need the ketogenic diet started as soon as possible to prevent long-term disability. Folate supplementation may help children with cerebral folate deficiency. CSF glucose and folate levels should be sent in children with refractory epilepsy and no identified cause of seizures3) Amino and organic acidopathies, most notably maple syrup urine disease--Dietary avoidance may be required in some conditions. Metabolic testing including newborn screening, urine organic acids, plasma amino acids, serum acylcarnitine profile are needed in all children with seizures and no identified cause.4) Mitochondrial disorders, most notably Leigh's disease and pyruvate dehydrogenase deficiency. All children with seizures and no identified cause should have serum and CSF lactate and pyruvate testing. Treatment may include vitamins and supplements such as co-enzyme Q10.5) Urea cycle defects. All children with seizures and no identified cause should have serum ammonia testing. Dietary avoidance may be needed.6) Neurotransmitter disorders. All children with refractory seizures and no identified cause should have CSF neurotransmitters sent, including CSF biopterin.3) Genetic testing: CGH, epilepsy genetic panel, genetics instituteFrom a genetic standpoint, there is a growing list of neonatal onset epilepsies that have been identified, some with specific treatments. Recent series have found diagnosable genetic epilepsies in 12% (EuroEPINOMICS-RES Consortium, Am J Hum Gen, 2014), 18% (Trump et al, J Med Genet 2016), 23% (Moller et al, Mol Syndromol, 2016), 28% (Mercimek-Mahmutoglu et al, Epilepsia 2015), to 33% (Herbig et al, Genet Med, 2016) in patients with no clear provoking cause of seizures. Many of those source report their highest yield in neonatal seizures; in the Trump study, the overall hit rate was 18% but the neonatal hit rate was 39%, while the Hieberg study had a hit rate of 43% in children with silent encephalopathy. Most common were the SCN family of mutations, STXBP1 and the KCNQ family of genetic epilepsies. Most importantly, identification of these genetic epilepsies can have profound implications for immediate and long-term clinical care. For example, one review (Poduri et al, Nat Rev Neurol, 2014) included the table below showing how specific mutations influence care:From our experience and discussion with other providers (especially utilizing data from Dr. Poduri), we recognize AT LEAST the following mutations that may influence care:Gene TreatmentALDH7A1 PyridoxineGRIN2A Memantine (potentially)KCNQ2 Ezogabine (potentially)KCNT1 Quinidine (potentially)PLCB1 InositolPNPO Pyridoxal-5-phosphatePRRT2 CarbamazepineSCN1A Avoid phenytoin and lamotrigineSCN2A High-dose phenytoinSCN8A High-dose phenytoinSLC2A1 Ketogenic dietSLC1A5SLC7E7 Evacuation (and potentially other medication)



# Step 7: Translate phenotypes to a hierarchical standardized vocabulary



# Step 8: Pattern Recognition creates a comprehensive differential diagnosis

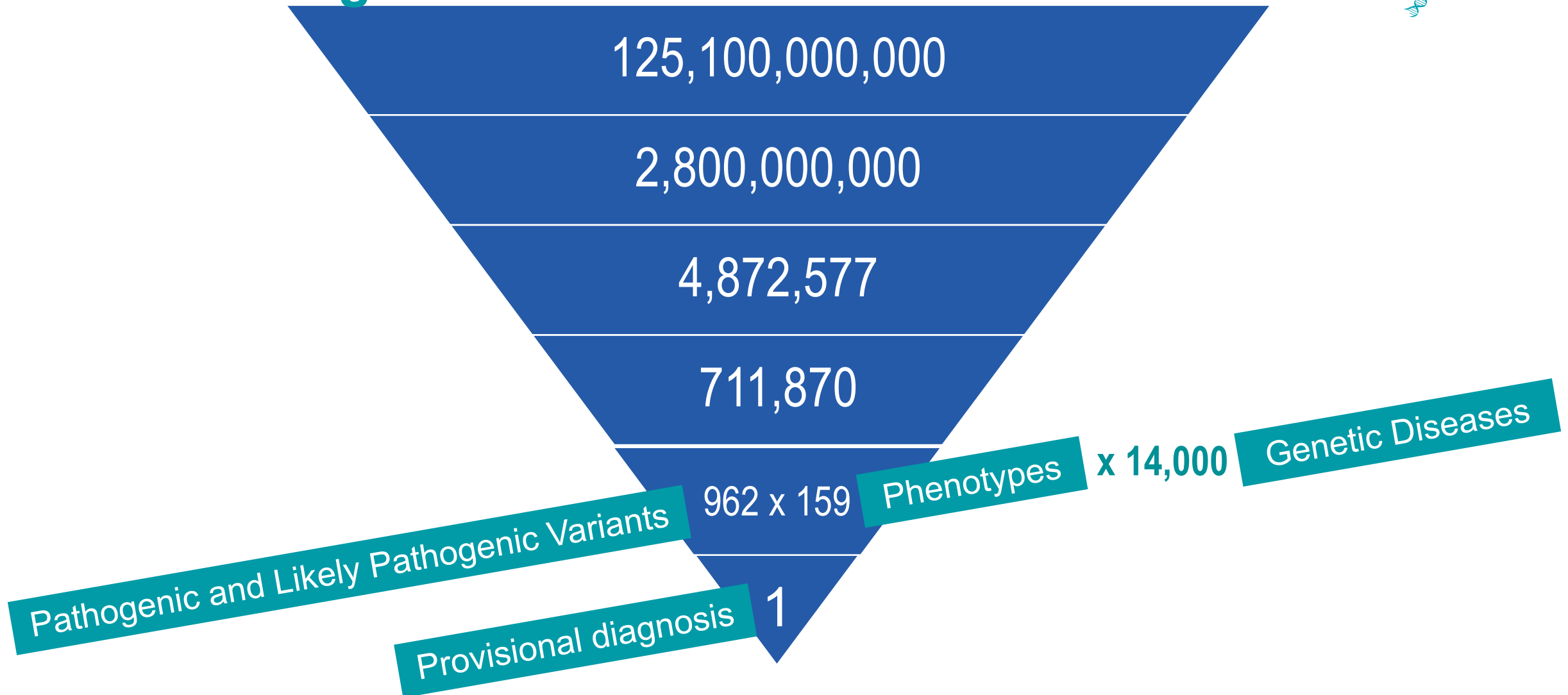
Patient's Features.	
HPO.	Feature. ▲
category.: Abnormality of blood and blood-forming tissues (1 Item)	
HP:0001882	Leukopenia
category.: Abnormality of metabolism/homeostasis (3 Items)	
HP:0011227	Elevated C-reactive protein level
HP:0001945	Fever
HP:0001942	Metabolic acidosis
category.: Abnormality of the abdomen (2 Items)	
HP:0002014	Diarrhea
HP:0002013	Vomiting
category.: Abnormality of the cardiovascular system (1 Item)	
HP:0011106	Hypovolemia
category.: Abnormality of the immune system (4 Items)	
HP:0001882	Leukopenia
HP:0100806	Sepsis
HP:0100806	Sepsis
HP:0000988	Skin rash
category.: Abnormality of the integument (1 Item)	
HP:0000988	Skin rash
category.: Abnormality of the respiratory system (1 Item)	
HP:0012418	Hypoxemia

Patient's Features.		Diagnosis.		
Algorithm: resnik (Unsymmetric).		10 Features.		
<input type="checkbox"/>	p-value. ▲	Disease Id.	Disease name.	Genes.
<input checked="" type="checkbox"/>	0.0010	OMIM:26...	#260920 HYPER-IGD SYNDROME; HIDS;;HYPERIMMUNOGLOBULINEMIA D AND PERIODIC FEVER SY...	MVK (4598)
<input checked="" type="checkbox"/>	0.0010	ORPHAN...	LEGIONELLOSIS	
<input checked="" type="checkbox"/>	0.0010	OMIM:61...	DENGUE FEVER	
<input checked="" type="checkbox"/>	0.0010	ORPHAN...	LASSA FEVER	
<input checked="" type="checkbox"/>	0.0010	ORPHAN...	EBOLA HEMORRHAGIC FEVER	
<input checked="" type="checkbox"/>	0.0010	ORPHAN...	MARBURG HEMORRHAGIC FEVER	
<input checked="" type="checkbox"/>	0.0010	ORPHAN...	CRIMEAN-CONGO HEMORRHAGIC FEVER	
<input checked="" type="checkbox"/>	0.0010	OMIM:60...	STEVENS-JOHNSON SYNDROME	IKZF1 (10320...
<input checked="" type="checkbox"/>	0.0010	OMIM:26...	RETICULAR DYSGENESIA	AK2 (204)
<input checked="" type="checkbox"/>	0.0010	ORPHAN...	LUJO HEMORRHAGIC FEVER	
<input checked="" type="checkbox"/>	0.0010	OMIM:61...	#611762 FAMILIAL COLD AUTOINFLAMMATORY SYNDROME 2; FCAS2	NLRP12 (916...
<input checked="" type="checkbox"/>	0.0010	ORPHAN...	SPONTANEOUS PERIODIC HYPOTHERMIA	
<input checked="" type="checkbox"/>	0.0010	OMIM:13...	GASTRITIS, FAMILIAL GIANT HYPERTROPHIC	
<input checked="" type="checkbox"/>	0.0010	OMIM:16...	CYCLIC HEMATOPOIESIS	ELANE (1991)
<input checked="" type="checkbox"/>	0.0010	OMIM:60...	ENTEROPATHY, FAMILIAL, WITH VILLOUS EDEMA AND IMMUNOGLOBULIN G2 DEFICIENCY	
<input checked="" type="checkbox"/>	0.0010	OMIM:14...	HYPERTHERMIA, CUTANEOUS, WITH HEADACHES AND NAUSEA	
<input checked="" type="checkbox"/>	0.0018	ORPHAN...	SCRUB TYPHUS	
<input checked="" type="checkbox"/>	0.0018	OMIM:60...	600643 CAROLI DISEASE, ISOLATED	
<input checked="" type="checkbox"/>	0.0023	OMIM:25...	#251000 METHYLMALONIC ACIDURIA DUE TO METHYLMALONYL-COA MUTASE DEFICIENCY;;METHY...	MUT (4594)
<input checked="" type="checkbox"/>	0.0023	OMIM:24...	#243500 ISOVALERIC ACIDEMIA, IVA;;ISOVALERIC ACID COA DEHYDROGENASE DEFICIENCY;;IVD D...	IVD (3712)
<input checked="" type="checkbox"/>	0.0023	OMIM:61...	#615592 IMMUNODEFICIENCY 15; IMD15	IKBKB (3551)
<input checked="" type="checkbox"/>	0.0026	ORPHAN...	TYPHOID	
<input checked="" type="checkbox"/>	0.0026	ORPHAN...	RABIES	
<input checked="" type="checkbox"/>	0.0026	OMIM:61...	#614102 IMMUNOGLOBULIN KAPPA LIGHT CHAIN DEFICIENCY; IGKCD;;KAPPA CHAIN DEFICIENCY	IGKC (3514), ...
<input checked="" type="checkbox"/>	0.0026	OMIM:26...	260570 PELGER-HUET-LIKE ANOMALY AND EPISODIC FEVER WITH ABDOMINAL PAIN	
<input checked="" type="checkbox"/>	0.0030	ORPHAN...	LYELL SYNDROME	
<input checked="" type="checkbox"/>	0.0030	OMIM:61...	#614699 IMMUNODEFICIENCY, COMMON VARIABLE, 7; CVID7	CD19 (930), ...



# Step 9: Automated Diagnosis: 2 mins

## Manual Diagnosis: 1 – 10 hours



# Step 9: Automated Diagnosis: 4 mins

## Manual Diagnosis: 10 hours

The patient's phenotype might be caused by:

BTK

X:100,613,603

G

ref: A

splice donor

c.974+2T>C

Agammaglobulinemia, x-linked

XR

- X-linked recessive
- Inherited from mother
- Loss of splice donor site of intron 11
- Classified as pathogenic
- Confirmed by functional studies

		Ref Range & Units
Total IgG	<135 ▼	413-1,112 mg/dL
IgM	16 ▼	30 - 146 mg/dL
IgA	<5 ▼	21 - 117 mg/dL
		2wk ago
LYMPHOCYTES ABSOLUTE	2962 ▼	4000 - 10500 cells/uL
CD19 ABSOLUTE	<20 ▼	830 - 1880 cells/uL
CD19 PERCENTAGE	1 ▼	20 - 38 %

# Hospital Course

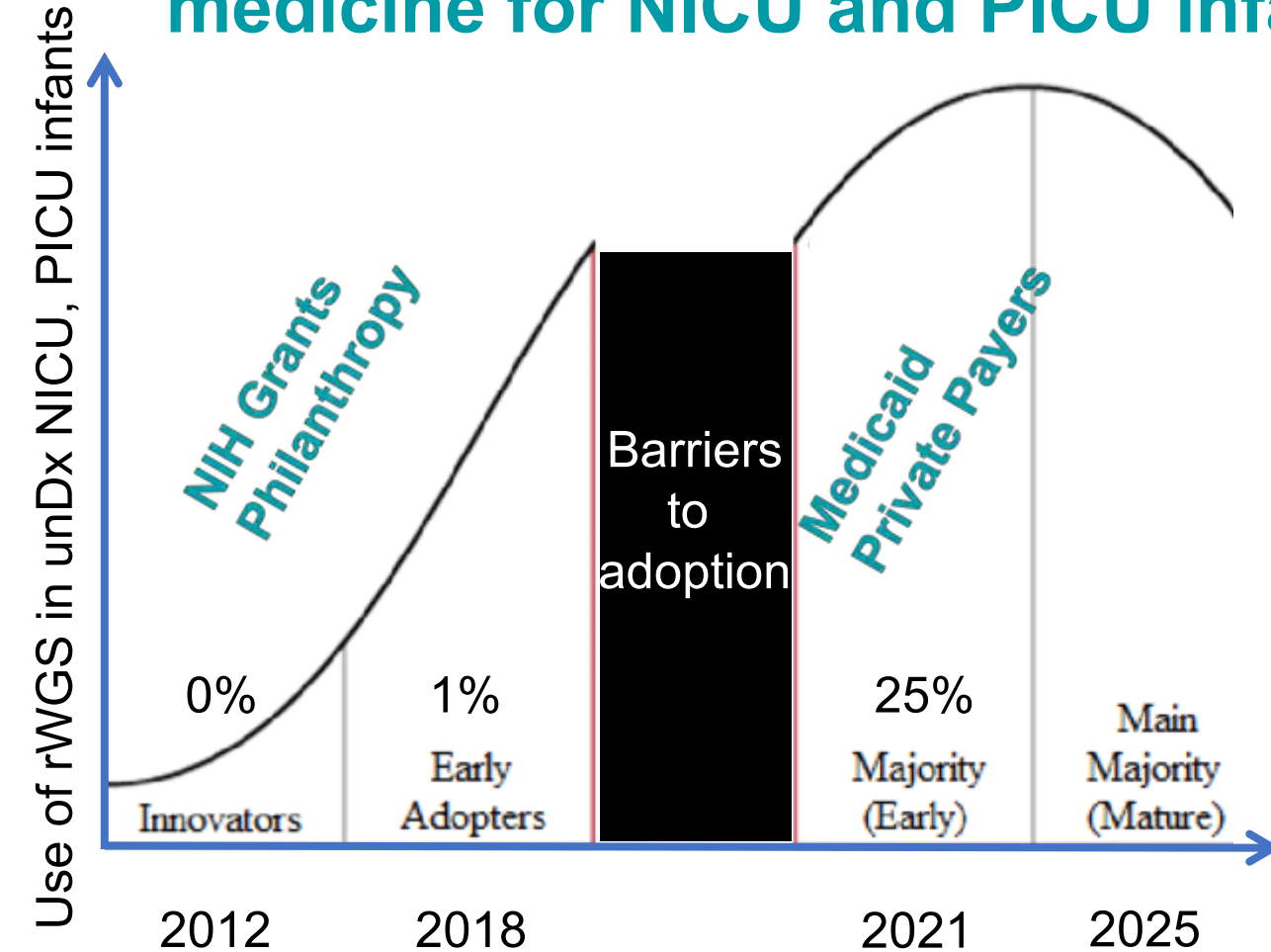
- **Diagnosis after 22 hours**
- **Individualized medicine**
  - Double coverage, double duration antibiotics
  - Intravenous immunoglobulin to maintain IgG level >600mg/dL
  - Magnetic resonance imaging: no additional septic emboli
- **Prognosis**
  - Normal life
  - 10% have significant infections despite treatment
- **Genetic counseling**
  - Mother is a carrier
  - Maternal relatives at-risk
- **Discharged home on day 13**

# Diagnostic performance of 3<sup>rd</sup> generation rWGS-based individualized medicine

- Retrospective, n=84 children with 86 diagnoses
  - Expert manual interpretation: Precision 98%, Recall 98%
  - Automated interpretation: Precision 99%, Recall 95%

Subject ID Age	Retrospective Patients				Prospective Patients													
	263 8 days	6124 14 years	3003 1 year	6194 5 days	290 3 days	352 7 weeks	362 4 weeks	374 2 days	7052 17 months		412 3 days							
Abbreviated Presentation	Neonatal seizures	Rhabdo- myolysis	Dystonia, Dev. delay	Hypoglycemia seizures	Pulmonary hemorrhage	Diabetic ketoacidosis	Neonatal seizures	HIE, anemia		Pseudomonal septic shock		Neonatal seizures						
Method	Auto.	Auto.	Auto.	Auto.	Auto.	Std.	Auto.	Std.	Auto.	Std.	Auto.	Std.	Auto.	Std.	Auto.	Std.		
Total (hours)	20:25	19:56	19:20	19:14	20:42*	56:03	19:29	48:46	19:11	42:04	19:10	57:21	31:02†	34:38	22:04	38:37	20:53	48:23
Molecular Diagnosis	Early Infantile Epileptic Encephalo-	Glycogen Storage Disease V	Dopa- Responsive Dystonia	None	None	Permanent neonatal diabetes	None	None	X-linked agamma- globulinemia	Benign familial neonatal seizures 1								
Gene and Causative Variant(s)	KCNQ2 c.727C>G	PYGM c.2262delA c.1726C>T	TH c.785C>G c.541C>T	n.a.	n.a.	INS c.26C>G	n.a.	n.a.	BTK c.974+2T>C	KCNQ2 c.1051C>G								

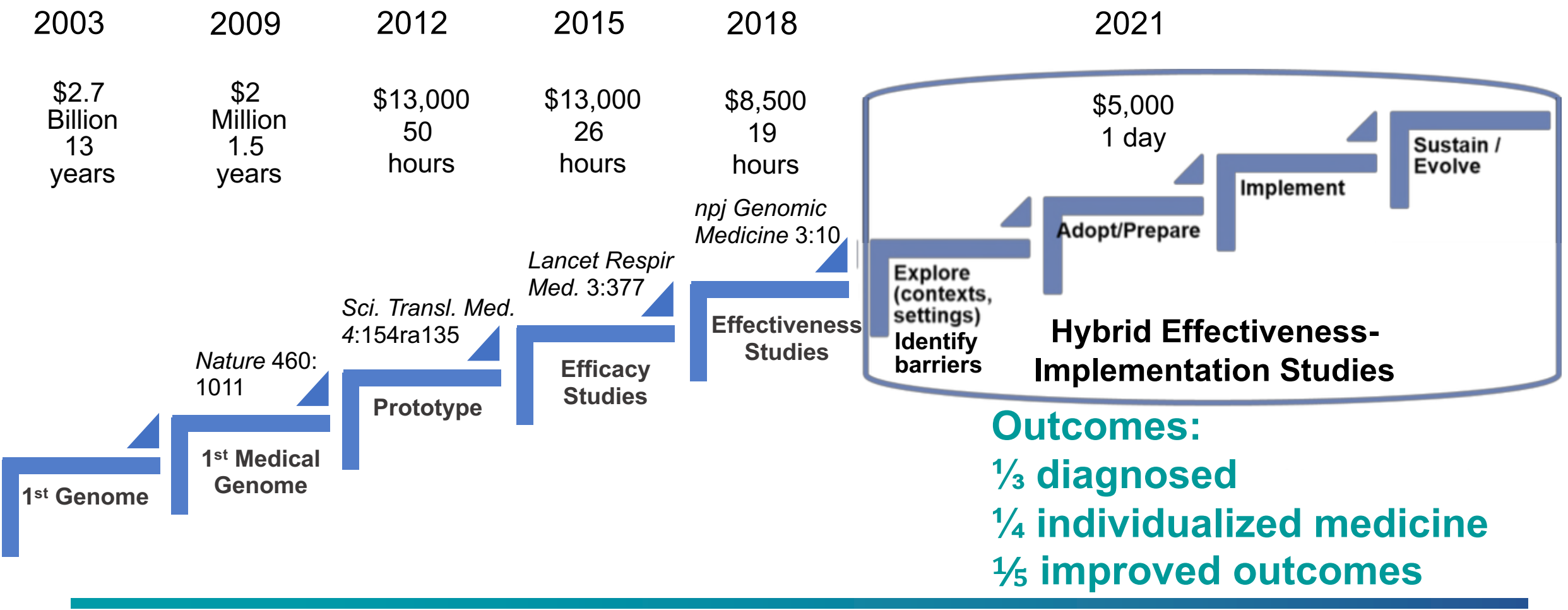
# Summary: Strategies are being implemented to address barriers to rWGS-based individualized medicine for NICU and PICU infants



- Automated 20-hour diagnosis by rWGS
- Lack of clinician familiarity with individualized medicine
  - APIs for FAQs, counseling
  - Case-based learning via podcast/webinar
- Insufficient evidence of efficacy
  - Cost effectiveness studies
  - Payor collaborations
- Many genetic diseases lack effective treatments
  - APIs for reference individualized management guidance



# Summary: By 2021 we predict the early majority of children's ICUs to implement individualized medicine



# Acknowledgments

## Executive Team

Stephen Kingsmore MD, DSc  
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Matt Niedzwiecki

## Leadership

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