As Science Moves to Genetic Testing & Treatment: Part 2, Genetic-Informed Treatments

Stephen Kingsmore MD DSc FRCPath
President & CEO

Rady Children's Institute
Genomic Medicine

1

Conflict of Interest

Rady Children's Institute
Genomic Medicine

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Learning objectives

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Explain	Explain how genetics/genomics may influence treatment plans for individuals
Identify	Identify resources to investigate current evidence for treatment of diseases
Explore	Explore the importance of data & evidence regarding current & upcoming gene therapies/genetic-informed treatments

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Background 1: Staggering ↑ in knowledge of genetic diseases

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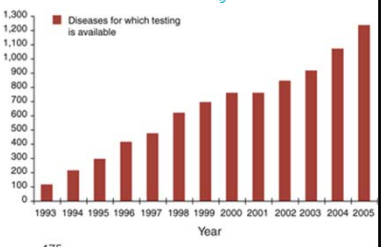
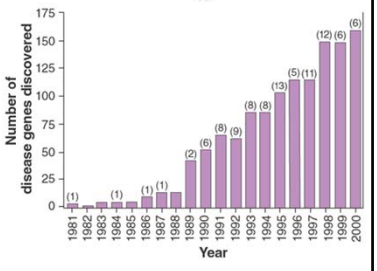
- Number of genetic diseases for which molecular basis is known: 5,961 (11/9/20)
- Rate of increase in known genetic diseases: 1 per day (idiopathic → molecular basis known)
- Prominent examples:
  - Seizures: 1,539 genetic diseases
  - Intellectual disability: 5,786 genetic diseases
  - Recurrent infection: 3,916 genetic diseases
  - Congenital heart disease: 4,140 genetic diseases
  - Congenital deafness: 2,328 genetic diseases
  - Metabolic abnormalities: 3,402 genetic diseases





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Background 2: Staggering ↓ in cost & time of whole genome sequencing tests

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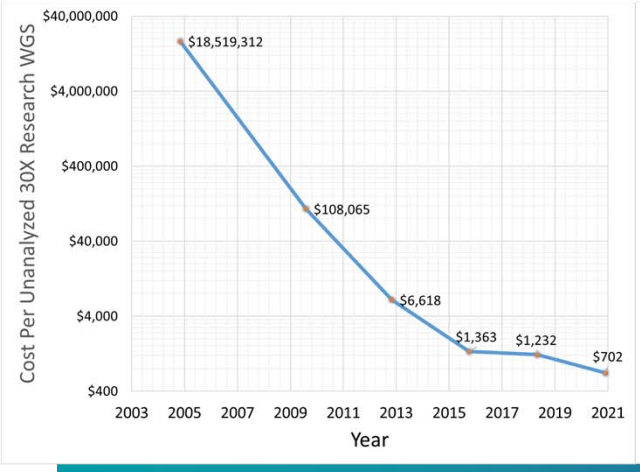

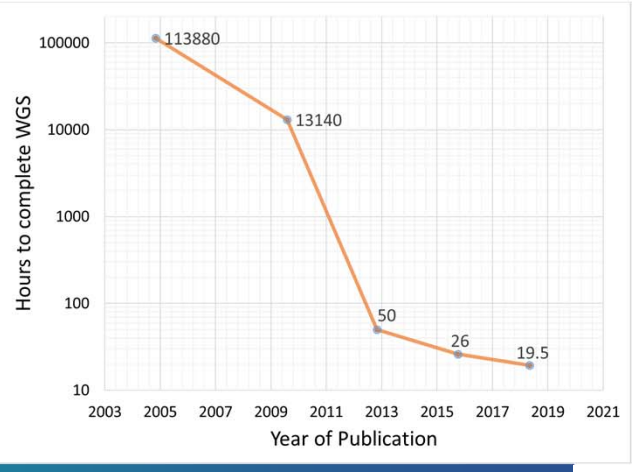

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Background 3: Explosion of evidence supporting genomic medicine

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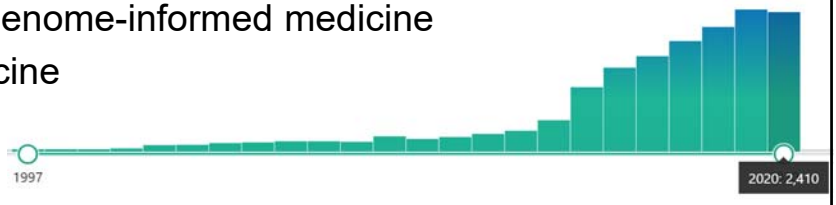
- Genomic medicine=genome-informed medicine
- a.k.a. precision medicine



1 Symposium on **Genomic Medicine**, University of Maryland, Shady Grove Campus, Rockville, Maryland, March 17-18, 1997.

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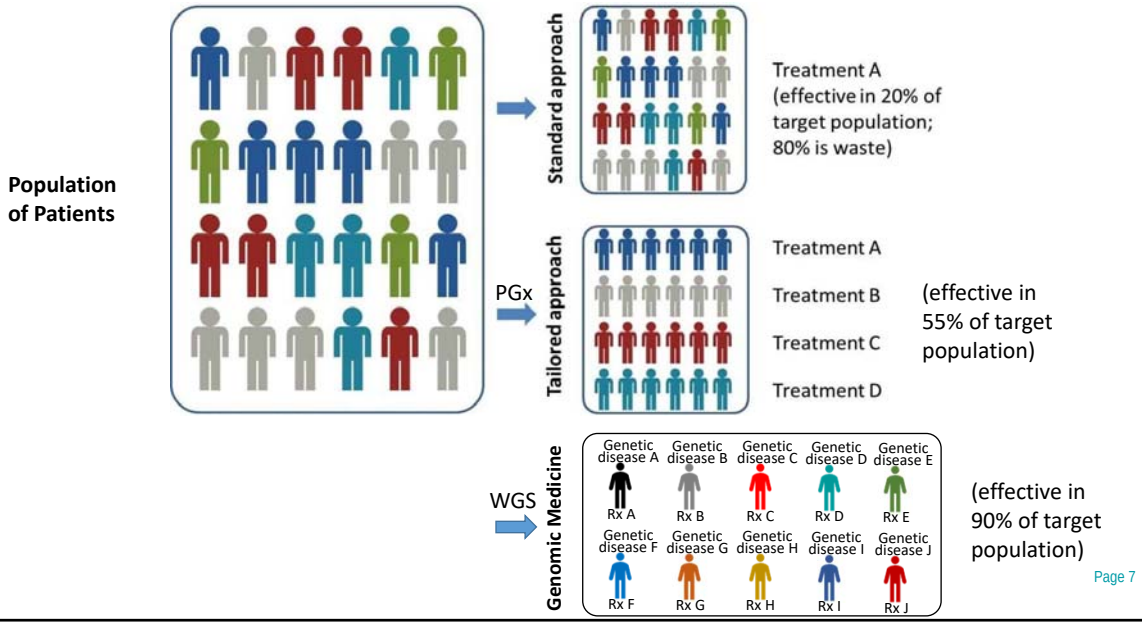
Explain

Explain how genetics/genomics may influence treatment plans for individuals



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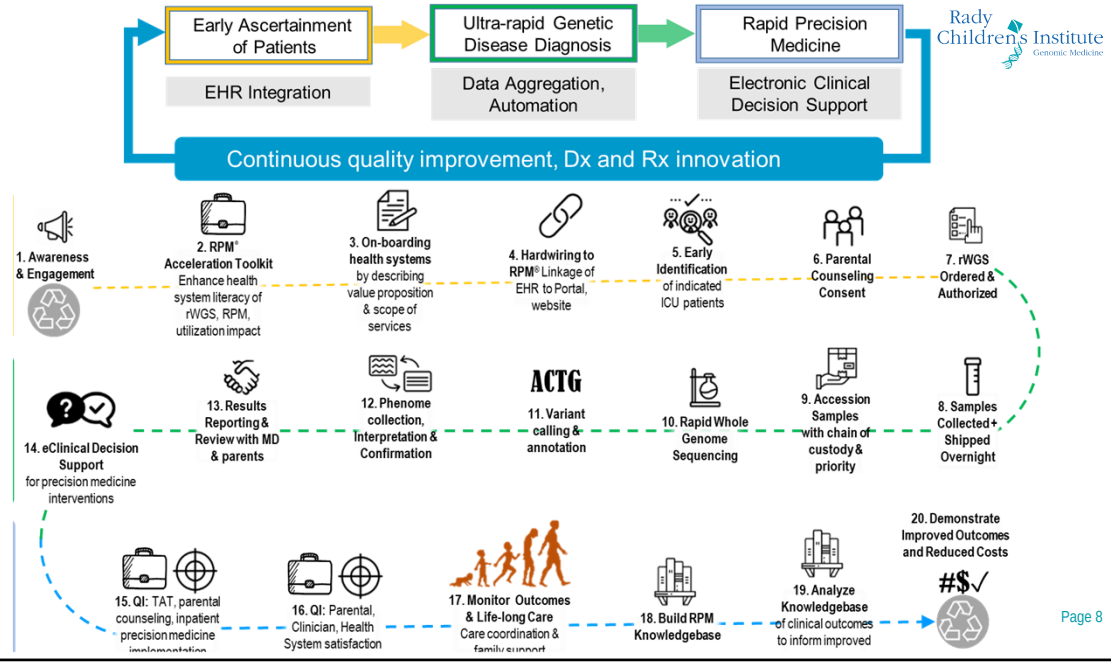
Rapid precision/genomic medicine



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Case Example

Explain how genetics/genomics may influence treatment plans for individuals

- 5-week-old previously healthy ♂ who presented to ED with inconsolable crying for 2 hours, extreme irritability & change in cry
- Downward eye deviation noted on neurological examination
- Parents consanguineous

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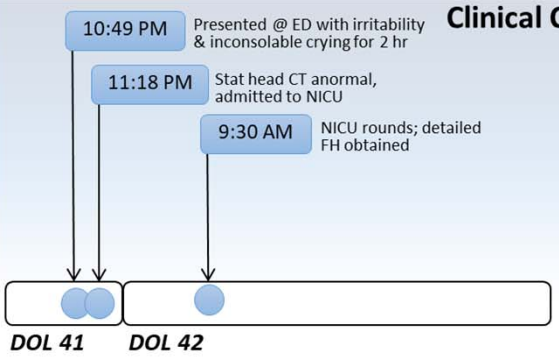
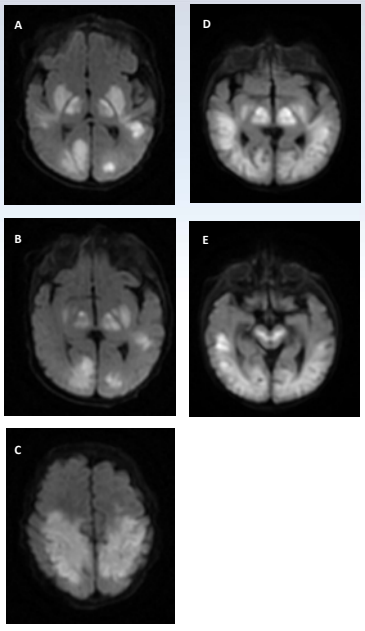
Clinical Course





- Stat CT head showed evidence of profound hypoxic ischemic injury with basal ganglia damage
- Sibling presented in same manner at same age. Died undiagnosed 9 years ago @ age 1 year with seizures, profound developmental delay

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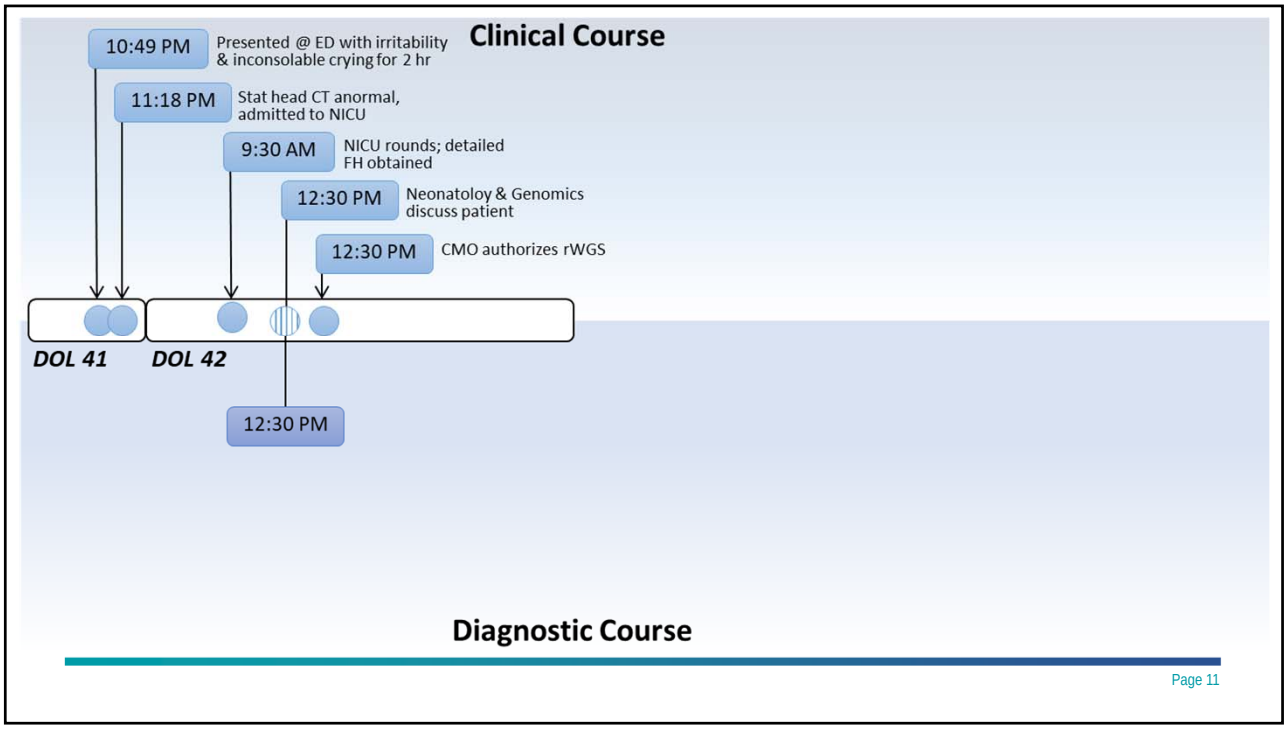
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11:18 PM
Stat head CT anormal, admitted to NICU
9:30 AM
NICU rounds; detailed FH obtained
12:30 PM
Neonatoloy & Genomics discuss patient
12:30 PM
CMO authorizes rWGS
DOL 41
DOL 42
12:30 PM
Diagnostic Course
Page 11

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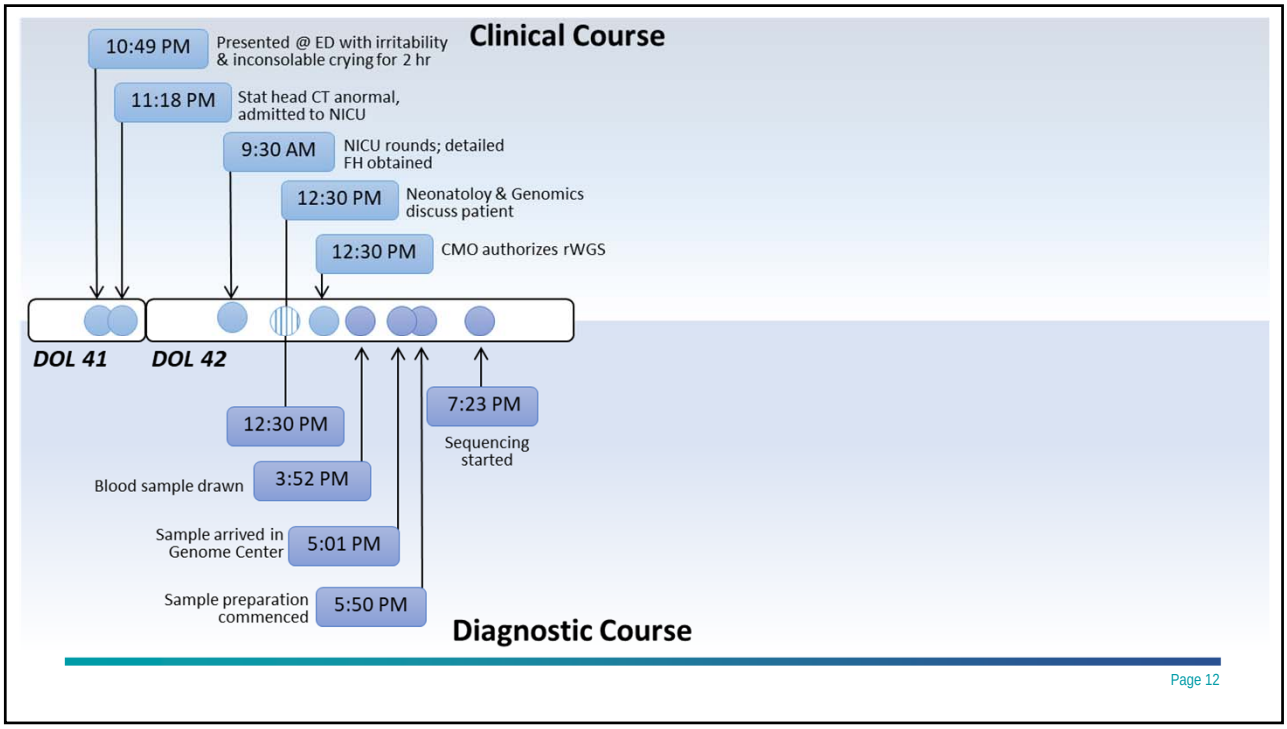
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Sequencing started
Blood sample drawn
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Sample arrived in Genome Center
5:01 PM
Sample preparation commenced
5:50 PM
Diagnostic Course
Page 12

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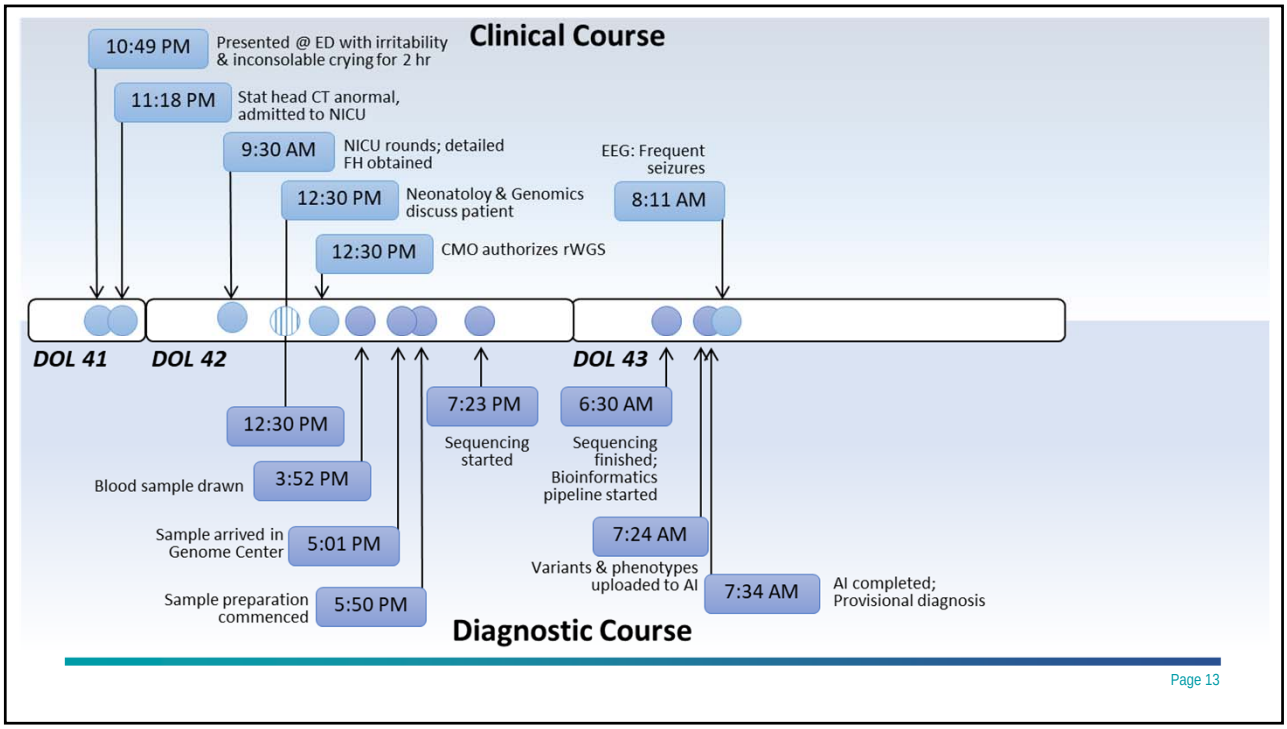
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EEG: Frequent seizures
8:11 AM
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Sequencing finished; Bioinformatics pipeline started
7:24 AM
Variants & phenotypes uploaded to AI
7:34 AM
AI completed; Provisional diagnosis
Diagnostic Course
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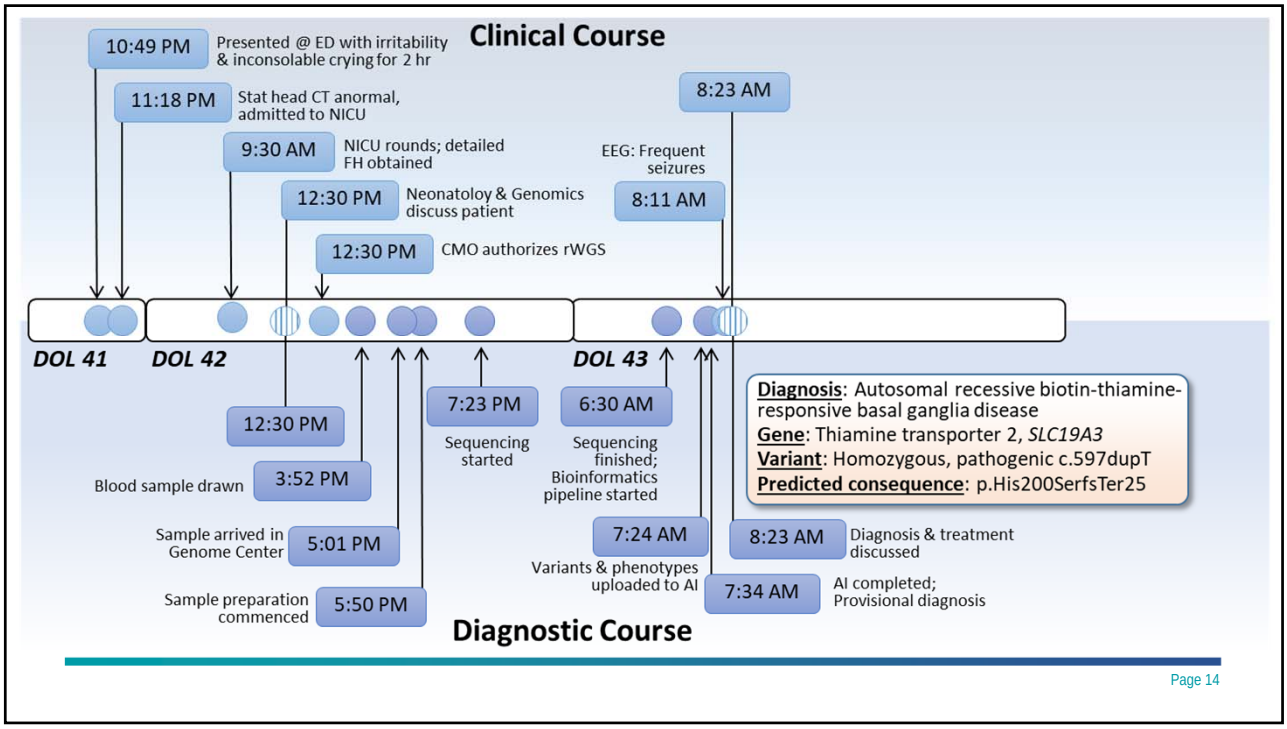
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Diagnosis: Autosomal recessive biotin-thiamine-responsive basal ganglia disease
Gene: Thiamine transporter 2, SLC19A3
Variant: Homozygous, pathogenic c.597dupT
Predicted consequence: p.His200SerfsTer25
Diagnostic Course
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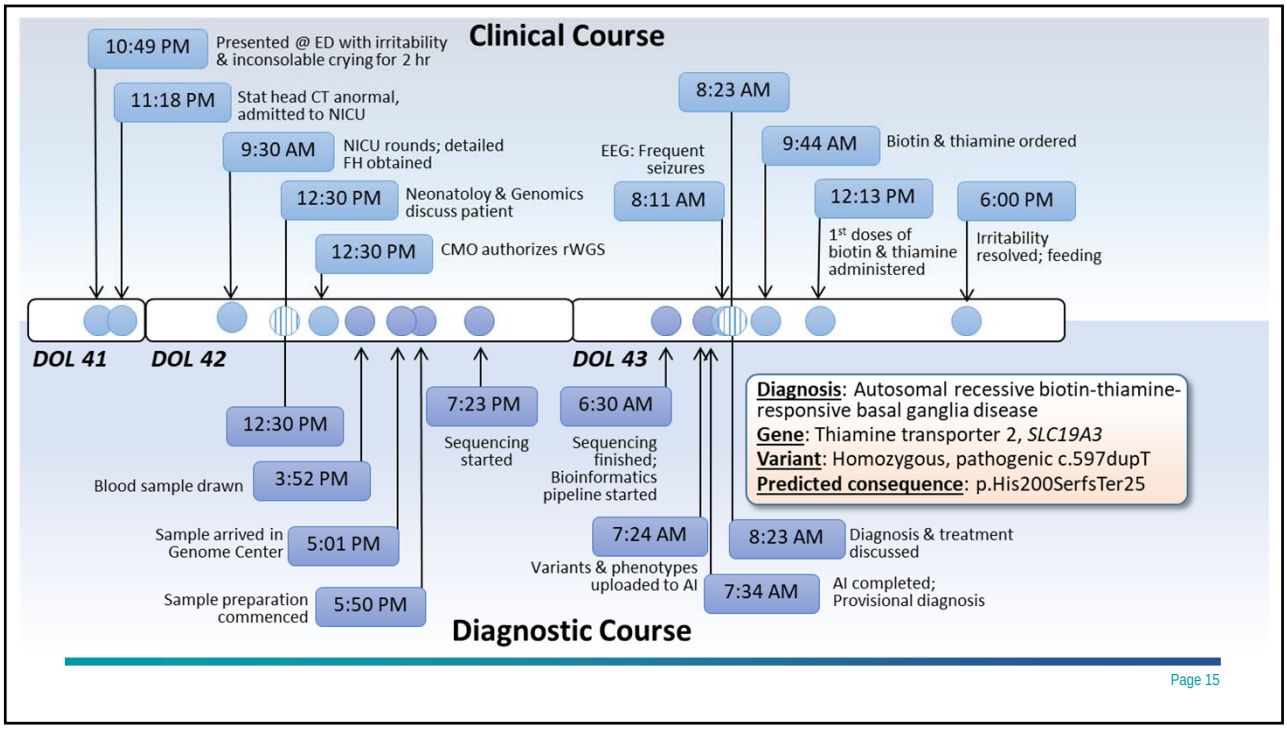
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8:23 AM
EEG: Frequent seizures
8:11 AM
9:44 AM
Biotin & thiamine ordered
12:13 PM
1st doses of biotin & thiamine administered
6:00 PM
Irritability resolved; feeding
DOL 41
DOL 42
DOL 43
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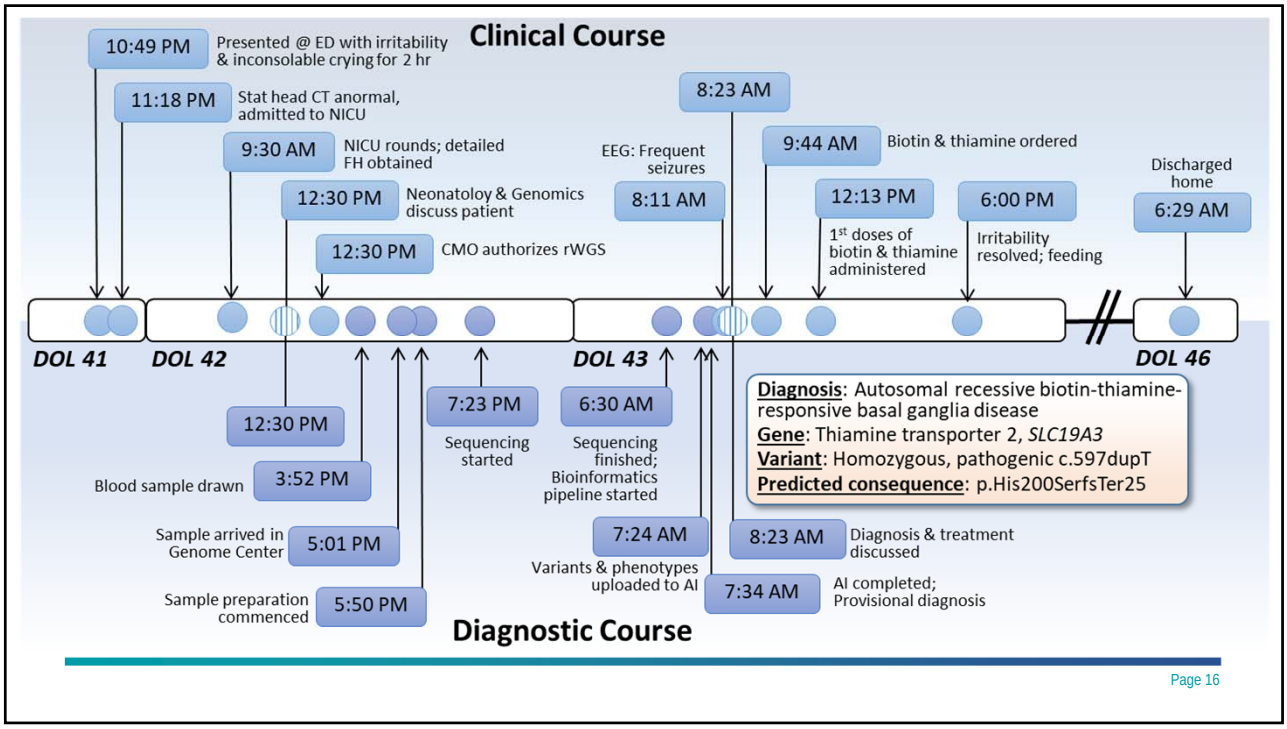
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But is this generalizable?

ARTICLE

A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants

Stephen F. Kingsmore,[1,*] Julie A. Cakici,[1,2] Michelle M. Clark,[1] Mary Gaughran,[1] Michele Feddock,[1] Sergey Batalov,[1] Matthew N. Bainbridge,[1] Jeanne Carroll,[1,3] Sara A. Caylor,[1] Christina Clarke,[1] Yan Ding,[1] Katarzyna Ellsworth,[1] Lauge Farnaes,[1,3] Amber Hildreth,[1,3,4] Charlotte Hobbs,[1] Kiely James,[1] Cyrielle I. Kint,[5] Jerica Lenberg,[1] Shareef Nahas,[1] Lance Prince,[1] Iris Reyes,[1] Lisa Salz,[1] Erica Sanford,[1,3] Peter Schols,[5] Nathaly Sweeney,[1,3] Mari Tokita,[1] Narayanan Veeraraghavan,[1] Kelly Watkins,[1] Kristen Wigby,[1,3] Terence Wong,[1] Shimul Chowdhury,[1] Meredith S. Wright,[1] David Dimmock,[1] and the RCIGM Investigators

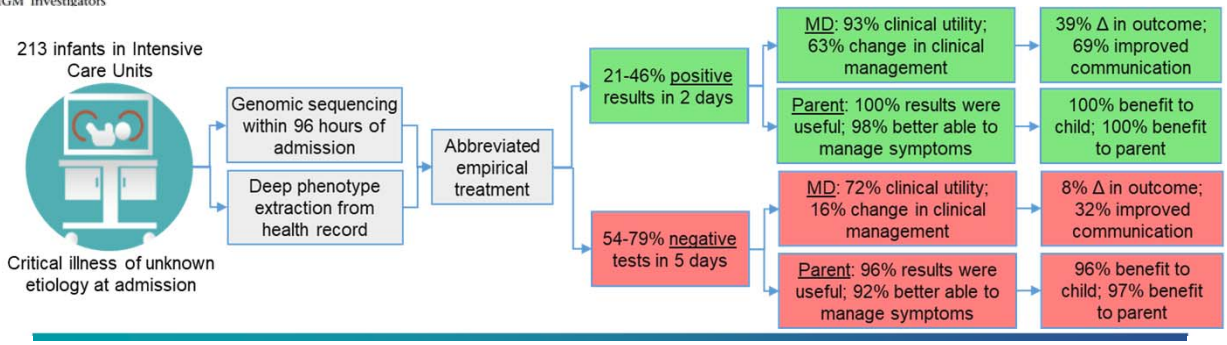
ARTICLE

An RCT of Rapid Genomic Sequencing among Seriously Ill Infants Results in High Clinical Utility, Changes in Management, and Low Perceived Harm

David P. Dimmock,[1,2,*] Michelle M. Clark,[1,2] Mary Gaughran,[1,2] Julie A. Cakici,[1,2,3] Sara A. Caylor,[1,2] Christina Clarke,[1,2] Michele Feddock,[1,2] Shimul Chowdhury,[1,2] Lisa Salz,[1,2] Cynthia Cheung,[3,4] Lynne M. Bird,[2,5] Charlotte Hobbs,[1,2] Kristen Wigby,[1,2,5] Lauge Farnaes,[1,2] Cinnamon S. Bloss,[3,4] Stephen F. Kingsmore,[1,2] and the RCIGM Investigators

A Prospective Study of Parental Perceptions of Rapid Whole-Genome and -Exome Sequencing among Seriously Ill Infants

Julie A. Cakici,[1,2,3] David P. Dimmock,[2] Sara A. Caylor,[2] Mary Gaughran,[2] Christina Clarke,[2] Cynthia Triplett,[4] Michelle M. Clark,[2] Stephen F. Kingsmore,[2] and Cinnamon S. Bloss[1,3,*]



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Identify

Identify resources to investigate current evidence for treatment of diseases

Reference	Date	Study Type	Sequencing Type	Neonatal and Pediatric Intensive Care Unit (NICU, PICU) Enrollment Criteria	Study Size	Rate of Diagnosis	Rate of Change in Management	Rate of Change in Outcome	Time to Result (days)
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 h of admission	94	19%	24%	10%	11
			rWES		95	20%	20%	18%	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%	15.0

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Sites implementing Rapid Precision Medicine

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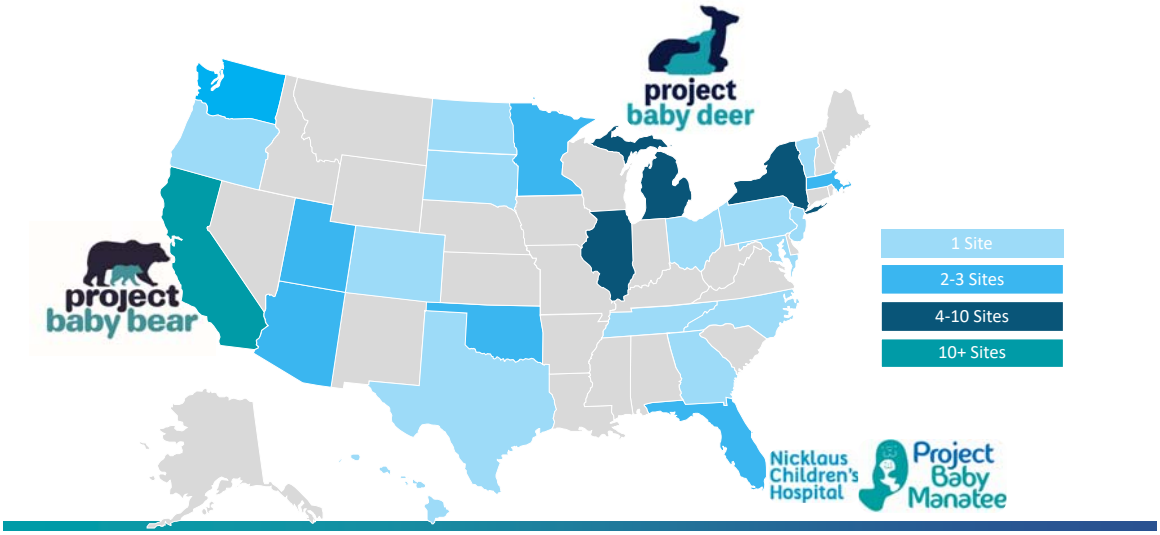

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Project Baby Bear Goal

project baby bear

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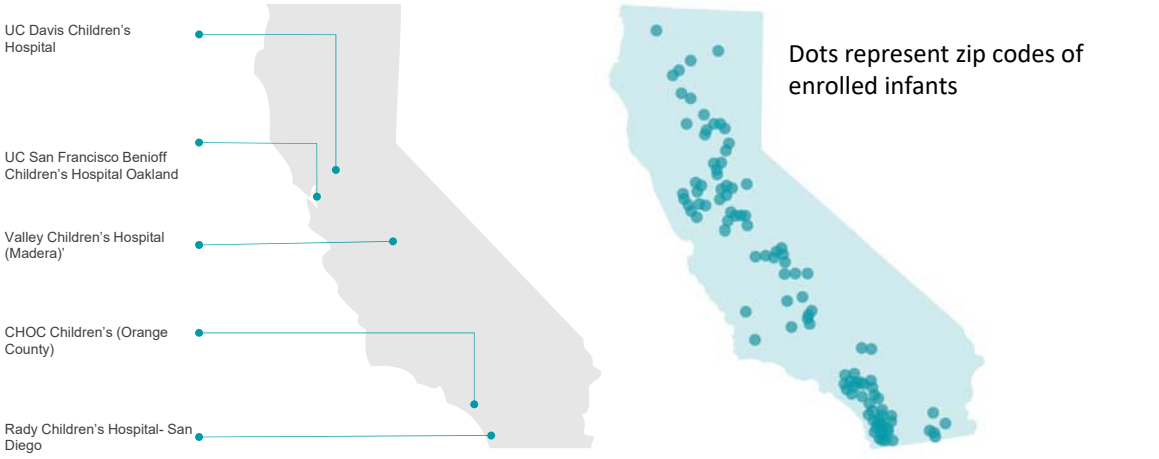
Evaluate clinical and economic value of rapid Whole Genome Sequencing for Medicaid infants hospitalized in critical care



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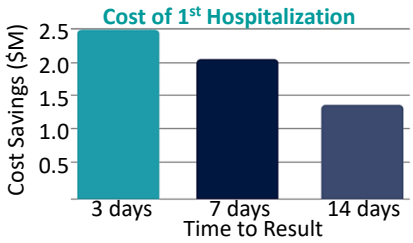
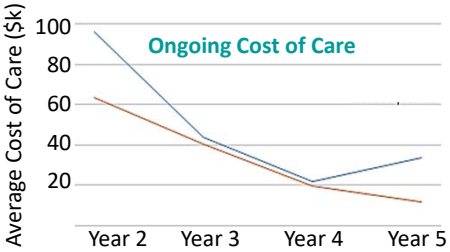
Project Baby Bear Results

PILOT SITES	# OF BABIES	BABIES DIAGNOSED	BABIES WHOSE CARE WAS CHANGED*	DAYS TO RESULTS**
CHILDREN'S HOSPITAL ORANGE COUNTY	23	12 (52%)	9 (39%)	2.5
RADY CHILDREN'S HOSPITAL-SAN DIEGO	59	22 (37%)	19 (32%)	3
UC DAVIS CHILDREN'S HOSPITAL *(Sacramento)*	34	12 (35%)	8 (24%)	2
UCSF BENIOFF CHILDREN'S HOSPITAL OAKLAND	24	12 (50%)	9 (38%)	3
VALLEY CHILDREN'S HOSPITAL *(Madera)*	38	18 (47%)	10 (26%)	3
TOTAL PROJECT BABY BEAR CASES	178	76 (43%)	55 (31%)	3

** Results confirmed 21 babies were already receiving appropriate care*
*** Median # days to delivery of provisional positive results*





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Identify

Identify resources to investigate current evidence for treatment of diseases

NIH U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Tabarki B, Al-Hashem A, Alfadhel M. Biotin-Thiamine-Responsive Basal Ganglia Disease. 2013 Nov 21 [Updated 2020 Aug 20]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

GeneReviews

Biotin-Thiamine-Responsive Basal Ganglia Disease

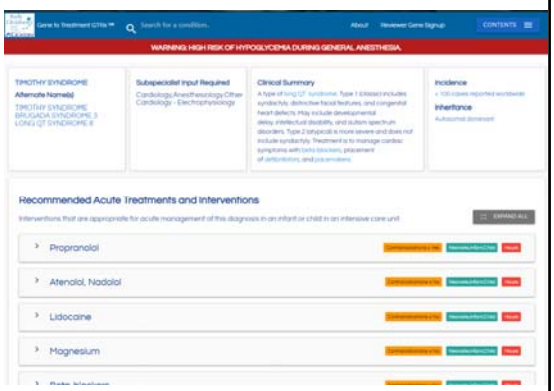
Synonyms: Biotin-Responsive Basal Ganglia Disease (BBGD), BTBGD, Thiamine Metabolism Dysfunction Syndrome-2, Thiamine Transporter-2 Deficiency

Brahim Tabarki, MD,[1] Amal Al-Hashem, MD,[1] and Majid Alfadhel, MD, MHSc, FCCMG[2]

Created: November 21, 2013; Revised: August 20, 2020.

Management

Treatment of manifestations: Biotin (5-10 mg/kg/day) and thiamine (up to 40 mg/kg/day with a maximum of 1500 mg daily) are given orally as early in the disease course as possible and are continued lifelong. Symptoms typically resolve within days. Acute encephalopathic episodes may require care in an ICU to manage seizures and increased intracranial pressure; during acute decompensations thiamine may be increased to double the regular dose and be given intravenously. Antiepileptic drugs are used to control seizures. Treatment of dystonia is symptomatic and includes administration of trihexyphenidyl or L-dopa. Rehabilitation, physiotherapy,



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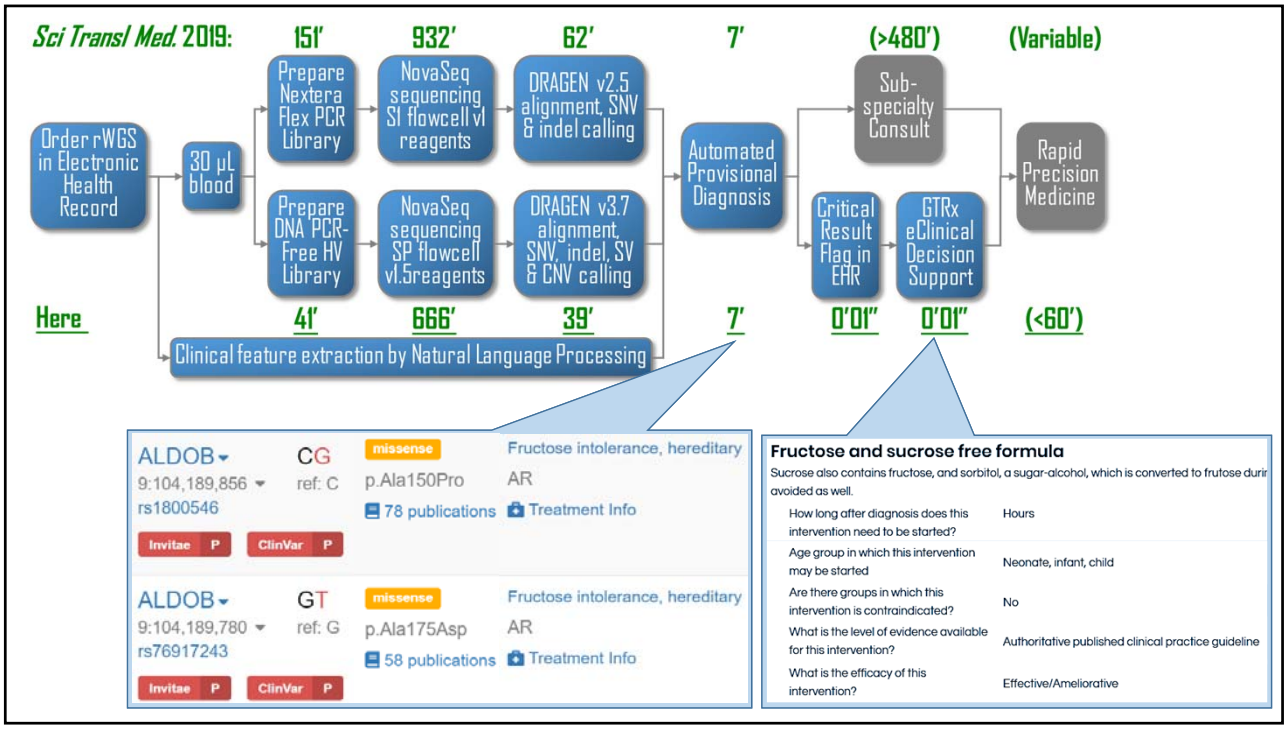

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Identify resources to investigate current evidence for treatment of diseases

Expert Opin Biol Ther. 2020 Jul;20(7):823-827. doi: 10.1080/14712598.2020.1772747. Epub 2020 Jun 11.

Will the US$5 million onasemnogene abeparvosec treatment for spinal muscular atrophy represent 'value for money' for the NHS? A rapid inquiry into suggestions that it may be cost-effective

Martin Connock [1], Lazaros Andronis [1], Peter Auguste [1], Claude Dussart [2], Xavier Armoiry [1 3]

Abstract

Objectives: Nusinersen (Spinraza®, Biogen) and onasemnogene abeparvosec (Zolgensma®, Novartis) are novel gene-based therapies for the orphan disease Spinal Muscular Atrophy. Onasemnogene abeparvosec has been allocated an acquisition cost of up to US$5 million per patient. We undertook a rapid inquiry to evaluate if onasemnogene abeparvosec is likely to be cost-effective for the UK NHS.

Methods: We used publicly available cost-effectiveness data and recommended methodology to perform cost-utility evaluation of onasemnogene abeparvosec versus best supportive care and nusinersen.

Results: Our evaluations highlight wide variations in cost and benefit estimates of nusinersen and indicate that onasemnogene abeparvosec is unlikely to represent value for money according to current standards of reimbursement. Results are discussed in the context of reimbursement decisions for orphan diseases.

Conclusion: Commonly implemented commercial confidentiality practices combined with uncertain data obscure scrutiny and justification of past and present reimbursement decisions for orphan drugs. Future cutting edge expensive therapies will be numerous, they will entail very substantial economic strains. We conclude that there is an urgent and increasing need for the development of improved procedures that can lead to equitable, consistent, and transparent decision-making.

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Explore

Explore the importance of data & evidence regarding current & upcoming gene therapies/genetic-informed treatments

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Impact of the Orphan Drug Act on Approvals

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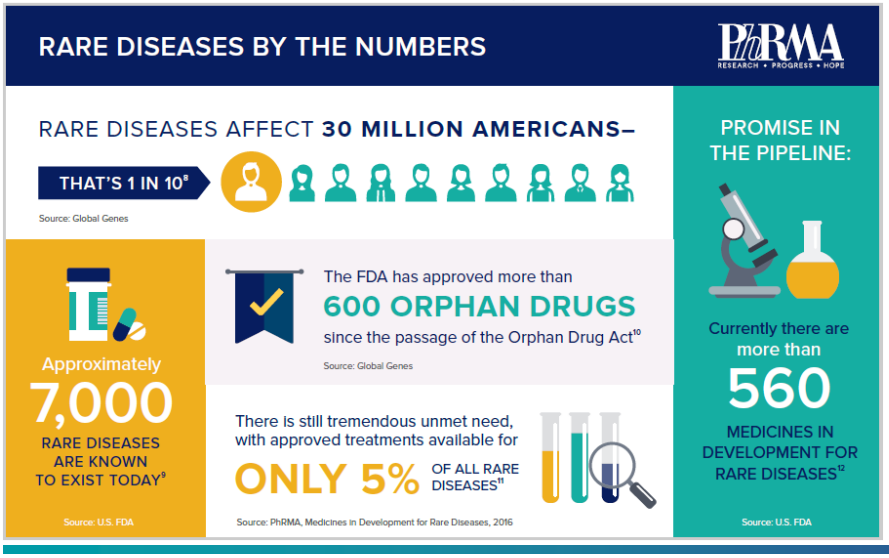

Source: https://www.phrma.org/rare-disease

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Impact of the Orphan Drug Act on Approvals

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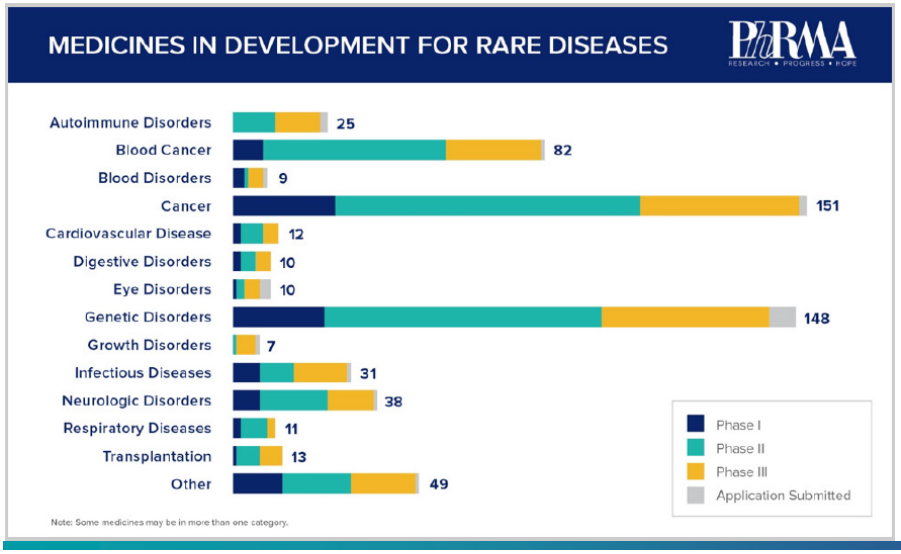

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Orphan Drugs & FDA

Rady Children's Institute Genomic Medicine

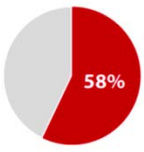
Drugs for Rare Diseases

In 2018, 34 of CDER's 59 novel drugs (58%) were approved to treat rare or "orphan" diseases that affect 200,000 or fewer Americans. Patients with rare diseases often have few or no drugs available to treat their conditions. Novel drugs approved in 2018 with the orphan drug designation were: Asparlas, Braftovi, Copiktra, Crysvita, Daurismo, Diacomit, Elzonris, Epidiolex, Firdapse, Galafold, Gamifant, Krintafel, Lorbrena, Lumoxiti, Lutathera, Mektovi, moxidectin, Omegaven, Onpattro, Oxervate, Palynziq, Poteligeo, Revcovi, Symdeko, Takhzyro, Tavalisse, Tegsedi, Tibsovo, Tpoxx, Trogarzo, Ultomiris, Vitrakvi, Vizimpro, and Xospata.

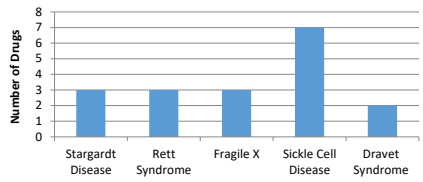
Notable examples of novel approvals of 2018 that advance the care of patients with rare diseases approved in 2018 include:

- **Crysvita (burosumab-twza)**, the first FDA-approved drug to treat adults and children ages one year and older with **x-linked hypophosphatemia**

34 of CDER's 59 novel drugs (58%) were approved to treat rare or "orphan" diseases.



Number of Drugs in Phase II/III and Phase III Development for Rare Genetic Diseases



2018 FDA key facts:

- 95% of drugs approved on 1st cycle
- 71% approved in US before any other country
- Expedited Development & Review Pathways:
  - 41%: Fast Track (unmet medical need)
  - 24%: Breakthrough Rx (preliminary clinical evidence)
  - 73%: Priority Review (within 8 months)
  - 7%: Accelerated Approval (flexible endpoints)

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Sources: Medicines in Development: Rare Diseases, Pharma 2016 ; Center for Drug Evaluation and Research Advancing Health Through Innovation 2018 New Drug Therapy Approvals, FDA: January 2019

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Impact of Orphan Drug Act on approvals

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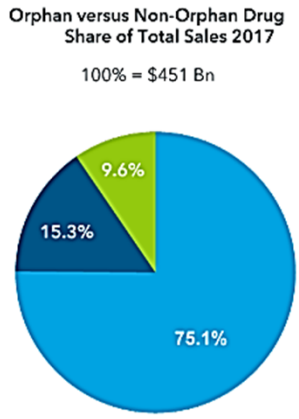
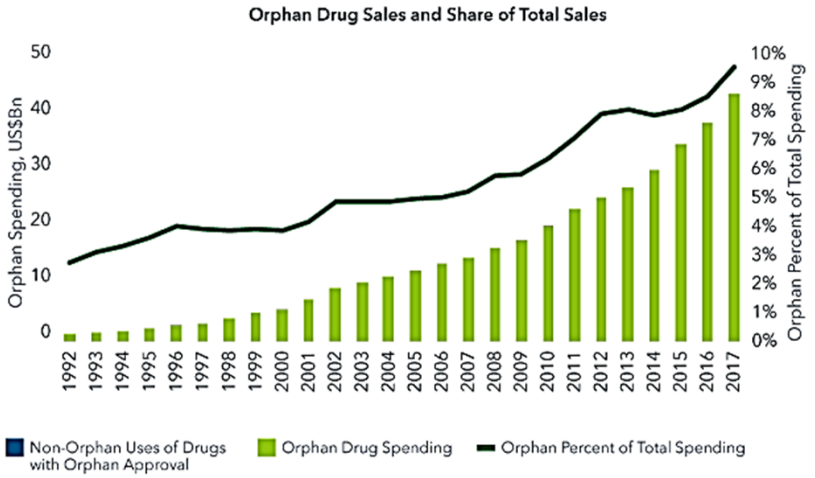
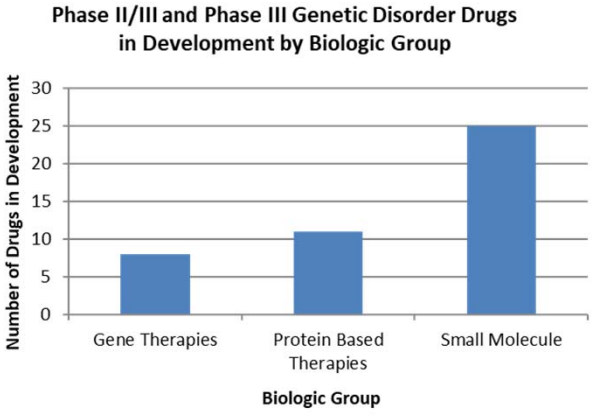




Sources: 1. Orphan Drugs in the United States Growth Trends in Rare Disease Treatments. IQVIA Institute. October 2018. 2. Addressing challenges in the diagnosis and treatment of rare genetic disorders. Nature Reviews Drug Discovery. 2018.

Explore

Explore the importance of data & evidence regarding current & upcoming gene therapies/genetic-informed treatments



Approach to treatment depends on mutation type

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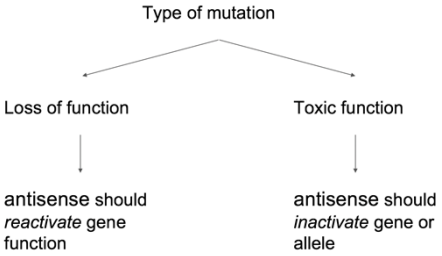

Gene therapy to replace function

Gene editing to restore gene function

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Spinal Muscular Atrophy

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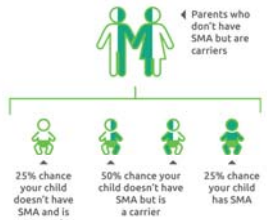
#1 SMA is a progressive, rare genetic disease, yet it is the number one genetic cause of infant death.

How SMA is inherited

Spinal muscular atrophy (SMA) is an autosomal recessive disorder. This means a person must inherit one copy of a nonworking or missing gene from each parent to have the disease.

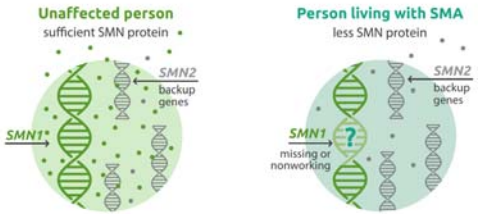


About 1 in 50 people in the United States (or 6 million* Americans) is a genetic carrier of SMA, and most don't know it.

*Calculations are based on an estimated US population of 300 million.

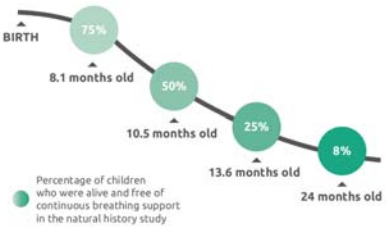
/10K SMA affects about 1 in every 10,000 babies born each year.

The *SMN1* and *SMN2* genes



SMA Type 1 is life threatening

Only 8% of children in the natural history of SMA Type 1 were alive and free of continuous breathing support at 24 months old. Continuous breathing support means that children needed a machine to help them breathe for at least 16 hours per day for 2 weeks or more.



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Spinal Muscular Atrophy Gene Therapy

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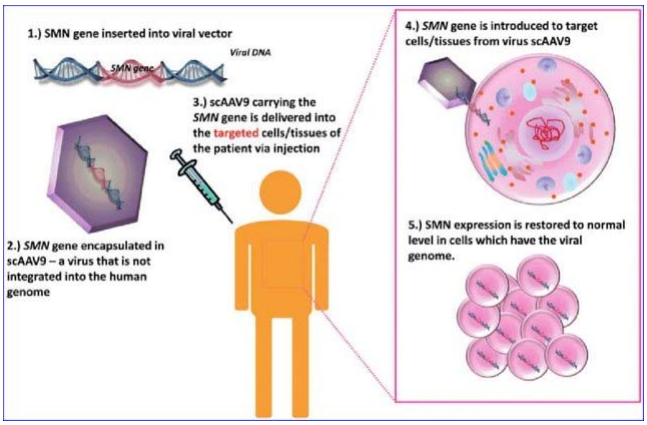
Exploring the evidence:

1. FDA approval/indication
2. Evidence:
   1. Number of publications
   2. Journal quality
   3. Author independence
   4. Who paid for study?
   5. Experimental design
   6. Number of subjects
   7. Relevance of end-points
   8. Statistical tests use
   9. P-values
3. Cost effectiveness - QALYs



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Onasemnogene abeparvosec vs Nusinersen

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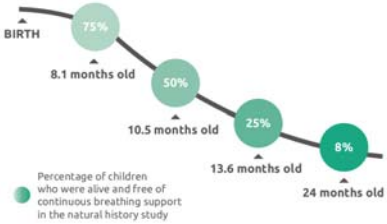
- FDA approved 2019
- 36 publications

- Expected predicted survival 37.2 life years for AVXS-101 (discounted QALYs, 15.7)
- AVXS-101 $2.5-5.0M/treatment.
- Average lifetime cost/patient: $4.2-6.6M
- Incremental cost-effectiveness ratio -$203,072 –$ nusinersen)



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Patient-specific Antisense Oligonucleotide Therapy for Genetic Diseases
Jinkuk Kim, Ph.D., …Austin Larson, M.D., et al. 2019;381:1644-1652

The NEW ENGLAND JOURNAL of MEDICINE

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- Recessive neuronal ceroid lipofuscinosis 7 (Batten's disease 7)
  - Onset age 2-7
  - Progressive developmental regression, speech impairment, loss of vision, personality disorders
  - Most nonambulatory 2 years after onset
  - Death/vegetative state with intractable seizures age ~12
- Proband
  - Onset age 3
  - Diagnosis age 6
  - 1 year development of patient-specific Antisense Oligonucleotide Therapy

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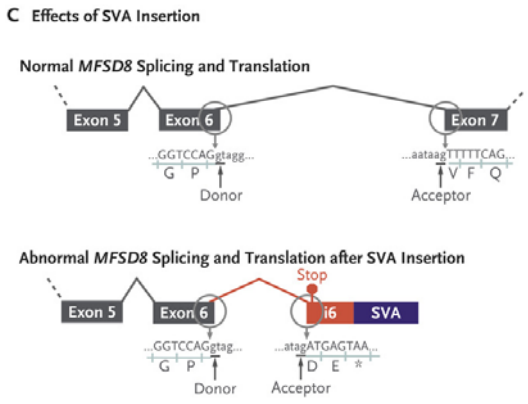
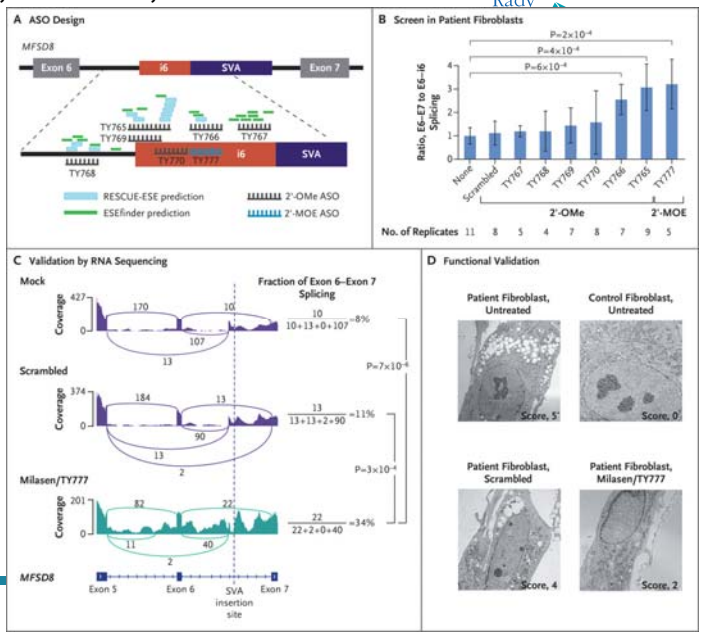


Other allele: *MFSD8* c.1102G>C



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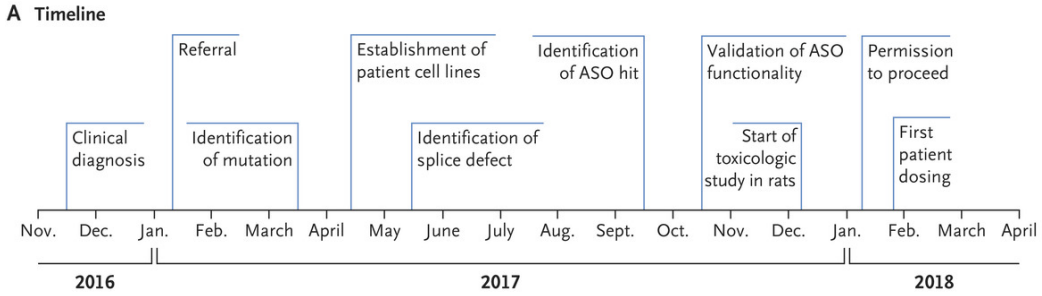
- Treatment started age 7
- Before: 15-30 seizures/day x 1-2 mins
- After: 0-20 seizures x < 1 min. No significant adverse events



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Summary

Rady Children's Institute Genomic Medicine

Explain	Genetics/genomics will increasingly drive treatment plans for individuals with chronic or critical illness especially rare genetic diseases
Identify	There exists a dearth of authoritative resources of evidence for genomic / precision medicine. GeneReviews and GTRx are two examples
Explore	Ongoing case-based education is needed to upskill MDs regarding current & upcoming gene therapies/genetic-informed treatments