



**Central Pennsylvania Clinic**  
 A Medical Home for Special Children & Adults  
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D. Holmes Morton MD, Senior Physician, Consultant in Pediatrics, Metabolism, and Genomic Medicine

**SUMMARY within two families – the mothers of the two infants are sisters – unrecognized cases of two lethal recessive genetic disorders – BRAT1 & TSPYL - led to prolonged NICU stays for weeks of medically futile care.** Combined medical bills for emergency transport, medical tests, and prolonged NICU management exceeded \$3-million dollars. Parents at risk can be identified by targeted gene mutation tests for specific BRAT1 & TSPYL mutations or by Plain-Insight-Profiles. Midwife & Physician Awareness of an infant at risk allows immediate recognition by physical exam and cord blood diagnosis confirms the presence of a lethal genetic disorder.

**21 Mar 2026:** I was called by the grandfather, Jonas [REDACTED] of a baby named Abram [REDACTED] - parents Daniel & Katie [REDACTED] [REDACTED]. Daniel is Jonathan [REDACTED] brother, Jonathan & Leah [REDACTED] – Leah has PK deficiency and they have a baby Martha who has Gitelman disorder. Katie is the sister of Mary [REDACTED] who is married to Shem [REDACTED] – Shem & Mary had the infant Linda at Hershey described below, who had TSPYL.

**PIP RESULTS FOR A BROTHER OF DANIEL’S** – We know Daniel had a 67% risk of carrying BRAT1 c638dupA and CHRNG c.459\_460dup, another lethal disorder, and his wife had a 67% chance of carrying TSPYL p.X.

D

*Established Pediatric and/or Adult Onset Disease Variants (Tier 1):*

Disease	Gene	c.name	p.name	Res	Inheritance	Interpretation
PHENYLKETONURIA	PAH	c.284_286delTCA	p.Ile95del	0/1	recessive	carrier
CILIARY DYSKINESIA, PRIMARY, 5	HYDIN	c.2047G>T	p.Glu683*	0/1	recessive	carrier
MULTIPLE PTERYGIUM SYNDROME, ESCOBAR VARIANT	CHNG	c.459_460dupA		0/1	recessive	carrier
HEREDITARY HEMOCHROMATOSIS	HFE	c.845G>A	p.Cys282Tyr	0/1	recessive	carrier
LETHAL NEONATAL RIGIDITY AND MULTIFOCAL EP...	BRAT1	c.638dupA	p.Val214Glyfs	0/1	recessive	carrier
GITELMAN SYNDROME	SLC12A3	c.1-1471_893del		0/1	recessive	carrier

*Predicted Pediatric and/or Adult Onset Disease Variants (Tier 2):*

CORTICOSTEROID-BINDING GLOBULIN DEFICIENCY	SERPINA6	c.344T>A	p.Leu115His	0/1	recessive	carrier
RETINITIS PIGMENTOSA 26	CERKL	c.1164_1165delTG	p.Cys388fs	0/1	recessive	carrier

Midwives were Tina Byler & Mary Catherine - they offered PIPs, parents declined. Why? The Cost of \$150 seemed high. **Starting April 20th, the PIP will be \$350 / sample or \$650 / couple (if sent at the same time).** The result of this price increase will be more refusals of the test and more examples of lost opportunities for early diagnosis & intervention of both treatable & untreatable disorders. Their baby was delivered at Lewistown - **Why was the transfer made from mid-wife to Lewistown?** – and, he was immediately Life-Flighted to Danville to the NICU.

After transport to the NICU there were several weeks of NICU-care including a cooling blanket and phenobarbital induced coma with ventilation. EEG monitoring probably showed seizures which were thought to be the result of birth asphyxia. Brain CT scans & MRIs were done. Meningitis was treated empirically and ruled out by cultures. The accumulated cost of

futile care has been more than \$1-million. The midwives in Kish Valley & physicians at Geisinger did not remember, or recognized, the BRAT1 phenotype.

When was targeted testing set to CSC?

I talked to the mother & grandfather and told them I'd call the NICU and talk to an attending.

Daniel & Katie live near Allenville and will need home hospice care.

RACHEL [REDACTED] DOB [REDACTED]

## **CONSULT IN NICU: D. Holmes Morton MD July 20, 2012 NOTES FROM A HOME VISIT IN LANCASTER COUNTY 7 26 2012 –**

*Discharged home on nasogastric feedings of mother's milk 8 – 10 oz per day to advance as tolerated to 12-14 oz.*

*Birthweight ~ 2.5 kg. Mother and Mid-wife, Marsena Howard, will weigh periodically. No apparent desaturations, apneic or bradycardic episodes. The parents do have home O2 but have not used it.*

*EXAM shows the typical overlap of coronal sutures. She does open her eyes. She is mildly jaundiced. HEENT – No dysmorphic facial features. Palate intact. Lungs clear. No murmurs and perfusion is normal. ABD soft, no enlargement of spleen or liver. GU female. EXT nl. NEUROLOGICAL Her exam is dominated by generalized co-contraction of opposing muscle groups. This dystonic rigidity decreases in sleep. Frequent, brief, multifocal seizures or myoclonic jerks are seen, including some high-pitched abnormal vocalizations and an absence of normal suck & swallow. Muscle development normal. DTR cannot be obtained because of rigidity.*

*Rachel is not on anti-convulsants. I suggested a trial of Benadryl 6 mg BID and/or diazepam 1 mg BID. Parents at this time have declined to use medications.*

*John and Rachel Esh and Mel King and his wife have visited the Stoltzfus'.*

## **CONSULT IN NICU: D. Holmes Morton MD July 20, 2012**

**A DNA sample was sent to the lab for Trisomy 18 testing. I examined the infant and did not find features of T-18 except for clasped thumbs and full body rigidity. A cardiac echo was normal. Fetal movements were decreased and she had maintained a foot-presentation through the later stage of a 35-week pregnancy. Mom was not aware of seizure activity before birth. The infant did not suck & swallow, had a faint cry, and was increasingly stiff post-delivery. Observations suggest continuous multifocal seizure activity. This presentation is consistent with a newly reported autosomal recessive disorder arising from a mutation in a gene called BRAT1.**

**TESTING FOR THE DISORDER WAS COMPLETED ON 7/21/2012 AT 9:30 AM AND WAS POSITIVE – HOMOZYGOUS FOR MUTATIONS IN BRAT1. This conforms the diagnosis of “Lethal neonatal rigidity and multifocal seizure syndrome,” which is described below.**

## **Genetic Mapping and Exome Sequencing Identify Variants Associated with Five Novel Diseases**

Erik G. Puffenberger<sup>1,2\*</sup>, Robert N. Jinks<sup>2</sup>, Carrie Sougne<sup>3</sup>, Kristian Cibulskis<sup>3</sup>, Rebecca A. Willert<sup>2</sup>, Nathan P. Achilly<sup>2</sup>, Ryan P. Cassidy<sup>2</sup>, Christopher J. Fiorentini<sup>2</sup>, Kory F. Heiken<sup>2</sup>, Johnny J. Lawrence<sup>2</sup>, Molly H. Mahoney<sup>2</sup>, Christopher J. Miller<sup>2</sup>, Devika T. Nair<sup>2</sup>, Kristin A. Politi<sup>2</sup>, Kimberly N. Worcester<sup>2</sup>, Roni A. Setton<sup>2</sup>, Rosa DiPiazza<sup>2</sup>, Eric A. Sherman<sup>4</sup>, James T. Eastman<sup>5</sup>, Christopher Francklyn<sup>6</sup>, Susan Robey-Bond<sup>6</sup>, Nicholas L. Rider<sup>1,2,7</sup>, Stacey Gabriel<sup>3</sup>, D. Holmes Morton<sup>1,2,7</sup>, Kevin A. Strauss<sup>1,2,7</sup>

<sup>1</sup> Clinic for Special Children, Strasburg, Pennsylvania, United States of America, <sup>2</sup> Department of Biology and Biological Foundations of Behavior Program, Franklin & Marshall College, Lancaster, Pennsylvania, United States of America, <sup>3</sup> The Broad Institute, Boston, Massachusetts, United States of America, <sup>4</sup> Department of Biology, Swarthmore College, Swarthmore, Pennsylvania, United States of America, <sup>5</sup> Department of Pathology and Laboratory Medicine, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin, United States of America, <sup>6</sup> College of Medicine, University of Vermont, Burlington, Vermont, United States of America, <sup>7</sup> Lancaster General Hospital,

Abstract: The Clinic for Special Children (CSC) has integrated biochemical and molecular methods into a rural pediatric practice serving  
Among the Plain people, we have used single nucleotide polymorphism (SNP) microarrays to genetically map recessive disorders to large  
that contain many genes (mean = 79). For some, uninformative mapping or large gene lists preclude disease-gene identification by Sang  
for exome sequencing at the Broad Institute; all had been previously mapped at the CSC using low density SNP microarrays coupled with  
1 and 5 patient samples per disorder, we identified sequence variants in the known disease-causing genes SLC6A3 and FLVCR1, and p  
of variants identified in TUBGCP6, BRAT1, SNIP1, CRADD, and HARS. Our results reveal the power of coupling new genotyping technologies  
and robust clinical data.

### ***Lethal neonatal rigidity and multifocal seizure syndrome.***

*Episodic jerking begins in utero. Newborns have small heads (1.5 to 2 SD below normal for age), overlapping cranial sutures, small or absent fontanelles, and depressed frontal bones. Hands are fisted and extreme axial and limb rigidity prohibit volitional movements and tendon reflexes. Brief focal jerks of the tongue, face and arms are prominent soon after birth and occur in a nearly continuous sequence throughout each child's short life. Neuroimaging is normal or reveals mild hypoplasia of the frontal lobes. Electroencephalograms show bilateral medium- high voltage spikes over temporal and central regions, frequent multifocal seizures, background slowing, and no posterior rhythm.*

*Seizures are only partially responsive to anticonvulsants and not affected by high-dose pyridoxine.*

*Affected children have stagnant head growth, remain visually inattentive, do not feed independently, and make no developmental progress. They have frequent spontaneous apnea and bradycardia that uniformly culminates in cardiopulmonary arrest before age 4 months.*

*The brain of a child who died at 4 weeks of age was small, weighed 382 grams (expected for age 433 +/2 50 g), but was otherwise normally developed. Primary lesions were localized to most regions of the corpus striatum and cerebral cortex with relative sparing of the anterior caudates and parietal lobes. Lesions consisted of neuronal loss associated with a striking microglial reaction and proliferation of Alzheimer type 2 astrocytes (Figure 1, A–C). Loss of BRAT1 gene function affects DNA repair, mitochondrial function and replication. BRAT1 is a mitochondrial depletion syndrome not unlike POLG.*

BRAT1 deficiency is indeed a severe, autosomal recessive mitochondrial disease that shares phenotypic similarities with POLG-related disorders, often presenting as a severe infantile mitochondrial depletion syndrome

. Wiley Online Library +1

While **POLG** mutations directly affect the catalytic subunit of DNA Polymerase Gamma—the engine responsible for replicating mitochondrial DNA (mtDNA)—**BRAT1** (BRCA1-associated protein required for ATM activation-1) acts as a nuclear-encoded protein that, when deficient, induces severe mitochondrial dysfunction and fragmentation.

National Institutes of Health (.gov) +2

### **Key Similarities and Comparisons:**

- **Clinical Presentation:** Both can present with severe neurodevelopmental issues, including refractory epilepsy, microcephaly, spasticity, and severe motor delays. BRAT1 is specifically associated with Lethal Neonatal Rigidity and Multifocal Seizure Syndrome (RMFSL).
- **Pathophysiology:** BRAT1 knockdown leads to reduced mtDNA-encoded protein expression, decreased ATP production, and increased Reactive Oxygen Species (ROS), mimicking the "bioenergetic crisis" seen in POLG depletion syndromes.
- **Disease Spectrum:** Similar to POLG, BRAT1 mutations show a spectrum of severity, with some cases presenting as rapidly fatal, while others show slower progression (moderate severity) with survival past infancy.
- **Molecular Mechanism:** While POLG directly replicates mtDNA, BRAT1 is thought to regulate mitochondrial fission/fusion dynamics and mitochondrial-dependent apoptosis.

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Although both are classified under the umbrella of mitochondrial diseases and share clinical features like early-onset epilepsy, they arise from distinct defects in mitochondrial maintenance (DNA replication for *POLG* vs. mitochondrial dynamics/metabolism for *BRAT1*).

RECESSIVE DISORDERS THAT PRESENT IN NEONATES WITH SIMILAR LETHAL NEUROLOGICAL PHENOTYPES

- **BRAT1** Lethal neonatal seizures with diffuse brain degeneration
- **CHRNA3** Congenital Myasthenia Syndrome, Obstructive Breathing, Multiple Pterygium, Arthrogyposis, Scoliosis & Tethered Cords
- **GLB1** GM1 gangliosidosis, nystagmus, seizures, apnea & bradycardia
- **LONP1** CODAS syndrome, Abnormal Pharyngeal Innervation, Seizures, Often Lethal in Infancy Because Airway Obstruction & Aspiration
- **POMT1** Lethal Brain Malformations, Hydrocephalus, Muscular Dystrophy
- **TSPYL** Lethal Neonatal Apnea & Bradycardia, Brainstem & Cortical Malformations
- **ZDHHC16** Lethal Neonatal Apnea & Bradycardia, Brainstem, Cortical Malformations

LETHAL DISORDERS OF INFANCY-RECESSIVE THAT PRESENT A SIMILAR NEUROLOGICAL PHENOTYPE	GENE & VARIANT	MAF % Minor Alleles in 640	Carriers per 1000 = (2pq*1000)	Cases per 1000 births = q^2*10,000	Cases per 10,000 = q^2*10,000
WDR73 - Yoder Dystonia & Nephrotic Syndrome	WDR73 c.888delT; p X	1.56%	31	0.2	2
Lethal Apnea & Bradycardia	TSPYL c.457dupG; p X	1.56%	31	0.2	2
Lethal Seizures & Rigidity	BRAT1 c.226A.G; p.Met76Val	1.56%	31	0.2	2
Brain Palmatation Hypoplasia Syndrome	ZDHHC16 c.4C>T;p.Arg2X	1.50%	29	0.2	2
Multiple pterygium syndrome, escobar variant	CHRNA3 c.459_460dupA	1.25%	25	0.2	2
GM3 Synthase Deficiency	ST3GAL5 c.862C>T; p.Arg288*	1.25%	25	0.2	2
GM1 Gangliosidosis	GLB1 c.902C>T; p.Ala301Val	1.09%	22	0.1	1
Cockayne	ERCC6 c.2709+1G>TX	0.94%	19	0.1	1
Walker-Warburg Syndrome	POMT1 c.777_778insA; p.cys260fs	0.2%	3	0.0	0.02
Walker-Warburg Syndrome (Javin Hoover)	POMT1 c.818C>T; p.Pro273Leu	0.2%	3	0.0	0.02
Codas Syndrome	LONP1 c.2161C>G; p.Arg721Gly	0.16%	3	0.0	0.02
	COMBINED AVERAGE MAF	1.02%	20.0	0.1	1.3

AI 21 Mar 2026

BRAT1 genetic disorder is a rare, autosomal recessive, neurodevelopmental, and epileptic encephalopathy primarily causing [Lethal Neonatal Rigidity and Multifocal Seizure syndrome \(RMFSL\)](#). It is characterized by severe, often fatal, infantile seizures, microcephaly, and rigid muscle tone due to biallelic mutations in the *BRAT1* gene, affecting DNA repair and mitochondrial function.

Nature +3

#### Key Aspects of BRAT1-Related Disorders:

- **Clinical Presentation:** Severe neonatal-onset epilepsy (often refractory), profound hypotonia that evolves into hypertonia/rigidity, microcephaly, and developmental arrest.
- **Disease Spectrum:**

RMFSL is the most common, usually fatal before age 2. A milder, less common, or moderate phenotype exists, termed Neurodevelopmental Disorder with Cerebellar Atrophy and Seizures (NEDCAS).
- **Genetics:** Autosomal recessive; caused by biallelic mutations (compound heterozygous or homozygous) in the *BRAT1* gene.
- **Diagnosis:** Confirmed via genetic testing (whole-exome sequencing).
- **Prognosis:** Historically, most cases are fatal within infancy due to respiratory failure or status epilepticus, though some, particularly in the milder spectrum, may survive longer.

Nature +6

#### Key Functions of the BRAT1 Protein:

- **DNA Repair & Signaling:** Acts as an activator for the ATM kinase, crucial for responding to DNA damage.
- **Mitochondrial Regulation:** Involved in maintaining mitochondrial function, and its loss can increase cellular apoptosis.
- **Brain Development:** Essential for neuronal growth and survival.

ScienceDirect.com +4

There is currently no specific cure for BRAT1-related disorders; treatment is supportive and focused on seizure management.

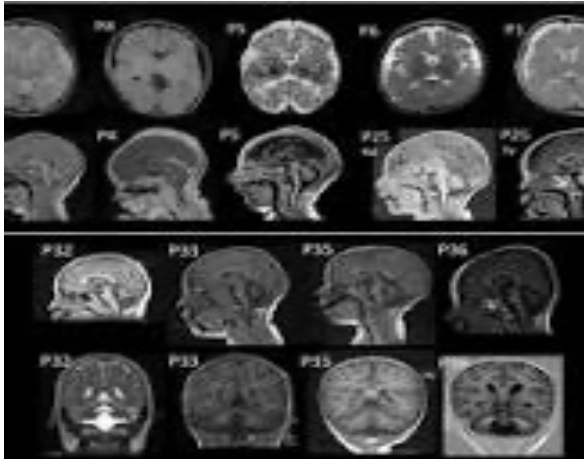
National Institutes of Health (.gov) +3

- BRAT1-related disorders: phenotypic spectrum and phenotype-genotype correlations from 97 patients | European Journal of Human Genetics

BRAT1, or BRCA1-associated protein required for ATM activation-1, is a nuclear protein that interacts with ATM and BRCA1. BRAT1 is...

Nature

- **BRAT1-mutation-causes-lethal-neonatal-rigidity-and-multifocal-seizure-syndrome**  
This is an autosomal recessive epileptic encephalopathy. Reported cases are limited, but in all but two cases, the infant died bef...



aesnet.org

- **BRAT1 | Test catalog - Invitae**  
Associated disorders. The BRAT1 gene is associated with a spectrum of autosomal recessive conditions including neonatal-lethal rig...

GDF15 (Growth Differentiation Factor 15) is increased in mitochondrial depletion syndromes as a biomarker of the [Integrated Stress Response \(ISR\)](#), triggered by cellular stress from mitochondrial failure. Mitochondrial dysfunction activates transcription factors, notably ATF4 and CHOP, which drive high production of GDF15 to help cells cope with energy deficits and maintain homeostasis.

Mayo Clinic Laboratories +3

### **Mechanism of Elevated GDF15:**

- **Integrated Stress Response (ISR) Activation:** Mitochondrial depletion leads to inefficient oxidative phosphorylation, creating severe cellular stress.
- **ATF4 and CHOP Signaling:** This stress triggers a signaling pathway that results in the activation of the transcription factor ATF4, which in turn induces GDF15 expression.
- **Mitokine Release:** GDF15 functions as a "mitokine," a signalling protein released by stressed mitochondria to signal metabolic distress to other tissues.

National Institutes of Health (.gov) +4

## Significance:

- **Diagnostic Biomarker:** Because GDF15 is heavily overexpressed in response to mitochondrial dysfunction, it is used as a sensitive serum biomarker for mitochondrial diseases.
- **Clinical Relevance:** Elevated GDF15 levels correlate with disease severity, fatigue, and muscular symptoms in patients with mitochondrial depletion and damage.
- **Systemic Response:** It is believed that this increased expression is an adaptive response to manage mitochondrial dysfunction and related metabolic disorders.

Mayo Clinic Laboratories +4

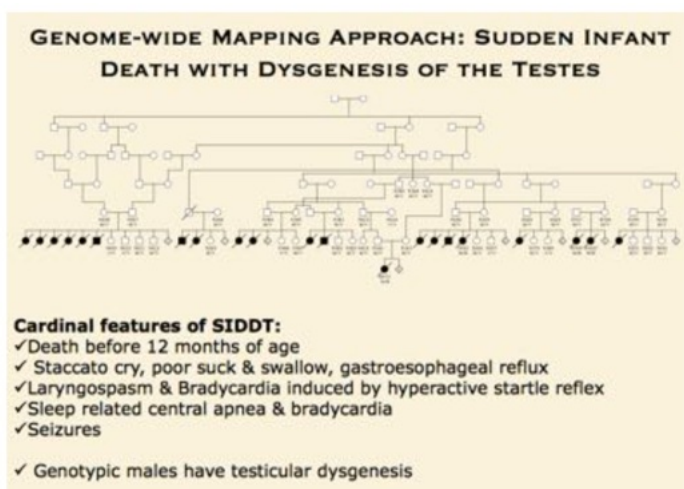
## TSPYL – CASE STUDIES AND NEUROPATHOLOGY

### D. Holmes Morton MD

December 19, 2014

**SIDDT** A 7 month old infant died suddenly at home while being fed in the middle of the night by her 14-year old sister. She gagged, became apnic, bradycardic, and died. She was the fifth child in her family with a recessive disorder characterized by a weak peculiar cry, poor feeding, trunkal hypotonia, and an exaggerated startle reflex that causes obstructive apnea and bradycardia. An autopsy was ordered by the Coroner because the infant had not been seen by a doctor before her death. She was found to be *male* with ambiguous genitalia. **In the autopsy report the gross and microscopic examination of the brain was mistakenly reported to be “normal.”**

*Mapping of sudden infant death with dysgenesis of the testes syndrome (SIDDT) by a SNP genome scan and identification of TSPYL loss of function.* Proc Natl Acad Sci U S A. 2004 Aug 10;101(32):11689-94. Epub 2004 Jul 23. Puffenberger EG, Hu-Lince D, Parod JM, Craig DW, Dobrin SE, Conway AR, Donarum EA, Strauss KA, Dunckley T, Cardenas JF, Melmed KR, Wright CA, Liang W, Stafford P, Flynn CR, Morton DH, Stephan DA.



After our paper about SIDDT was published in 2004, Dr. HC Kinney in Boston re-examined the brain of the infant. She reported hypoplasia of the inferior olives. This important landmark on the ventral brainstem existed as only a few isolated cells. She also described diffuse malformations of the posterior reticular formation. The brainstem malformations are likely the cause of apnea, bradycardia and sudden death. Pneumograms of SIDDT infants show severe apnea, both central and obstructive, associated with prolonged periods of bradycardia, and hypoxia. SIDDT infants do not suck, swallow, or protect

their airway. Aspiration pneumonias are common. Their cries are pathological - staccato, goat or lamb-like – and likely indicate pathological innervation of the larynx and hypopharynx. Death typically occurs suddenly as a result of an exaggerated startled reflex, as in infants with hyperekplexia syndromes.

NOTE – The impression that TSPYL is a common disorder is the results of a few families having many affected children. The Minor Allele frequency of the variant in the population is relatively low BRAT1 MAF 1.56%, 31-carriers/1000 people, (969-non-carriers/1000 people), 2 cases per 10,000 births. This is true for all the lethal disorders in the Table below – the average MAF is 1%, 20 carrier/1000, 980-non-carriers per 1000. A young person who knows she is a carrier for BRAT1 or TSPYL will find 969 & 980 non-carriers in the community...It is relatively easy to avoid specific diseases if the carrier-tests or Family Risk Tests are affordable and easily obtained at the place like the Central PA Clinic.

LETHAL DISORDERS OF INFANCY- RECESSIVE THAT PRESENT A SIMILAR NEUROLOGICAL PHENOTYPE	GENE & VARIANT	MAF % Minor Alleles in 640	Carriers per 1000 = (2pq*1000 )	Cases per 1000 births = q <sup>2</sup> *10 00)	Cases per 10,000 = q <sup>2</sup> *10,0 00)
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	COMBINED AVERAGE MAF	1.02%	20.0	0.1	1.3

*Subtle developmental abnormalities in the inferior olive: an indicator of prenatal brainstem injury in the sudden infant death syndrome.* J Neuropathol Exp Neurol. 2002 May;61(5):427-41. Kinney HC, McHugh T, Miller K, Belliveau R, Assmann SFD. After being told the brain of the TSYPL was “normal.” I asked that the autopsy slides be sent to Dr.

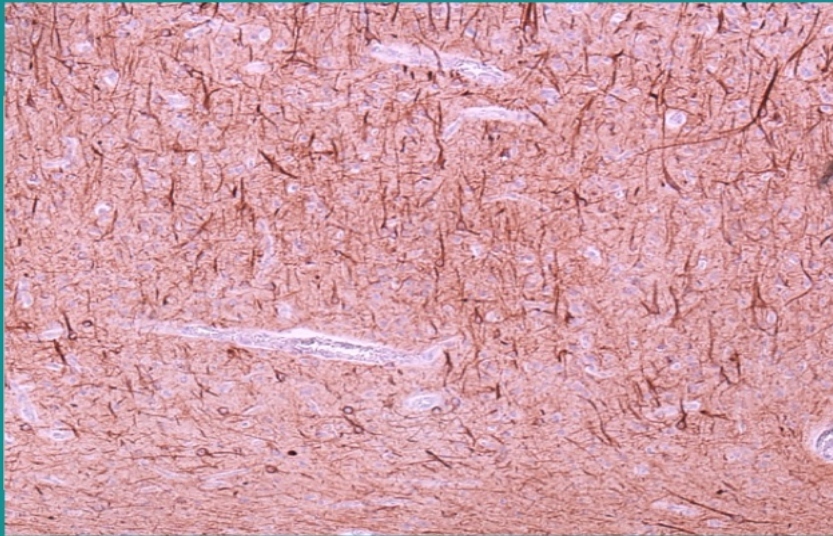
Kinney at Children’s of Boston because of this paper. Dr. Kinney did find the inferior olives were grossly abnormal – virtually absent. In fact the brain was everywhere abnormal. Dr. Kinney would not issue a formal neuropathology report of her findings because she did not want to anger or embarrass the neuropathologist at Hershey Medical Center.

I recruited my friend and the renowned neuropathologist Dr. Lucy Rorke at Children’s of



Philadelphia to re-examine the brain of the SIDDT above infant. *Neu-N Stains* revealed diffuse abnormalities in neuronal migration. Pathological collections of neurons were found throughout the white matter as a result of arrested migration of cortical neurons early in fetal life. TSPYL is a lethal brain malformation syndrome with undeveloped brain-stem ganglia – atrophic inferior olives - causing recurrent aspirations and ultimately a fatal episode of apnea & bradycardia. The cerebral cortex was also diffusely abnormal and patients have abnormal EEGs and intractable seizures.

## Cortex Neurofilament 10 X



*Neurofilament Staining* showed abnormal orientation of neuronal cell bodies and axons, particularly within cortical layers IV & V. Parents do observe seizure activity in these infants. EEGs show diffuse background slowing but are not diagnostic of seizures. As is often true in infants, seizure remains a clinical diagnosis. Little is known about how the gene TSPYL1 is involved human brain-stem and cortical development.

### MOLECULAR FEATURES OF TSPYL IN AN ANIMAL MODEL:

*OMIM As with the mouse Tspyl gene, the human TSPYL gene appears to lack introns. RT-PCR detected human TSPYL expression in the 3 tissues tested, namely liver, kidney, and smooth muscle. Northern blot analysis and RT-PCR showed ubiquitous expression of mouse Tspyl1, with testis, ovary, prostate, brain, spleen, kidney, lung, heart, and liver tested.*

Vogel, T., Dittrich, O., Mehraein, Y., Dechend, F., Schnieders, F., Schmidtke, J. **Murine and human TSPYL genes: novel members of the TSPY-SET-NAP1L1 family.** Cytogenet. Cell Genet. 81: 265-270, 1998.

SIDDT – TSPYL by family history and exam. – dystrophic testes, micro penis, staccato cry, frequent changes in perfusion, respiratory effort, continuous posturing, which may be seizure-equivalents, and startle associated with breath holding.

He was febrile and heavily bundled when first seen T105 decreased to 100 over 20 minutes with no intervention. His lungs were clear, respiratory efforts irregular as is typical for SIDDT, O2 saturations were >95% but with frequent changes in perfusion associated with posturing and apnea. His fontanel was widely open and soft.

Shem & Mary's first infant Linda was in the NICU on ventilation for 10- weeks or more before it was recognized that she was male and was respirator dependent because of SIDDT. Once this diagnosis was made Linda was removed from the ventilator and died immediately. They specifically asked that Daniel not be subjected to futile medical interventions and asked to be allowed to take him home. They believed that once in hospital it would be difficult to prevent progressive interventions for respiratory distress or apnea and that given the natural history of the disorder that these interventions were futile...including antibiotics...

The decision to refuse hospital care was discussed with Mary's parents who agreed with Shem's decision. Shem's parents Daniel and Elizabeth [REDACTED] were killed last summer in a car-buggy accident...He talked openly about wanting his father's advice but believed that he would have agreed with him not to intervene

The screenshot shows a laboratory information system interface. At the top, there are tabs for 'Data', 'Other Tests', 'Invoice', and 'Genes and Diseases'. Below these, patient information is displayed: CSC # 37240, Login\_date 8/17/2015, and Login time 8:14 PM. The 'Ordering physician' section lists several doctors, with D. Holmes Morton, MD selected. The 'Additional data' section shows the father as Shem Swarey and the mother as Mary (Peachey). The 'Samples delivered to the lab' section has checkboxes for various sample types, with 'Cord blood' checked. The 'Supplemental instructions' section has checkboxes for STAT, Sendout, and Pipeline. At the bottom, a table shows the test order details:

Procedure	Specific Test	Billing Category	U Price	Quant.	Cost
DNA Isolation (CSC)		Billable	\$15	1	\$15

SIDDT is a universally fatal disorder that arises from mutations in TSPYL, which gives rise to diffuse neuronal migration abnormalities affecting cortical layering and the brain stem. Death is caused by apnea and cardiovascular instabilities. Infants also have continuous posturing and startling with are likely seizure-like events.

BRAT1 CASE AT GEISINGER 10-YEAR LATER: PLAIN-INSIGHT-PROFILES ARE NOW AVAILABLE TO FIND AT RISK FAMILIES/PARNETS: I have recently learned of the diagnosis of an Amish infant with BRAT1. He has been in the NICU at Geisinger for 3-weeks. This is an invariably lethal variant BRAT1 c.226A.G; p.Met76Val first described in our paper in 2012 *Genetic Mapping and Exome Sequencing Identify Variants Associated with Five Novel Diseases* in PLoS1. A few months after our publication a highly recognized effort to use rapid whole-exome-sequencing to investigate ill neonates in a NICU at Kansas City Children's uncovered compound heterozygous variants in BRAT1 as the cause of intractable seizure in an infant with Mexican ancestry. BRAT1 is 14 years later in 2026 one of many disorders associated with mitochondrial DNA depletion as the cause of progressive brain degeneration. Another mitochondrial depletion syndrome is found the Anabaptist Population – POLG, the two known variants are c.1399G>A; p.Ala467Thr and c.752C>T p.Thr251Ile. These POLG variants are relatively common in European populations.

There are 11 additional gene-variants that cause at least 90% of the infants deaths in the Amish-Mennonite populations of Central Pennsylvania. For each disorder a gene-variant is known and targeted pcr-based testing can be done in a CLIA Certified Molecular Lab run at the *Clinic for Special Children* in Lancaster County.

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Lethal Apnea & Bradycardia	TSPYL c.457dupG; p X	1.56%	31	0.2	2
Lethal Seizures & Rigidity	BRAT1 c.226A.G; p.Met76Val	1.56%	31	0.2	2
Brain Palmatation Hypoplasia Syndrome	ZDHHC16 c.4C>T;p.Arg2X	1.50%	29	0.2	2
Multiple pterygium syndrome, escobar variant	CHRNA10 c.459_460dupA	1.25%	25	0.2	2
GM3 Synthase Deficiency	ST3GAL5 c.862C>T; p.Arg288*	1.25%	25	0.2	2
GM1 Gangliosidosis	GLB1 c.902C>T; p.Ala301Val	1.09%	22	0.1	1
Cockayne	ERCC6 c.2709+1G>TX	0.94%	19	0.1	1
Walker-Warburg Syndrome	POMP1 c.777_778insA; p.cys260fs	0.2%	3	0.0	0.02
Walker-Warburg Syndrome (Javin Hoover)	POMP1 c.818C>T; p.Pro273Leu	0.2%	3	0.0	0.02
Codas Syndrome	LONP1 c.2161C>G; p.Arg721Gly	0.16%	3	0.0	0.02
	COMBINED AVERAGE MAF	1.02%	20.0	0.1	1.3
	TOTAL CASES PER 10,000 births				15

At the Central PA Clinic we offer a genetic risk panel to parents – Plain Insight Profile - which includes all of the above gene-variants and more than 1400 pathogenic gene-variants that were found by extracting data form approximately 15,000

whole exomes completed by the *Clinic for Special Children, Das Deutsch Center for Special Needs in Ohio*, and the *University of Maryland Amish Research Center*. This 900-Gene & 1400-pathogenic variant genotype is routinely offered to parents by regional midwives. Over the past 10 years aggregated data from the *Plain Insight Profile* has allow me to create a couple gene-variant database for 300-couples, 600-people, 1200-alleles for a small sub-population of approximately 10,000 Amish/Mennonite people where there are 500-1000 births per year. The gene-variant database can be sorted by gene and for any one pathogenic gene-variant allows an estimation of the **minor-allele-frequency** which can be used in the Hardy Weinberg Equation to estimate carriers-per-1000 people and disease incidence-per-10,000 births. For the 11 disorders listed above the total number of cases would be approximately 15-affected infants/10,000 births.

When parents elect to have the genetic risk profile done we can see those at risk for one of these lethal disorders, do cord-blood tests to identify affected infants with the single targeted mutation test guided by the parents carrier test. Although these are untreatable disorders, all with lethal effects upon the brain. Immediate diagnosis does not change outcome but it does help control costs for futile NICU interventions. In the single family in which the BRAT1 diagnosis was made, two sister have had infants with two different lethal disorders - BRAT1 & TSPYL.

The recent BRAT1 case was cared for through the Geisinger Medical Center. Midwives had offered parents the Plain-Insight-Profile and they declined the test. After labor started the mother was transferred to a regional hospital because poor progress during delivery and unstable fetal heart rates. After delivery the infant was immediately Life-Flighted to Danville to the NICU for presumed asphyxia during labor and delivery – “evolving cerebral palsy.” Admission to the NICU was followed by several weeks of NICU-care including phenobarbital induced coma with ventilation and a cooling blanket. EEG monitoring showed chaotic brain waves which were presumed to be the result of birth asphyxia. Meningitis was treated empirically and ruled out by cultures. Brain CT scans & MRIs were done. Tests to define the neurological problems and the accumulated daily costs of futile NICU care totals more than \$1.5-million.

Neither the midwives in Kish Valley nor the NICU physicians at Geisinger recognized the BRAT1 phenotype - overlap of coronal sutures & a small head – microcephaly. These infants do not open their eyes to make visual contact, the cry is abnormal, respiratory & heart rate control is poor – frequent apnea & bradycardias. The neurological exam is dominated by generalized co-contraction of opposing muscle groups - dystonic rigidity. There are frequent, brief, multifocal seizures or myoclonic jerks, often associated with high-pitched abnormal vocalizations and an absence of normal suck & swallow. DTR cannot be obtained because of dystonic rigidity. For health care providers who are familiar with the disorder, the phenotype allows diagnosis and a single molecular test confirms the diagnosis.

The mother of the BRAT1 infant was familiar with the second lethal neurological disorder TSPYL c.457dupG; p X because her sister had two affected infants. Infants who are homozygotes for the Amish TSPYL p.x are also visually inattentive, do not suck & swallow, have a pathological lamb-like cry, and also have severe apnea & bradycardic episodes, which are in many cases the cause of death. Fatal aspirations & aspiration pneumonias are common causes of death.

The first case in her sister’s family had been life-flighted to the NICU at Hershey Medical Center, was also presumed to be birth asphyxia but after 3 weeks could not be weaned from the ventilator. A genetic basis for her disorder was only discovered after 3-weeks of NICU care when a routine chromosome test showed the infant named “Linda” was in fact an Xy-male. I was then asked to do a genetic consult. A distinctive feature of TSPYL -Testes-Specific-Protein-Y-Like - is that male genitalia are underdeveloped and males infant are often mistaken for females. As soon as I heard the reason for the consult, I was able to remind the NICU Staff that our CLIA Certified lab did targeted mutation testing for \$35 and could confirm the diagnosis. I also reminded the physicians that the regional medical center had cared for 9-additional infants before and the pathology department had done the only autopsy on a case of TSPYL. By the time the diagnosis was made and the lethal nature of the disorder recognized the costs for 3-weeks of futile NICU care totaled more the \$1.5-million dollars. The couple later had a second affected infant that was diagnosed at birth, was cared for and died at home without NICU interventions.



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D. Holmes Morton MD, Senior Physician, Consultant in Pediatrics, Metabolism, and Genomic Medicine

THE BROAD IMPLICATIONS OF THESE CASES OF BRAT1 AND TSPYL BEING MANGED AS BIRTH ASPHYXIA AS PART OF A STANDARDIZED, NATIONWIDE, PROTOCOL TO PREVENT “CEREBRAL PALSY.” In retrospect this was obviously Futile Care in a NICU.

WHAT PORTION OF POOR NEUROLOGICAL OUTCOMES CALL "CEREBRAL PALSY" HAVE BIRTH HYPOXIA AS A DEFINITE CAUSE? WHAT PORTION OF POOR NEUROLOGICAL OUTCOMES CALL "CEREBRAL PALSY" HAVE A GENETIC CAUSE?

**Birth hypoxia accounts for less than 10% of cerebral palsy cases, while up to 30% of cerebral palsy cases have a substantial genetic contribution. [1-2]**

In a close population with increased genetic risks like those in Kish Valley the genetic contribution to “Cerebral Palsy” is high – in part because of selected founder gene-variants that are unique to this small-sub-population – THIS IS NOT UNIQUELY AMISH – WORLDWIDE ALL SUB-POPULATIONS HAVE FOUNDER GENE-VARIANTS – that increase the risk of “cerebral-palsy” and a unique collection of genetic disorders in those sub-population.

**Pediatric neurology, what we see more and what we see less**

	Africa	High Income Countries	Background		Africa	High Income Countries	Background
CNS Infections*	+++	+	Viral as well as ABM, parasitic	Spinal cord injury (medical and traumatic)	++	+/-	Generic outcome of burden of infection + trees/trees
HIE	++++	+	¼ of CP cases	Sciatic nerve injury	++	-	Gluteal injections standard of care all ages
Bilirubin Encephalopathy	++	+/-	Delayed to absent phototherapy, no ex transfusion	Neurotrauma	++	+	Mostly traffic and trees
Prematurity	++	++		Paraquat/OP/warfarin	++	-	Agricultural society with ready access
Post anoxic encephalopathy	+++	+	Poor perinatal monitoring, risk assessment	FND: PNEA	++	+	Minimal 1 <sup>st</sup> line healthcare with stigma on MH
Epilepsy	+++	+	Generic outcome of all of above	Chronic daily headache	++	++	No pharmacovigilance
Metabolic disorders	?	+	Unknown	Sydenham Chorea	+	+/-	Steady incidence, mild decrease
Major neurogenetic or neurodevelopmental dis	++	+	No prenatal screening and religious objection	Rabies, tetanus	+	-	Neglected tropical diseases which continue
Vitamin deficiencies	++	+/-	Supplementation is not standard care but incidence is decreasing	ADHD, dyslexia	-	-	Query ADHD: <10 times in 13y. Dyslexia: never.



In Dr. Dekker’s Pediatric Neurology Practice in Tanzania bilirubin toxicity “cerebral-palsy” is extremely common because of neonatal hemolysis caused by extremely high G6PD & Sickle-Cell-Carrier rates - under the evolutionary pressure of malaria in Sub-Sahara Africa. In Kish Valley Amish G6PD deficiency & Sickle Cell carriers do not exist but hemolytic crisis and kernicterus “cerebral-palsy” is cause by unrecognized and poorly managed

pyruvate kinase deficiency. In Dr. Dekker’s population congenital folate deficiency with spina bifida and other congenital CNS & hematological abnormalities are extremely common in the

Massai people because of dietary folate deficiency. In Kish Valley Vitamin K & D deficiencies are extremely common because diet and genetic risks. Unrecognized hemorrhagic disease of the newborn associated with vitamin K deficiency and intractable seizures and arrhythmias associated with congenital vitamin D deficiency will result in “cerebral palsy” or SIDS-like cardiac deaths.

## “The Practice”

Seizures are an important genetic problem for CSC, CPAC & the DDC – as the slides above have shown. In the US 4% of all pediatric hospitalizations are made necessary by seizures.

However, not all seizures are inherited.

SCN1A, SYNGAP1, MECP2, & WDR45 are denovo seizure syndromes that occur in a single case in a family.

**Some seizures are nutritional & preventable: congenital Vit D & K deficiencies caused by maternal malnutrition & should be prevented by prenatal vitamins.**

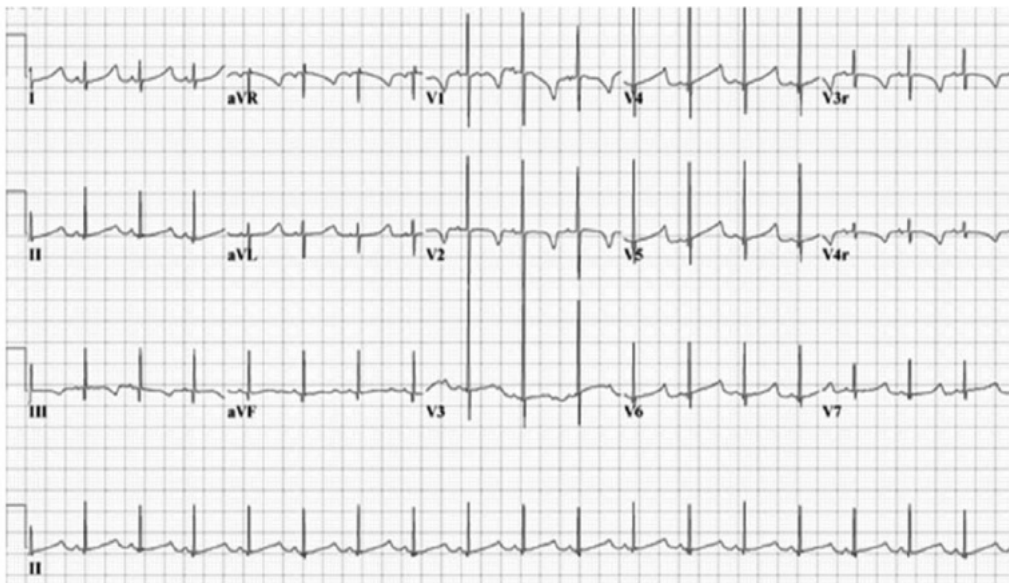
A 1-year-old Amish infant was brought to an emergency room with seizures. Chemistries showed a low calcium – 6.6 mg/dl (8.7-10.5) and high Alk. Phos. 475 u/L (145-320).

His Vit. D level was 7.2 ng/ml (30-100), his mother’s was 13 ng/ml. He had congenital & severe vitamin D deficiency.

**This infant went to 4 emergency rooms and 5 hospitals, at a cost of more than \$75,000, before hypocalcemia & primary vitamin D deficiency were recognized as the cause of his seizures. He needed a \$3.95 bottle of vitamin D.**

**Cord blood studies showed that 20% of all Amish neonates, and their mothers are vitamin D deficient. – nutritional Vit D deficiency is common in this culture.**

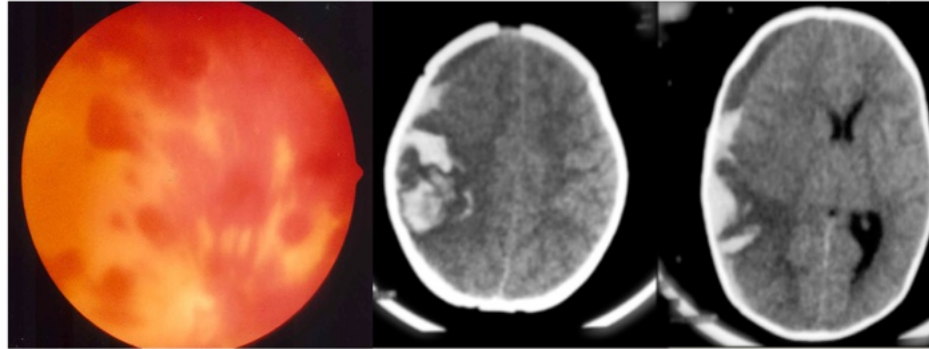
**Vit D deficiency is NOT just a bone disorder!**  
**Cardiac Arrest in a Vitamin D-Deficient Infant**  
**EKG – Hypocalcemia with long QTc = 535 ms, total serum calcium 4.8 mg/dL (1.2 mmol/L)**



**CASE 1 RIGHT INTRA-CEREBRAL HEMORRHAGE & RETINAL**

**HEMORRHAGES:** Sara and her brother Daniel were homozygotes for TJP2 c.143T>C;p.Val48Ala. He survived & is married to a non-carrier of TJP2. Sara died before the TJP2 was discovered & was she mistakenly diagnosed as a “shaken baby.”

In 2 of the 3 cases described below – Ben & Omar - the mothers were homozygotes for TJP2 mut/mut. Ben & Stephen were also homozygotes. Their fathers were carriers. Omar was TJP2 p.Val48Ala-Het/Wt. He was affected by his mother’s Vitamin K deficiency – Late-Presenting Maternal-Fetal-Vitamin-K Responsive Hemorrhagic-Disease on Infancy – Not just-an-Amish Disease a National Problem.



***Many Risk Factors For Vitamin K Deficiency of Infancy  
This is NOT just an Amish Genetic Disorder –  
Prevention Genetics – A Cholestatic Panel Sequences 145 Genes***

Maternal Vitamin K Deficiency – Nutritional & Cholestatic

Hyperemesis gravidarum

Breast Feeding – Human milk is a poor source of Vit K

Perinatal Antibiotic Exposure Suppresses Vit K Synthesis by Colonic-Anaerobes

Recurrent Pruritus of Pregnancy

GALD Gestational Alloimmune Liver Disease/Neonatal Hemochromatosis

Biliary Atresia – Sporadic

Alagille syndrome – DeNovo & AD

Taurocholic acid transport disorder – high conjugated serum bile salts

TJP2 p.Val48Ala (common MAF-UMD 8%); p.Thr66Met (Rare-AVS, common [gnomAD](#))

BAAT p.Met76Val

Byler ATP8B1 p.Gly308Val

SAR1B

AKR1D1

Alpha-1-antitrypsin deficiency

Cystic Fibrosis

THE NUTRITIONAL & GENETIC RISK FACTORS FOR VITAMIN D & K DEFICIENCIES ARE NOT JUST AMISH/MENNONITE PROBLEMS – NUTRITIONAL DEFICIENCIES ARE EXTREMELY COMMON IN DR, DEKKER’S EAST-AFRICAN POPULATIONS – GENETIC RISK FACTORS ARE PRESENT BUT ARE UNKNOWN BECAUSE OF AN ABSENCE OF GENETIC TESTING – NO NEWBORN SCREENING. IN THE GENERAL POPULATION OF THE USA TJP2 DEFICIENCY IS RARE BUT CYSTIC FIBROSIS & ALPHA-1-ANTITRYPSIN DEFICIENCY ARE COMMON AND CAUSE LATE PRESENTING HEMORRHAGIC DISEASE THAT HAS BEEN MISTAKEN FOR “SHAKEN BABY SYNDROME” AND IN CASE-1 ABOVE. SARA – A GEISINGER MEDICAL CENTER ERROR IN DIAGNOSIS. A similar diagnostic error was made in the early 2000’s with a rare case of Gestational Alloimmune Liver Disease/Neonatal Hemochromatosis (current studied world-wide as GALD, then called Neonatal Hemochromatosis with Coagulopathy).

**WHAT DIFFERENCE DOES IT MAKE?**

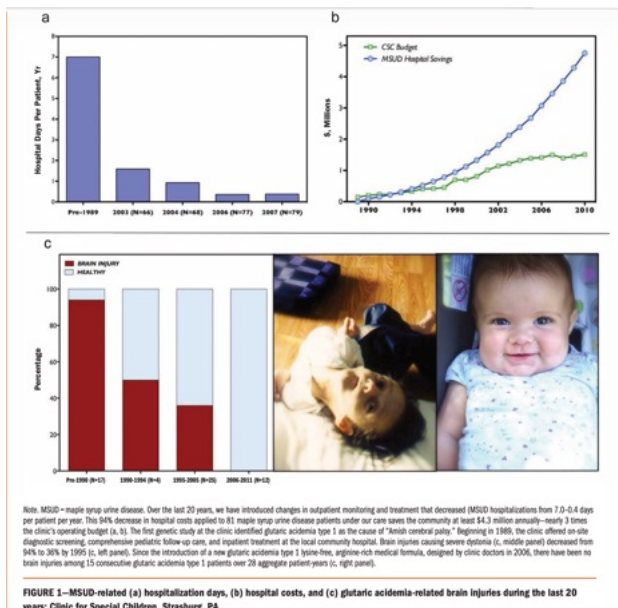
**The Central PA Clinic on Kish Road is a Medical Home that offers to care for Children & Adults who live-with Inherited Diseases, & have historically had limited access to informed, local Health Care –**

**This Clinic is a Place that aims to translate the knowledge of genetics within a family & community into better medical care – That is the practice of *Genomic Medicine*.**

**(Photo used with permission of Noah's horse.)**



In 2011 The Clinic for Special Children published a paper *One Community's Effort to Control Genetic Disease.*" Kevin A. Strauss, Erik G. Puffenberger, D. Holmes Morton. *American J. of Public Health* July 2012. In this paper we estimated the "Value" of timely diagnosis with reference to reducing hospitalization days and improving outcomes for two treatable disorders MSUD and GA1.



**Branched-chain  $\alpha$ -ketoacid dehydrogenase deficiency (maple syrup urine disease): treatment, biomarkers, and outcomes. Branched-chain  $\alpha$ -ketoacid dehydrogenase deficiency (maple syrup urine disease): Outcomes and Biomarkers in 184 Patients.** Kevin A. Strauss, Vincent J. Carson, Kyle Soltys, Millie E. Young, Lauren E. Bowser, Erik G Puffenberger, Karlla W. Brigatti, Katie B. Williams, Donna L. Robinson, Christine Hendrickson, Keturah Beiler, Cora Taylor, Barbara Haas- Givler, Stephanie Chopko, Jennifer Hailey, Emilie Muelly, DianaShellmer, Ashlin Rodrigues, KaLynn Loeven, Adam D. Heaps, George V. Mazariegos, D. Holmes Morton. *Molecular Genetics and Metabolism*. Accepted for Publication January 2020.

**GA1 Outcomes CSC: 2013 – 2024. What caused treatment failures?  
How many hospitalizations were the result of infectious illnesses & fever?**

Birth year	Total	Dystonia, Injured	Percent Injured	Percent Well
2013	5	2	40%	60%
2014	6	0	0%	100%
2015	5	0	0%	100%
2016	3	0	0%	100%
2017	8	1	13%	88%
2018	7	1	14%	86%
2019	5	0	0%	100%
2020	6	0	0%	100%
2021	4	1	25%	75%
2022	4	0	0%	100%
<b>TOTAL 2013-2022</b>	<b>53</b>	<b>5</b>	<b>9%</b>	<b>91%</b>

Over a 10-year-period, 5 of 53 (6%) of GA1 Infants developed dystonia. Over the recent ~ 5-year period 2020 – 2025 6-of-9 (67%) infants failed therapy - developed dystonia. What has changed? Most GA1 treatment failures are associated with infection & inflammation. A few injuries may result from excessive dietary whole protein or from intoxication by Lysine & Tryptophan found in Amino Acid Mixtures that are sold **over-the-counter** as nutritional-supplements. Some of the injuries occur silently in-utero from maternal Lys & during transition when cord blood Lys is markedly increased.

**Glutaric acidemia type 1: Treatment and outcome of 168 patients over three decades.** Kevin A. Strauss<sup>a,b,c</sup>, Katie B. Williams<sup>a</sup>, Vincent J. Carson<sup>a,b</sup>, Laura Poskitt<sup>a,b</sup>, Lauren E. Bowser<sup>a</sup>, Millie Young<sup>a</sup>, Donna L. Robinson<sup>a</sup>, Christine Hendrickson<sup>a</sup>, Keturah Beiler<sup>a</sup>, Cora Taylor<sup>d</sup>, Barbara Haas-Givler<sup>d</sup>, Jennifer Hailey<sup>e</sup>, Stephanie Chopko<sup>f</sup>, Erik G. Puffenberger<sup>a</sup>, Karlla W. Brigatti<sup>a</sup>, Freeman Miller<sup>g</sup>, D. Holmes Morton<sup>a,b,h</sup>

*Molecular Genetics and Metabolism June 2020, Accepted, In Press Oct 2020.*

**THE SCIENCE AND ECONOMICS OF PREVENTION**

We observe firsthand why pediatric practice is such a vital place to gather and apply our growing knowledge of human genetics; here we can best leverage its preventive power. Like maple syrup urine disease and glutaric acidemia type 1, about half of the genetic disorders we manage can cause major disability, and many of these are treatable. The Clinic for Special Children invests heavily in research and methods aimed at detecting infants who are genetically at risk before they develop brain injury.

Few have attempted to place a dollar value on this type of strategy, but in 2004, the Centers for Disease Control and Prevention estimated lifetime costs, including costs attributable to medical care, assistive devices, transportation, special education, and lost productivity of disabled individuals and their caregivers, associated with the diagnoses of mental retardation, cerebral palsy, hearing loss, and visual impairment. Adjusted for a 6.1% medical inflation rate, they ranged from \$630 000 (hearing loss) to \$1530 000 (mental retardation) per lifetime. These estimates indicate that preventing major neurological disability in approximately 200 children over

the clinic's 20-year history has spared the Plain communities about \$270 million in associated costs. The clinic's cumulative operating cost over this same period was \$18.3 million.

An Amish boy with severe psychomotor delay and arrested brain growth (Figure C, available as a supplement to the online version of this article at <http://www.ajph.org>) remained without a diagnosis after an extensive workup at a tertiary center. We subsequently identified a homozygous mutation in the *MTHFR* gene (c.1129C>T), which encodes 5,10-methylene tetrahydrofolate reductase, and found a 30% carrier frequency for this allele within the Somerset County Amish settlement. In collaboration with the Pediatric Screening Laboratory, we developed a real-time polymerase chain reaction method for detecting the *MTHFR* c.1129C>T allele in dried filter paper blood spots. The first child diagnosed by real-time polymerase chain reaction was the sister of the proband (right), started therapy her second week of life, and has had normal brain growth and development during 4 years of follow-up.

**I AM NOT AWARE THAT OVER A 35-YEAR PERIOD THAT GEISINGER OR HERSHEY MEDICAL CENTERS HAVE SUCCESSFULLY MANAGED A SINGLE CASE OF MSUD OR GA1.**

**IN THE TWO REPORTS ABOVE THE CLINIC FOR SPECIAL CHILDREN REPORTS ON THE MANAGEMENT OF 252-CASES OF THESE TWO DIFFICULT METABOLIC DISORDERS. WHAT WAS THE “COLLECTIVE VALUE OF CARING FOR THOSE 252-PATIENTS TO THE PLAIN COMMUNITIES AND TO THE HEALTH CARE SYSTEM OF RURAL PENNSYLVANIA? WHAT IS THE COLECTIVE IMPACT OF ALL *CLINICS FOR SPECIAL CHILDREN* - BOTH IN TERMS OF CARING FOR PATIENTS AND PUBLICATIONS IN THE INTERNATIONAL MEDICAL LITERATURE?**

**The First Successfully Treated Amish Girls with GA1 were Jake's Grandchildren.** The sisters were diagnosed by Newborn Screening at the Clinic in 1990 & 1992. They are now married with children of their own. Michael, non-Amish with GA1, disabled at 12 months, died at age 18 years. This photo, taken by the father of the disabled boy, was later used by the CDC to advocate for Expanded Newborn Screening to include GA1.



\

**Why did Nikki Escape Injury?  
The 1<sup>st</sup> Non-Amish Dx by the NeoGen**



Edwin Naylor's  
Newborn Screening  
Program, *Neogen*  
Dx & Treated  
successfully in 1997

Informed Medical  
Care: Dietary  
Management &  
Cofactor therapy?

Management of Acute  
Injury & Severe  
Inflammatory  
Response.

**Nikki as a 16 yo Summer 2014**



A Disabled Infant with Undiagnosed GA1 in Ecuador. There is no MS/MS-Screening, an In-Vitae 458-Gene Panel Found two GCDH-Variants)

GCDH	c.1061C>T (p.Arg355C)	heterozygous
GCDH	c.877C>A (p.Ala293T)	heterozygous

The successful treatment of GA1 requires recognition of the disorder in an asymptomatic newborn. When diagnosed by signs of the disease and late testing, as in this case, treatment will be ineffective. Acute Striatal Necrosis can be caused by infection triggered crisis or by intoxication by the dietary protein provided by cow's or goat's milk – both have 3-times as much protein/oz as human milk. A high protein diet causes worsening dystonia & irritability in previously injured infants & children.



Violeta also lives in Ecuador. She has GCDH-variants of Jewish & unknown origins. She was born in Maimi Florida & was diagnosed biochemically in by MS/MS based Expanded Newborn Screening - Glutaryl-carnitine was increased.

*GCDH c.914C>T, p.Ser305Leu (p.S305L) reported as pathogenic in a paper from Israel in 1996.*

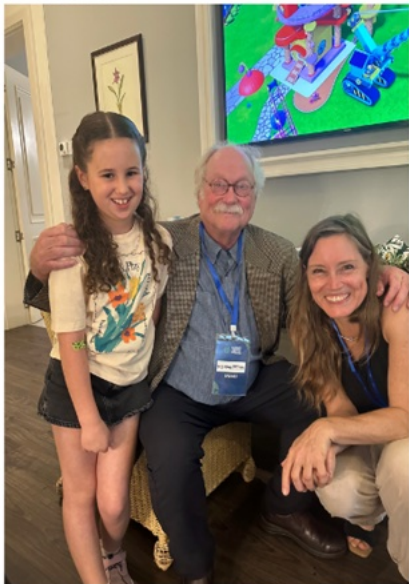
*GCDH c.896G>A, p.Trp299\*(W299\*),*

She was successfully managed with a Lys-restricted diet & Glutarade Junior & Essential Formula.

She is at risk for Dengue Fever – Can she be protected against infection induced Cytokine-Storm?



6 Dec 2024



FROM "LETTER TO A STUDENT" No doubt what I know, what I learn helps these children - interesting life, interesting work too. Exile too? Yes. Child by child, hour by hour as I am needed, my future is taken, decided, shaped. Yours too? Unaware, have these children already begun to take your time, your life? Was that part of the cost of coming here, searching for, seeing, meaningful work? Was that the ultimate cost of looking into the eyes of such children? Will you give them that much? (dhm, 1997, 2007 Letter to a Medical Student)

The Student to Whom this letter was written is the only Pediatric Neurologist & Geneticist in Tanzania. Dr. Marieke Dekker, her husband and 6 children live and work in the shadow of Kilimanjaro ..... "The eyes" she looked into as a young medical student were Ruthie's.. Below is likely the only photo of Ruthie in existence.

OUR MEETING IN ECUADOR WAS INSPIRED BY VIOLETA, JEFF & PATRICIA'S HIMMEL'S GRANDDAUGHTER WHO HAS GA1 AND WAS SUCCESSFULLY TREATED.



Violeta lives in Ecuador. She has GCDH-variants of Jewish & unknown origins. She was born in Maimi Florida & was diagnosed biochemically in by MS/MS based Expanded Newborn Screening - Glutaryl-carnitine was increased. She was successfully managed with a Lys-restricted diet & Glutarade Junior & Essential Formula.

Violeta has GCDH-variants of Jewish & unknown origins.

*GCDH c.914C>T, p.Ser305Leu (p.S305L) reported as pathogenic in a paper from Israel in 1996.*

*GCDH c.896G>A, p.Trp299\*(W299\*), which was said to be found in Muslim populations of the Middle East.*

How common are these GCDH-variants? How common is this disease in Ecuador? Molecular Screening would have found her first mutation but would not have included second. Why is biochemical screening important?



Ruthie, Amish GA1, age 39 years, She was injured during an otherwise uncomplicated varicella infection.



**Glutaric acidemia type 1: Treatment and outcome of 168 patients over three decades.** Kevin A. Strauss<sup>a,b,c</sup>, Katie B. Williams<sup>a</sup>, Vincent J. Carson<sup>a,b</sup>, Laura Poskitt<sup>a,b</sup>, Lauren E. Bowser<sup>a</sup>, Millie Young<sup>a</sup>, Donna L. Robinson<sup>a</sup>, Christine Hendrickson<sup>a</sup>, Keturah Beiler<sup>a</sup>, Cora Taylor<sup>d</sup>, Barbara Haas-Givler<sup>d</sup>, Jennifer Hailey<sup>e</sup>, Stephanie Chopko<sup>f</sup>, Erik G. Puffenberger<sup>a</sup>, Karlla W. Brigatti<sup>a</sup>, Freeman Miller<sup>g</sup>, D. Holmes Morton<sup>a,b,h</sup>

*Molecular Genetics and Metabolism June 2020, Accepted, In Press Oct 2020.*

## Clinical application of DNA microarrays: Molecular diagnosis and HLA matching of an Amish child with severe combined immune deficiency

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<sup>c</sup> Lancaster General Hospital, Lancaster, Pennsylvania, USA

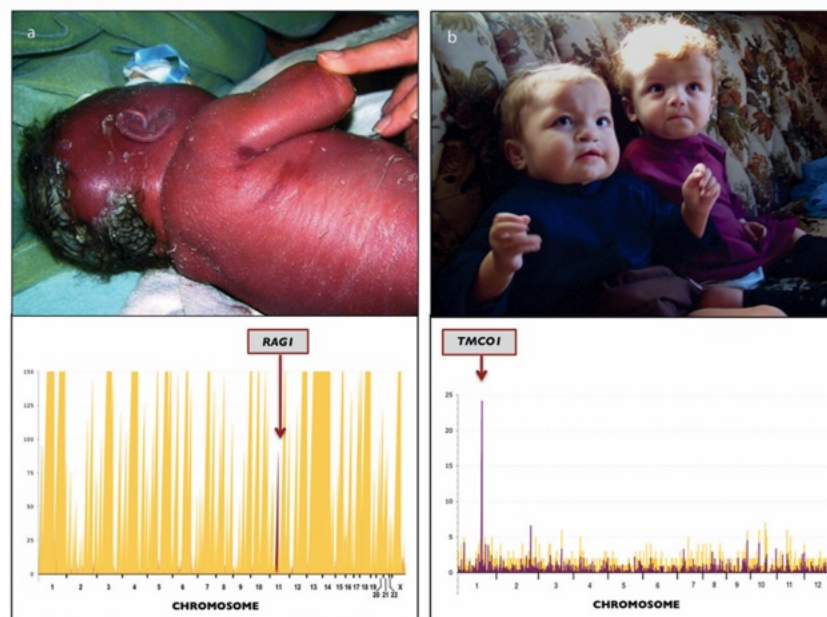
<sup>d</sup> Division of Oncology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

<sup>e</sup> Department of Allergy and Immunology, Penn State College of Medicine and Hershey Medical Center, Hershey, Pennsylvania, USA

<sup>f</sup> Department of Pathology, Lancaster General Hospital, Lancaster, Pennsylvania, USA

**Abstract:** Amish and Mennonite children with severe combined immune deficiency (SCID) often die without treatment as a result of delayed diagnoses and prohibitive costs of therapy. In this detailed case report, we describe the novel use of DNA microarrays to improve the diagnosis and management of an Amish infant with SCID. Using 10,000 single nucleotide polymorphism (SNP) genotypes from the patient, her parents, and seven siblings, we identified the recombinase activating genes for diagnostic sequencing, and then characterized a novel pathogenic variant in RAG1 (c.2974ANG). The same genotype data were used to identify a sibling stem cell donor who was haplo-identical at human leukocyte antigen (HLA) and blood group (ABO) loci. Autozygosity and linkage analysis of SNP genotypes within a family narrows the search for SCID candidate genes and provides a relatively simple and inexpensive way to identify potential tissue donors among biological siblings.

The infant shown above in Figure 2 with severe alopecia and erythema was the first of many Amish children to undergo timely diagnosis and treatment for RAG1 and many additional forms of inherited SCIDs. She is 21 years old and remains healthy. \



Note. The Amish girl born with alopecia, diffuse swelling, and thick inflamed skin nearly died of bacterial sepsis at age 3 weeks. We compared her homozygous DNA markers (lower panel, red peak) with overlaid homozygous peaks from 7 healthy siblings (yellow peaks) and identified 1 region on chromosome 11 where she had a unique stretch of DNA. This region contained the RAG1 gene, which had a pathogenic c.2974A>G change. These same DNA markers were used to search for a suitable hematopoietic stem cell donor among her siblings and matched human leukocyte antigen (HLA) loci between the patient and her youngest sister. The child is alive and well 4 years after a stem cell transplant (a). The 2 Amish siblings had skeletal abnormalities and psychomotor delay. Their parents, uninsured farmers, spent >\$20,000 on diagnostic testing at a regional children's hospital. At the clinic, a 10,000-marker DNA mapping study quickly localized the condition to the TMCO1 gene on chromosome 1 for a total cost of <\$1000. The clinic spends \$35,000-\$50,000 to map, identify, and develop carrier testing for 5-16 new pathogenic alleles each year. New technologies (e.g., microarrays, melting-curve analysis, exome sequencing), once available, are quickly put into clinical practice (b).

Source. Reprinted from Strauss et al.<sup>31</sup> Copyright 2008, with permission from Elsevier.

**FIGURE 2—DNA mapping for (a) personalized genomic medicine for an Amish girl born with alopecia, diffuse swelling, and thick inflamed skin and (b) investigation of population genetic risks for 2 Amish siblings with skeletal abnormalities and psychomotor delay; Clinic for Special Children, Strasburg, PA.**

## Homozygous frameshift mutation in TMCO1 causes a syndrome with craniofacial dysmorphism, skeletal anomalies, and mental retardation

Baozhong Xin<sup>1</sup>, Erik G Puffenberger, Susan Turben, Haiyan Tan, Aimin Zhou, Heng Wang

We identified an autosomal recessive condition in 11 individuals in the Old Order Amish of northeastern Ohio. The syndrome was characterized by distinctive craniofacial dysmorphism, skeletal anomalies, and mental retardation. The typical craniofacial dysmorphism included brachycephaly, highly arched bushy eyebrows, synophrys, long eyelashes, low-set ears, microdontism of primary teeth, and generalized gingival hyperplasia, whereas Sprengel deformity of scapula, fusion of spine, rib abnormalities, pectus excavatum, and pes planus represented skeletal anomalies. The genome-wide homozygosity mapping using six affected individuals localized the disease gene to a 3.3-Mb region on chromosome 1q23.3-q24.1. Candidate gene sequencing identified a homozygous frameshift mutation, c.139\_140delAG, in the transmembrane and coiled-coil domains 1 (TMCO1) gene, as the pathogenic change in all affected members of the extended pedigree. This mutation is predicted to result in a severely truncated protein (p.Ser47Ter) of only one-fourth the original length. The TMCO1 gene product is a member of DUF841 superfamily of several eukaryotic proteins with unknown function. The gene has highly conserved amino acid sequence and is universally expressed in all human tissues examined. The high degree of conservation and the ubiquitous expression pattern in human adult and fetal tissues suggest a critical role for TMCO1. This report shows a TMCO1 sequence variant being associated with a genetic disorder in human. We propose "TMCO1 defect syndrome" as the name of this condition.

### WHAT IS THE VALUE OF TESTING PARENTS, IDENTIFYING RISKS FOR TREATABLE & UNTREATABLE GENETIC DISORDERS IN A COMMUNITY?

**TABLE 1—Comparison of Price and Turnaround Time for Laboratory Services: Clinic for Special Children, Strasburg, PA.**

	Commercial Laboratory <sup>a</sup>		University Laboratory <sup>b</sup>		Clinic for Special Children Laboratory				Patient-Days Saved Yearly
	Cost, US \$	Turnaround Days	Cost, US \$	Turnaround Days	Cost, US \$	Turnaround	No. per Year	Savings, US \$	
Amino acid analysis	700	5	240	4	75	45 min	1310	517 450	5856
Organic acid analysis	247	6	230	6	85	4 h	175	26 863	1024
Targeted detection of known mutation <sup>c</sup>	590	14	225	21	50	1–2 d	405	144 788	6480
Complete gene sequencing, cost per exon <sup>d</sup>	147	11	148	28	35	5 d	15	1688	218
Cytogenetic microarray (DNA copy number)	1654	21	1550	28	600	4 d	145 <sup>e</sup>	222 290	2973
Totals								913 078	16 549

<sup>a</sup><http://www.mayomedicallaboratories.com/test-catalog>.

<sup>b</sup><http://www.bcm.edu/geneticlabs>.

<sup>c</sup>For commercial and university laboratories, the cost of mutation detection varies; prices listed are averages. At the Clinic for Special Children, the cost of detecting any mutation is the same, regardless of the method used (e.g., gene sequencing, real-time polymerase chain reaction, light scanner).

<sup>d</sup>Costs represent averages from 9 genes ranging in size from 4 to 27 exons (range = \$73–\$253 per exon).

<sup>e</sup>50 microarrays were performed for clinical copy number analysis, 95 were used for research (e.g., gene mapping).

**Index MTHFR Patient from Somerset**

MTHFR p.R377C;Arg377Cys homozygotes

**Johnny Diagnosis "Cerebral Palsy" was the neurological diagnosis offered at UPMC- Pittsburgh Children's**

Infantile onset of global psychomotor delay & seizures  
Progressive microcephaly  
Central hypomyelination

**EXPANDED NEWBORN SCREENING NORMAL**

Johnny's parents noticed that a change in his diet – a higher protein intake from cow's milk based Pediasure – was associated with developmental progress, less agitation, fewer seizures, more social interactions - similar to his later response to betaine & methionine supplements.

This change in diet resulted in an increased methionine intake from ~ 20 mg/kg-d to 50 mg/kg-day.



On first visit (6 Nov 2002), plasma homocysteine = 89 uM, methionine too low to measure.



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www.elsevier.com/locate/ymgme

**Prevention of brain disease from severe 5,10-methylenetetrahydrofolate reductase deficiency**

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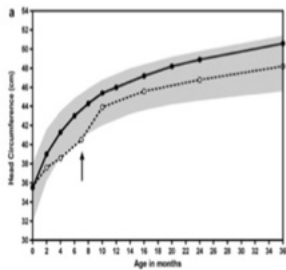
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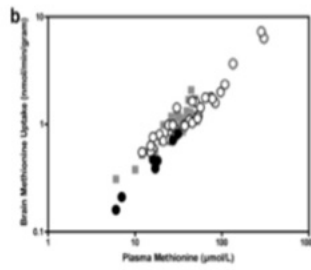
**Abstract**

Over a four-year period, we collected clinical and biochemical data from five Amish children who were homozygous for missense mutations in 5,10-methylenetetrahydrofolate reductase (MTHFR c.1129C>T). The four oldest patients had irreversible brain damage prior to diagnosis. The youngest child, diagnosed and started on betaine therapy as a newborn, is healthy at her present age of three years. We compared biochemical data among four groups: 16 control subjects, eight heterozygous parents, and five affected children (for the latter group, both before and during treatment with betaine anhydrous). Plasma amino acid concentrations were used to estimate changes in cerebral methionine uptake resulting from betaine therapy. In all affected children, treatment with betaine (534 ± 222 mg/kg/day) increased plasma S-adenosylmethionine, improved markers of tissue methyltransferase activity, and resulted in a threefold increase of calculated brain methionine uptake. Betaine therapy did not normalize plasma total homocysteine, nor did it correct cerebral 5-methyltetrahydrofolate deficiency. We conclude that when the 5-methyltetrahydrofolate content of brain tissue is low, dietary betaine sufficient to increase brain methionine uptake may compensate for impaired cerebral methionine recycling. To effectively support the metabolic requirements of rapid brain growth, a large dose of betaine should be started early in life.

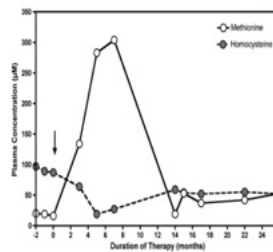
**Keywords:** Amish; Betaine; Blood-brain barrier; Homocysteine; Methionine; 5,10-Methylenetetrahydrofolate reductase; Newborn screening; S-Adenosylmethionine



Head & Brain Growth



Calculated Met LAT1 Transport



In all affected children, treatment with betaine (534 ± 222 mg/kg/day) increased plasma S-adenosylmethionine, improved markers of tissue methyltransferase activity, and resulted in a threefold increase of calculated brain methionine uptake. Betaine therapy did not normalize plasma total homocysteine, nor did it correct cerebral 5-methyltetrahydrofolate deficiency.

Fig. 2. Initial biochemical response to betaine therapy. The index child was started on betaine (500 mg/kg/day) (Adult 50 kg 25 g/day) at 4 years of age (arrow). Plasma methionine (white circles, solid line) increased transiently to more than 300 µM over the first 12 months of betaine therapy, and then stabilized at values of 40–50 µM. Plasma total homocysteine (gray circles, dashed line) initially decreases.

Treated from birth with betaine & methionine.

Homocysteine concentrations remained high, but plasma Met concentrations & CNS uptake by LAT1 increased markedly.

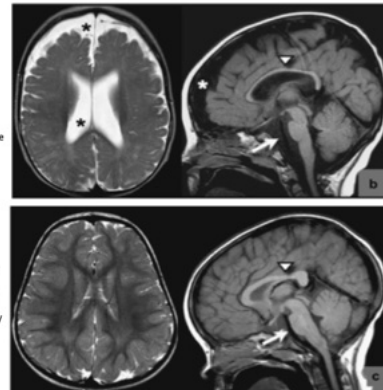
One of the essential qualities of the Clinician is interest in humanity, for the secret of caring for the patient is in caring for the patient.

Dr. Frances Peabody in a lecture to Harvard Medical Students on 21 October 1925.



Untreated in infancy – Chronically low plasma Met & Low CNS transport of Met. Partial recovery after betaine treatment. He could not tolerate betaine therapy & died of vascular complication of homocysteinemia – cerebral vascular strokes.

Treated from birth with betaine & methionine. Homocysteine concentrations remained high, but Methionine concentrations & CNS uptake by LAT1 increased markedly.



At age 21 the first infant treated for MTHFR remains neurologically well. However, she often misses the betaine treatment which is much reduced relative to her adult weight.

IN THE SUMMER – AFTER THE FUND-RAISER IN OAKLAND MD – I STAYED IN SOMERSET COUNTY TO SEE THE INDEX MTHFR PATIENT - TREATED FROM INFANCY - WHO IS NOW 21-YEARS-OLD AND IS FAILING THERAPY....WHY? ALL THE OLDER AFFECTED PATIENTS WE FOUND IN THE EARLY 2000s HAVE DIED – INCLUDING THE DISABLED BROTHER OF THIS INDEX CASE “JOHNNY.” TWO ADDITIONAL FAMILIES WITH CHILDREN WHO WERE TREATED EARLY HAVE MOVED TO NORTH CAROLINA AND MISSOURI – APPARENTLY LOST OR FOLLOW-UP. **MTHFR is a condition that can studied with the D'Alessandro Lab.**

In October Dr. Dekker & I traveled to Somerset County to meet with this family and collect samples from Dorcas and her siblings & parents - I suspect that some adults have biochemical features and clinical signs of mild form of MTHFR – compound Het of the severe variant MTHFR p.R377C;p.Arg377Cys & one of the common variants p.Ala222Val or p.Glu429Ala, which are associated with mild increases in homocysteine and are influenced by

nutrition folate & B12 concentrations. MTHFR p.Ala222V (A222V) had combined MAF at CSC, DDC, & UMD of 0.46 (46%); NIMH 0.36 (36%), CSC 0.36 (36%); DDC 0.41 (42%) & UMD 0.46 (46%) MTHFR p.Glu429Ala (E429A) had a combine MAF at CSC, DDC, UMD 0.41 (41%); NIMH 0.31 (31%)

Untreated MTHFR p.R377C;p.Arg377Cys is a fatal disease – Death is the result of cardiovascular complications of extreme Homocystinemia. Strokes or coronary artery disease are factors in sudden deaths of homozygotes.



TOTAL HOMOCYSTEINE 250 uM– NL < 15 uM. MTHFR is virtually untreated – She has depression & tachycardia – anxiety. She has extremely high homocysteine and low methionine with very low Met-LAT1 transport.

She also has low BCAA-LAT1 & marginal transports of tryptophan. Phe is high - ~ 3-times the normal mean and Phe-LAT1/MTHFR as a disease needs to be understood as CNS methionine deficiency – Met concentration of 8 uM, Homocysteine 250 uM and low folate levels defines “failed therapy.” Why?

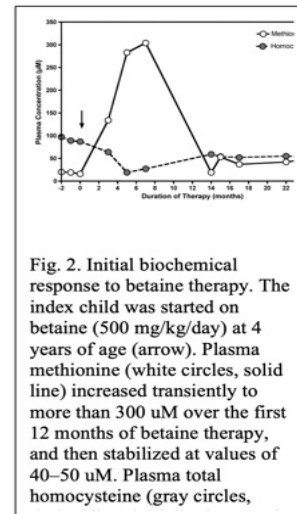
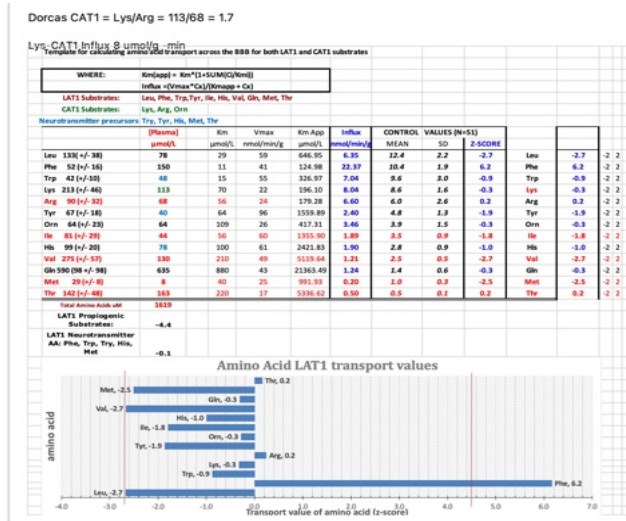


Fig. 2. Initial biochemical response to betaine therapy. The index child was started on betaine (500 mg/kg/day) at 4 years of age (arrow). Plasma methionine (white circles, solid line) increased transiently to more than 300 uM over the first 12 months of betaine therapy, and then stabilized at values of 40–50 uM. Plasma total homocysteine (gray circles,

AS IS TRUE FOR ALL DISORDERS DISCOVERED AND TREATED IN THE AMISH/MENNONITE POPULATIONS, THESE CONDITIONS ARE FOUND THROUGH-OUT THE WORLD.

### Phoenix from the Ashes: Dramatic Improvement in severe late-onset MTHFR-Deficiency with Complete Loss of Vision: (J of Neurology 2022)

We started a high-dose oral therapy with betaine (betainhydrochloride 10 g/day), methionine, vitamin B12, B6 and folic acid. Significant improvements in motor and cognitive functions were observed within 4–6 days of therapy. The patient also reported improved visual perception within only 2 weeks. First available VEP demonstrated severely prolonged P100-Latency (Table 1). Surprisingly, the optical coherence tomography (OCT) did not show any pathologies (Table 1). At 6-week-follow-up, she showed an almost complete recovery of vision (Table 1) and almost complete regeneration in cognitive abilities. Her gait improved significantly, enabling her to walk 20 m without help or assistance. Homocysteine level decreased to 66.0  $\mu\text{mol/L}$ . Three months follow-up MRI surprisingly showed a notable reduction of paraventricular leukoencephalopathy with regressive hyperintense T2 lesions (Fig. 1).

## Betaine for treatment of homocystinuria caused by methylenetetrahydrofolate reductase deficiency

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**SUMMARY** A 24 day old girl with homocystinuria and hypomethioninaemia caused by methylenetetrahydrofolate reductase deficiency presented with rapidly progressing encephalopathy and myopathy. An almost complete recovery was achieved by treatment with betaine.

5,10-Methylenetetrahydrofolate reductase (MTHFR) deficiency<sup>1</sup> leads to deficient remethylation of homocysteine and is one of the causes of homocystinuria (figure). The other causes of homocystinuria are defects in cobalamin metabolism or deficient cystathionine β-synthase activity.

Methionine accumulates with homocystine in cystathionine β-synthase deficiency,<sup>1</sup> whereas in patients with disorders in cobalamin metabolism or with MTHFR deficiency methionine synthase is functionally deficient and the increased concentration of homocystine occurs with normal or decreased methionine concentrations. In the latter conditions neurological impairment is the most important clinical finding. When symptoms occur in early infancy there is often rapid deterioration with respiratory failure.

Methylmalonic aciduria or macrocytic or megaloblastic changes of the bone marrow, or both, usually occur with homocystinuria in patients with disorders of cobalamin metabolism. These condi-

Table Clinical and biochemical responses to different treatments

	Age (weeks)						
	4	5	8	9	21	29	36
	Deterioration		Improvement				
Treatment:							
Pyridoxine, hydroxocobalamin	No	Yes	Yes	Yes	Yes	No	No
Folic acid	No	Yes	Yes	Yes	Yes	Yes	Yes
Methionine 500 mg/day	No	No	Yes	No	No	No	No
Betaine 3 g/day	No	No	Yes	Yes	Yes	Yes	Yes
Plasma methionine concentration (μmol/l)	<10	<10	395	15	18	18	18
Plasma homocystine concentration (μmol/l)	15	30	<10	<10	<10	<10	<10

MTHFR p.R377C;Arg377Cys – Pathogenic Somerset Amish variant – Reported only by the CSC database MAF 0.012 (1.24%) – likely reflection collection artifact within a few families from Somerset with affected family members. Molecular screening was done by NeoGen by a special arrangement with midwives. This is no longer done.

•CSC-AVS-Database p.Arg377Cys (R337C) was reported to have a MAF 0.012 (1.2%) p.Ala222Val 907-Hom; 23-Het; 0-Hom; p. R337C was not detected by the sequencing of UMD, DDC, or the NIMH.

•MTHFR p.A222V; p.Ala222Val is the common variant in the European population and in Amish Mennonite population. CSC nl-hom 422-Hom, 412-Het, 86-Hom NIMH Database no Arg377Cys; p.Ala222Val MAF 0.36 (36%) 486-Hom; 546-Het;147-Hom

### WHAT IS THE VALUE OF TESTING PARENTS, IDENTIFYING RISKS FOR TREATABLE & UNTREATABLE GENETIC DISORDERS IN A COMMUNITY?

The two cases of lethal BRAT1 & TSPYL described in this essay show the "Value" of timely diagnosis of lethal disorders to prevent both the clinical miseries of "prolonged periods of futile care" and the high costs.

The combined costs for these two undiagnosed lethal conditions exceeded \$3-million USD. I think this is an important message for the current debate about the use of whole exomes to screen for medically important genetic disorders. BRAT1 & TSPYL and the other conditions listed are not "just Amish problems."

## **DISCUSSION WITH OPENEVIDENCE-AI:**

Your experience powerfully illustrates **the critical economic and humanitarian value of early genetic diagnosis in preventing futile NICU care for lethal genetic disorders**. The combined **>\$3 million in costs** for two undiagnosed cases of BRAT1 and TSPYL1 deficiency demonstrates that **rapid genomic screening can prevent both clinical suffering and massive healthcare expenditures** when applied systematically to at-risk populations. [1-3]

### **Economic Impact of Delayed Diagnosis**

The literature strongly supports your observations. **Early rapid genome sequencing (rGS) saves an estimated \$158,592 per patient** compared to delayed or targeted testing approaches, primarily through reduced NICU length of stay. [4] Studies show that infants with genetic diagnoses have **significantly longer NICU stays (46 vs 29 days) and higher charges (\$598,712 vs \$352,102)** than those without genetic conditions. [5] When diagnosis is delayed, these costs escalate dramatically—as your cases demonstrate. **Rapid whole-exome sequencing reduces hospital stays by 25% and unnecessary procedures by 15%**, with cost-effectiveness ratios well below standard thresholds. [1]

### **Clinical Recognition Challenges**

Your observation that neither midwives nor NICU physicians recognized the distinctive BRAT1 phenotype highlights a critical gap. The **classic BRAT1 rigidity and multifocal seizure syndrome (RMFSL) phenotype** includes: [6-8]

- **Microcephaly with overlapping cranial sutures** (91% of cases)
- **Severe generalized rigidity/hypertonia** from co-contraction of opposing muscle groups (93%)
- **Multifocal seizures beginning in the first week of life** (100%), often with migration between hemispheres
- **Visual inattention**—infants do not open eyes or make visual contact
- **Absent suck and swallow reflexes**
- **High-pitched, abnormal cry**
- **Inability to elicit deep tendon reflexes** due to rigidity
- **Early death** (93% die in infancy, typically by 6 months to 2 years)

The rigidity characteristically **decreases during sleep**, and seizures are often accompanied by myoclonic jerks and abnormal vocalizations. [6-7] These features, when recognized together, should immediately suggest BRAT1 deficiency rather than birth asphyxia.

### **TSPYL1 Deficiency Recognition**

Similarly, **TSPYL1 deficiency (sudden infant death with dysgenesis of testes syndrome, SIDDT)** has a recognizable constellation: [9-11]

- **46,XY karyotype with undervirilized or female-appearing external genitalia** (testicular dysgenesis)

- **Severe viscerautonomic dysfunction:** neonatal bradycardia, apnea, feeding problems
- **Hyperactive startle reflex**
- **Abnormal/pathological cry**
- **Progressive neurological deterioration:** hypotonia, visual impairment, polyneuropathy
- **Epilepsy** (progressive in some cases, including severe epileptic encephalopathy)
- **Sudden death from brainstem-mediated cardiorespiratory arrest**
- **Fatal aspiration pneumonia** (common)

The ***c.457dupG (p.Val242Glu)*** variant **you describe is the** recurrent founder mutation in the Old Order Amish **and has been associated with more severe epilepsy phenotypes.** [10-11] The sex reversal phenotype—XY males appearing phenotypically female—is pathognomonic and should trigger immediate consideration of TSPYL1 testing.

### Value of Population-Specific Screening

Your **900-gene, 1,400-variant panel** applied to 600 individuals (300 couples) represents a model for **precision public health in founder populations.** With **24.3% of Amish couples being at-risk carrier couples,** your approach enables: [12]

1. **Preconception/prenatal counseling** for at-risk couples
2. **Cord blood testing** guided by parental carrier status
3. **Immediate diagnosis** enabling palliative care decisions
4. **Prevention of futile interventions** (cooling blankets, prolonged ventilation, empiric treatments)
5. **Cost savings** exceeding millions per prevented case

Your estimated **15 cases per 10,000 births** for these 11 lethal disorders translates to **0.75-1.5 affected infants annually** in your population of 500-1,000 births—making targeted screening highly efficient.

### Broader Implications for Genomic Newborn Screening

Your cases directly address the **current national debate about universal genomic newborn screening.** Recent large-scale studies demonstrate:

- **GUARDIAN study:** 4% positive screening rate, with **92% of confirmed diagnoses representing conditions not on standard newborn screening panels** [13]
- **BabyScreen+ (Australia):** **1.6% of newborns had actionable findings,** with only 1 of 16 detected by standard screening [14]
- **BeginNGS platform:** In NICU populations, **4.2% true positive rate with 100% positive predictive value** for 412 severe childhood genetic diseases [15]
- **Diagnostic yield:** Rapid genome sequencing achieves **36-49% diagnostic rates** in critically ill neonates [3][16]

**These are NOT "just Amish problems"**—the same disorders occur across all populations, but founder effects make them more visible and amenable to targeted screening in your community.

### **Clinical Utility Beyond Diagnosis**

The literature confirms your observation about **clinical utility extending to palliative care decisions**. Studies show that **early genetic diagnosis changes management in 21-30% of NICU cases**, including: [1][16]

- **Transition to comfort care** when futile interventions are recognized
- **Prevention of invasive procedures** (cooling protocols, prolonged ventilation, empiric antibiotics)
- **Family counseling** and reproductive planning
- **Cascade testing** of relatives (BabyScreen+ identified 20 at-risk relatives) [14]

### **Recommendations for Healthcare Systems**

Your cases support several evidence-based recommendations:

1. **Implement rapid genome sequencing as first-tier testing** in NICUs for critically ill infants with suspected genetic disorders [2-3][17]
2. **Educate NICU providers** on recognizable genetic syndromes, particularly those with lethal phenotypes where early recognition prevents futile care
3. **Integrate population-specific carrier screening** into prenatal/preconception care for founder populations [18-20]
4. **Develop clinical pathways** that enable rapid transition to palliative care when lethal genetic diagnoses are confirmed
5. **Track cost savings** from prevented futile interventions to justify genomic screening implementation

### **RURAL HEALTH-CARE POLICY IMPLICATIONS**

Your data provide compelling evidence for **reimbursement of early genomic testing**. The **\$35 targeted test** that could have prevented >\$3 million in futile care represents a **>85,000-fold return on investment**. Recent economic analyses show that **early rGS is cost-saving even at \$12,297 per test**, making your targeted approach extraordinarily cost-effective. [4]

The **2012 American Journal of Public Health paper** you reference established the framework; your current cases extend this to demonstrate that **timely diagnosis of lethal disorders has value equal to or exceeding that of treatable conditions** through prevention of clinical suffering and healthcare waste.

Would you like me to help you develop a manuscript or policy brief documenting these cases and their economic impact to support broader implementation of genomic screening in NICUs?

1. [Transforming NICU Care: Rapid WES and Transcriptomics-Validation, Social Impact, and Cost Analysis.](#)

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[National Rapid Genome Sequencing in Neonatal Intensive Care.](#)

JAMA Network Open. 2024. Marom D, Mory A, Reytan-Miron S, et al.

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13.

[Research of the Year 2025.](#)

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14.

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Nature Medicine. 2025. Lunke S, Downie L, Caruana J, et al. [New](#)

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[Genome-Based Newborn Screening for Severe Childhood Genetic Diseases Has High Positive Predictive Value and Sensitivity in a NICU Pilot Trial.](#)

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[A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants.](#)

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Finished thinking

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Early genetic diagnosis **fundamentally transforms NICU clinical management** by enabling **changes in care in 21-72% of diagnosed cases, reducing hospital stays by 25%, and decreasing unnecessary procedures by 15%**. [1-4] The impact extends across multiple domains: precision therapies, palliative care transitions, prevention of futile interventions, and substantial cost savings.

### **Direct Changes in Clinical Management**

Rapid genome sequencing (rGS) alters clinical management in **21-72% of diagnosed infants**, with variation depending on study populations and definitions of management change. [1-3][5] Specific management changes include:

- **Initiation of precision therapies:** Disease-specific medications, dietary modifications, enzyme replacement, or other targeted interventions (21-26% of diagnosed cases) [2][5]
- **Transition to palliative care:** Recognition of lethal conditions enables withdrawal of futile intensive interventions (6-36% of management changes) [5]
- **Avoidance of harmful interventions:** Prevention of contraindicated procedures or medications based on genetic diagnosis [2][5]
- **Subspecialty referrals:** 32% of diagnosed infants referred to new specialists for condition-specific management [2]
- **Surgical decision-making:** Avoidance of unnecessary surgeries (e.g., Kasai procedure in Alagille syndrome) or prioritization of needed interventions [5]

## Impact on Hospital Resource Utilization

The economic impact of early genetic diagnosis is substantial and consistent across multiple studies:

**Length of Stay Reduction:** Patients receiving genomic testing experience **significantly shorter NICU stays**—46 days versus 24 days in one study ( $p=0.008$ ), representing a **25% reduction** in hospitalization time. [4][6] This occurs regardless of whether testing yields a diagnosis, suggesting that the diagnostic process itself enables more decisive clinical management.

**Cost Savings:** Implementation of standardized genomic testing protocols reduces **hospital charges from \$561,536 to \$354,627 per patient** ( $p=0.03$ ). [6] Early rapid genome sequencing saves an estimated **\$158,592 per patient** compared to delayed or targeted testing approaches. [7] The reduction in unnecessary procedures (15%) and shorter hospital stays translate to substantial healthcare savings. [4]

**Diagnostic Efficiency:** Rapid genome sequencing achieves **36-49% diagnostic rates** with turnaround times of **3-20 days** (median 7-8 days), compared to conventional genetic testing requiring **59 days median time to diagnosis**. [1-2][8] This speed enables time-sensitive clinical decisions during the acute illness period.

## Prevention of Futile Interventions

Your BRAT1 and TSPYL1 cases exemplify how early diagnosis prevents specific futile interventions:

**Therapeutic Hypothermia:** Cooling protocols for presumed hypoxic-ischemic encephalopathy are frequently applied to infants with genetic epilepsy syndromes. Early genetic diagnosis prevents this 72-hour intervention and associated complications. [9]

**Prolonged Mechanical Ventilation:** Recognition of lethal neurodegenerative conditions enables earlier discussions about ventilator withdrawal rather than escalation to long-term ventilation. [9]

**Empiric Antimicrobial Therapy:** Genetic diagnoses prevent prolonged courses of antibiotics for presumed sepsis or meningitis. [2]

**Invasive Diagnostic Procedures:** Brain biopsies, repeated lumbar punctures, and extensive metabolic workups can be avoided when genetic diagnosis is established. [4]

## Palliative Care and End-of-Life Decision-Making

Early genetic diagnosis plays a **critical role in facilitating palliative care transitions** for infants with lethal conditions. Studies show that **19-36% of management changes following genetic diagnosis involve transition to palliative care**. [5] This has profound implications:

**Informed Decision-Making:** Genetic diagnosis of severe, life-limiting conditions enables families to make informed choices about treatment intensity versus comfort care. [9-10] The American Academy of Neurology position statement emphasizes that **rapid genomic testing in neonates creates new opportunities for neuropalliative care** but also challenges for informed consent and parental decision-making. [10]

**Reduction of Suffering:** Early recognition of lethal conditions allows **withdrawal of invasive interventions that would be ineffective**, reducing infant suffering and allowing focus on comfort measures. [5][11]

**Parental Psychological Impact:** Studies show that achieving a diagnosis **reduces parental anxiety by 30%**, while failure to diagnose increases anxiety by 15%. [4] However, the emotional complexity of receiving life-limiting diagnoses in the acute NICU setting requires careful counseling and support. [9][11]

**Ethical Considerations:** Research demonstrates that neonatologists may **inappropriately apply uncertain genetic findings** (variants of uncertain significance) or diagnoses predicting neurodevelopmental impairment to recommend palliative rather than intensive care. [12] This highlights the need for **genetics education and careful interpretation** of results in clinical decision-making.

### Implementation Barriers and Solutions

Despite clear benefits, widespread implementation faces several barriers identified in systematic reviews: [13]

**Provider Knowledge Gaps:** Clinicians report concerns about **lack of genetics knowledge, informed consent processes, and appropriate results interpretation**. Your observation that NICU physicians failed to recognize the BRAT1 phenotype illustrates this gap. [13]

**Personnel Availability:** Shortage of genetic counselors and genetics-trained physicians limits capacity for timely testing and results interpretation. [13]

**Equitable Access:** **Lack of translated consent documents** limits participation of non-English/Spanish-speaking families, and racial disparities exist in who qualifies for and receives genetic services. [6][13]

**Standardization Solutions:** Implementation of **clinical guidelines standardizing genomic testing criteria** significantly improves outcomes. One study showed that standardized protocols increased genetics consultations from 25.6% to 31.2% ( $p=0.007$ ), genomic testing completion from 9.0% to 24.6% ( $p<0.001$ ), and confirmed diagnoses from 8.2% to 11.6% ( $p=0.02$ )—while **reducing admission length and hospital charges**. [6]

### Regional NICU Protocol Recommendations

Based on the evidence, regional NICUs should implement:

1. **First-tier rapid genome sequencing** for critically ill infants with suspected genetic disorders, rather than sequential targeted testing [1][8]
2. **Standardized clinical criteria** for genomic testing to ensure equitable access across racial and birth weight categories [6]
3. **Integrated genetics teams** including genetic counselors, clinical geneticists, and trained neonatologists for rapid interpretation and family counseling [13]
4. **Phenotype recognition training** for NICU staff on recognizable genetic syndromes, particularly lethal conditions where early recognition prevents futile care
5. **Palliative care pathways** that enable rapid transition to comfort care when lethal genetic diagnoses are confirmed [10-11]

6. **Pre-test counseling protocols** that prepare families for the range of possible outcomes, including life-limiting diagnoses [9]

Your experience demonstrates that the **\$35 targeted test preventing >\$3 million in futile care** represents the extreme end of cost-effectiveness, but even broader implementation of rapid genome sequencing at \$12,297 per test remains cost-saving through reduced hospital stays and prevented interventions. [7]

Would you like me to help develop specific clinical pathways or educational materials for regional NICU staff to improve recognition of lethal genetic syndromes like BRAT1 and TSPYL1?

1.

[National Rapid Genome Sequencing in Neonatal Intensive Care.](#)

JAMA Network Open. 2024. Marom D, Mory A, Reytan-Miron S, et al.

2.

[Application of Full-Spectrum Rapid Clinical Genome Sequencing Improves Diagnostic Rate and Clinical Outcomes in Critically Ill Infants in the China Neonatal Genomes Project.](#)

Critical Care Medicine. 2021. Wu B, Kang W, Wang Y, et al.

3.

[Effect of Whole-Genome Sequencing on the Clinical Management of Acutely Ill Infants With Suspected Genetic Disease: A Randomized Clinical Trial.](#)

JAMA Pediatrics. 2021. Krantz ID, Medne L, Weatherly JM, et al.

4.

[Transforming NICU Care: Rapid WES and Transcriptomics-Validation, Social Impact, and Cost Analysis.](#)

European Journal of Pediatrics. 2025. Martín López-Pardo B, Barbosa-Gouveia S, Vázquez-Mosquera ME, et al.

5.

[Genomic Medicine for Undiagnosed Diseases.](#)

Lancet. 2019. Wise AL, Manolio TA, Mensah GA, et al.

6.

[Standardized Criteria for Genomic Testing in the NICU.](#)

Pediatrics. 2025. Helm BM, Hays M, Swaggart KA, et al.[New](#)

7.

[Rapid Genome Sequencing Compared With a Gene Panel in Critically Ill Infants With a Suspected Genetic Disorder: An Economic Evaluation.](#)

[The Journal of Pediatrics.](#) 2025. Lavelle TA, Maron JL, Kingsmore SF, et al.

8.

[Rapid Exome Sequencing as a First-Tier Test in Neonates With Suspected Genetic Disorder: Results of a Prospective Multicenter Clinical Utility Study in the Netherlands.](#)

European Journal of Pediatrics. 2023. Olde Keizer RACM, Marouane A, Kerstjens-Frederikse WS, et al.

9.

[Rapid Genome Sequencing: Consent for New Technologies in the Neonatal Intensive Care Context.](#)

Pediatrics. 2022. Lynch F, Prentice T, Gillam L, Stark Z, Gyngell C.

10.

[Clinical Guidance in Neuropalliative Care: An AAN Position Statement.](#)

Neurology. 2022. Taylor LP, Besbris JM, Graf WD, et al.[Guideline](#)

11.

[Rapid Challenges: Ethics and Genomic Neonatal Intensive Care.](#)

Pediatrics. 2019. Gyngell C, Newson AJ, Wilkinson D, Stark Z, Savulescu J.

12.

[Influence of Genetic Information on Neonatologists' Decisions: A Psychological Experiment.](#)

Pediatrics. 2022. Callahan KP, Flibotte J, Skraban C, et al.

13.

[Benefits and Barriers to Broad Implementation of Genomic Sequencing in the NICU.](#)

American Journal of Human Genetics. 2025. Goldin MR, Ruderfer DM, Bick A, et al.



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**D. Holmes Morton MD, Senior Physician, Consultant in Pediatrics, Metabolism, and Genomic Medicine**

**THE PAPER NEJM 1986 ANTECEDENTS OF CEREBRAL PALSY IS OF MORE THAN HISTORICAL INTEREST:**

WHAT ARE THE BROAD IMPLICATIONS THAT THESE CASES OF BRAT1 AND TSPYL WERE MANAGED FOR WEEKS AS *BIRTH ASPHYXIA CASES*, AS PART OF A STANDARDIZED, NATIONWIDE, PROTOCOL TO PREVENT "CEREBRAL PALSY." To say the least, this was obviously Futile Care in a NICU for BRAT1 & TSPYL.

WHAT PORTION OF POOR NEUROLOGICAL OUTCOMES CALL "CEREBRAL PALSY" HAVE BIRTH HYPOXIA AS A DEFINITE CAUSE? WHAT PORTION OF POOR NEUROLOGICAL OUTCOMES CALL "CEREBRAL PALSY" HAVE A GENETIC CAUSE?

**Birth hypoxia accounts for less than 10% of cerebral palsy cases, while up to 30% of cerebral palsy cases have a substantial genetic contribution. [1-2]**

**WHAT IS THE VALUE OF TESTING PARENTS, IDENTIFYING RISKS FOR TREATABLE & UNTREATABLE GENETIC DISORDERS IN A COMMUNITY?**

**"AMISH CEREBRAL PALSY"**

Ruthie, Amish GA1, age 39 years. She was injured by a GA1-crisis at 6-months of age, during an otherwise uncomplicated "chicken-pox" infection.



**ANTECEDENTS OF CEREBRAL PALSY**

**Multivariate Analysis of Risk**

KARIN B. NELSON, M.D., AND JONAS H. ELLENBERG, PH.D.

**Abstract** We examined prenatal and perinatal factors predicting cerebral palsy, using multivariate analysis to investigate which factors were most important and the proportion of cases for which they accounted. Maternal mental retardation, birth weight below 2001 g, and fetal malformation were among the leading predictors. Breech presentation was also a predictor, but breech delivery was not. A third of the children with cerebral palsy who had breech presentations had a major noncerebral malformation.

Among 189 children with cerebral palsy, 40 (21 percent) had at least one of three clinical markers suggestive of asphyxia; only 17 of these 40 children (9 percent of all cases) lacked major congenital malformation or other intrinsic defects that might have contributed

to an unfavorable outcome.

When all the principal risk factors present by the time labor began were considered, the 5 percent of the population at highest estimated risk was seen to have contributed 34 percent of the cases. When all the risk factors present during the period beginning before pregnancy and extending through the nursery stay were included, the 5 percent at highest risk was seen to have contributed 37 percent of the cases. Thus, the inclusion of information about the events of birth and the neonatal period accounted for a proportion of cerebral palsy only slightly higher than that accounted for when consideration was limited to characteristics identified before labor began. (N Engl J Med 1986; 315:81-6.)

**Glutaric acidemia type 1: Treatment and outcome of 168 patients over three decades.** Kevin A. Strauss<sup>a,b,c</sup>, Katie B. Williams<sup>a</sup>, Vincent J. Carson<sup>a,b</sup>, Laura Poskitt<sup>a,b</sup>, Lauren E. Bowser<sup>a</sup>, Millie Young<sup>a</sup>, Donna L. Robinson<sup>a</sup>, Christine Hendrickson<sup>a</sup>, Keturah Beiler<sup>a</sup>, Cora Taylor<sup>d</sup>, Barbara Haas-Givler<sup>d</sup>, Jennifer Hailey<sup>e</sup>, Stephanie Chopko<sup>f</sup>, Erik G. Puffenberger<sup>a</sup>, Karlla W. Brigatti<sup>a</sup>, Freeman Miller<sup>g</sup>, D. Holmes Morton<sup>a,b,h</sup>  
*Molecular Genetics and Metabolism June 2020, Accepted, In Press Oct 2020.*

- 1) Maternal mental retardation, birth weight below 2001 grams (4 lb 4 oz), fetal malformations –
  - 2) Breech presentation was a predictor of cerebral palsy, but breech delivery was not.
  - 3) A third of children with cerebral palsy who had breech presentation (also) had a major non-cerebral malformation.
- When all the principle factors present at the time of labor were considered, the 5 percent at highest risk was seen to have contributed 34 % of the cases (of cerebral palsy.)

*When all the risk factors present during the period ...before pregnancy and extending through the nursery stay were included, the 5 percent at highest risk was seen to have contributed 37 % of the cases (of cerebral palsy.)*

**CONCLUSION:** Events during labor, delivery, and the neonatal period accounted for an increase in the incidence of "cerebral palsy" of only 3%.

The majority of cases of cerebral palsy are associated with problems that pre-date labor, delivery, and neonatal transition - that is to say - the majority of cases of cerebral palsy are caused by Genetic Disorders.

For the Plain Sub-Populations of Pennsylvania we now know what the underlying disorders are - 35 years forward in Time from the important NEJM paper by Karen Nelson & Jonas Ellenberg "Antecedents of Cerebral Palsy, Multivariant Analysis of Risk" NEJM 1986; 315:81-6.

#### DISORDERS ASSOCIATED WITH SEIZURES – AUTISM – MENTAL RETARDATION

- ADAR Acardi-Goutieres VI, inflammation induced seizures & strokes
- BRAT1 Lethal neonatal seizures with diffuse brain degeneration
- BTD Biotinidase Deficiency, three variants
- CNTNAP2 Seizures & Autism, a Dravet Syndrome variant, MTOR Seizures
- CACNA1C Timothy Syndrome Long-QTc, Sudden Death & Seizures (AD-Denovo)
- CACNA1G Atonic seizures, Recessive, Somerset, single case.
- DEPDC5 AD Mennonite
- HPRT1 Lesch-Nyhan Disease Generalized New x-linked Variant
- LONP1 CODAS syndrome, Abnormal Pharyngeal Innervation, Seizures, Often Lethal in Infancy Because Airway Obstruction & Aspiration
- ELP2 Global developmental delay and seizures
- ERCC6 Lethal Cockayne Variant with diffuse brain degeneration
- GJC2 Central hypomyelination, congenital nystagmus, late onset seizures
- GLB1 GM1 gangliosidosis, congenital nystagmus, seizures, Lethal Apnea
- KRIT1 CNS Cavernous venous malformations, headache and seizure syndrome
- MECP2 Development arrest - girls late onset seizures, males early feature
- MELAS Poor growth, Deafness, lactic acidemia, strokes and seizures
- MMACHC Cobalamin C Deficiency, CNS methionine deficiency
- MTHFR Development stagnation, Autism, Seizures

#### DISORDERS WITH SEIZURES AS A CLINICAL PROBLEM

- NPRL3 AD, Mennonite
- PCCB Propionic Acidemia
- POLG Development regression and seizures – Lethal
- RYR1 Seizures with Malignant Hyperthermia
- SCN1A Complex partial, intractable, fever associated (AD- denovo)
- SAMHD1 Acardi-Goutieres V, inflammation induced seizures & strokes
- SIAT9 GM3 Synthase Deficiency – Lethal?
- SYNGAP1 Severe anxiety, complex partial seizures. (AD, denovo)
- SNIP1 Skull malformations, Mental Retardation, Seizures
- SCN1B AD, Mennonite, complex partial, late onset
- STRADA Macrocephaly, Dysmorphology, Intractable MTOR Seizures
- SYN1 Cerebellar Ataxia and Seizures – Lethal Adult Onset
- STZ2 Intractable Seizures, mTOR Brain Overgrowth (2 variants)
- TSPYL Lethal Neonatal Apnea & Bradycardia, Brainstem & Cortical Malformations
- VIT K & D Deficiency Associated Seizures: How Common?
- WDR73 Congenital nystagmus, dystonia, ataxia, seizures, Lethal Childhood
- WDR45 x-linked, Intractable seizures of infancy neurodegeneration (De-novo)
- ZDHC16 Lethal Neonatal Apnea & Bradycardia, Brainstem & Cortical Malformations
- ZFYVE26 Childhood onset, later onset Spasticity & Seizures, Adult Lethal

#### LETHAL INHERITED DISORDERS OLDER CHILDREN & ADULTS

- ABCB7 Ataxia & Dystonia Associated with Sideroblastic Anemia & Lethal Hypertrophic Cardiomyopathy x-linked
- ERCC6 Lethal Cockayne Variant with Diffuse Brain Degeneration
- GJC2 Central hypomyelination, congenital nystagmus, late onset seizures Lethal
- HPRT1 Lesch-Nyhan Disease Generalized Dystonia x-linked Variant
- LONP1 CODAS syndrome, Abnormal Pharyngeal Innervation, Seizures, Often Lethal in Infancy Because Airway Obstruction & Aspiration
- MECP2 Development arrest - girls late onset seizures, males early feature
- POLG Development regression and seizures - Lethal
- POMT1 Lethal Brain Malformations, Hydrocephalus, Muscular Dystrophy
- RYR1 Malignant Hyperthermia & Seizures
- RYR2 Cardiac Arrhythmia & Dilated Heart Failure – Two Variants
- SIAT9 GM3 Synthase Deficiency – Childhood Lethal
- STRAD-A Macrocephaly, Characteristic Dysmorphology, Intractable Seizures
- SYN1 Cerebellar Ataxia and Seizures – Progressive, Lethal Adult-Onset
- WDR73 Congenital nystagmus, dystonia, ataxia, seizures, Lethal Childhood
- ZFYVE26 Childhood onset, progressive spasticity, seizures, Adult Lethal

#### BIRTH DEFECTS IN THE “GENERAL POPULATION” ARE COMMON: March of Dimes

Reports 1/6 (17%) of infants are born with problems called “Birth Defects.” In Pennsylvania the Birth Rate in 2016 was 139,400 > ~23,200 infants will be born each year with a birth defect. In all populations the rate of Birth-Defects 1/6 or 17%: 166/1000, 1666 per 10,000 births. Oregon where women have access to medical abortion recently reported the prevalence of birth defects to be 7.6% - approximately ½ the rate in Pennsylvania.

#### TABLES BELOW LIST DISORDERS IN THE AMISH & MENNONITE POPULATIONS THAT WERE PREVIOUSLY UNDIAGNOSED AND WERE OFTEN REFERRED TO IN THE MEDICAL RECORD AS “CEREBRAL-PALSY.

” “AUTISM,” “MENTAL RETARDATION,” “EPILEPSY” SIDS OR SUDDEN UNEXPLAINED INFANT-DEATHS OR ATTRIBUTED TO “VACCINATIONS.” *I was recently told by a mother that she was not going to give vaccines to her children because she had two nephews who had gotten all their shots and were “autistic” and she believed the “baby-shots” had caused their “autism.”*

#### OPENEVIDENCE -AI

WHAT PORTION OF POOR NEUROLOGICAL OUTCOMES CALL "CEREBRAL PALSY" HAVE BIRTH HYPOXIA AS A DEFINITE CAUSE? WHAT PORTION OF POOR NEUROLOGICAL OUTCOMES CALL "CEREBRAL PALSY" HAVE A GENETIC CAUSE?

**BIRTH HYPOXIA ACCOUNTS FOR LESS THAN 10% OF CEREBRAL PALSY CASES, UP TO 30% OF CEREBRAL PALSY CASES HAVE A SUBSTANTIAL GENETIC CONTRIBUTION. [1-2]**

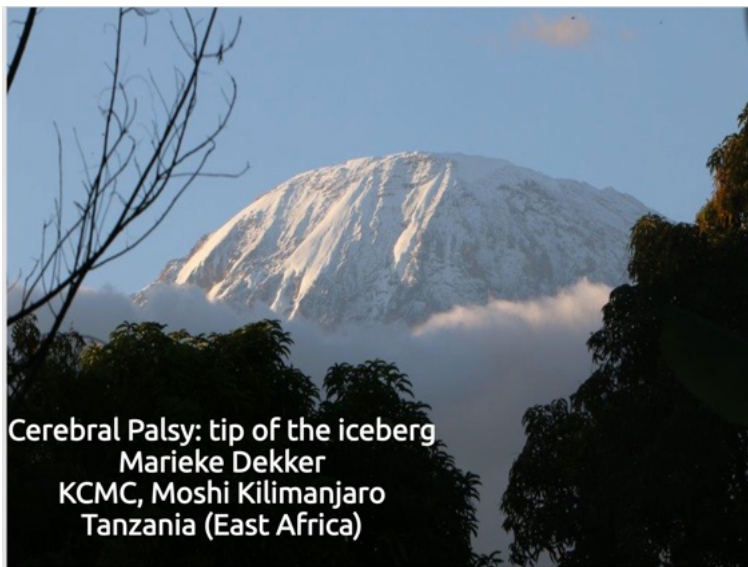
The historical assumption that birth asphyxia is a leading cause of cerebral palsy has been definitively refuted by large population-based studies. Despite widespread use of electronic fetal monitoring and a five-fold increase in cesarean section rates, the incidence of cerebral palsy has remained unchanged over 50 years. [2] Multiple controlled studies across different countries and populations have consistently shown that birth asphyxia is an uncommon cause of neonatal encephalopathy and accounts for less than 10% of cerebral palsy cases. [2] Even when both clinical and biochemical markers of severe perinatal hypoxia are present (Apgar score 0-3 combined with umbilical cord pH <7.00), only 15.2% of affected newborns develop cerebral palsy. [3]

Regarding genetic causes, recent advances in genomic testing have revealed a much larger genetic contribution than previously recognized. Up to 30% of people with cerebral palsy have

substantial genetic contributions involving gene variations associated with brain development, neuronal signaling, motor control, and musculoskeletal function. [1] A meta-analysis of exome sequencing studies found an overall diagnostic yield of 23% across all cerebral palsy cases, rising to 35% in cryptogenic cerebral palsy (cases without identified risk factors) compared to only 7% in cases with known risk factors. [4] The genetic landscape overlaps significantly with other neurodevelopmental disorders including intellectual disability, epilepsy, and autism. [5]

Pediatric neurology, what we see more and what we see less

	Africa	High Income Countries	Background		Africa	High Income Countries	Background
CNS Infections*	+++	+	Viral as well as ABM, parasitic	Spinal cord injury (medical and traumatic)	++	+/-	Generic outcome of burden of infection + trees/trees
HIE	++++	+	% of CP cases	Sciatic nerve injury	++	-	Gluteal injections standard of care all ages
Bilirubin Encephalopathy	++	+/-	Delayed to absent phototherapy, no ex transfusion	Neurotrauma	++	+	Mostly traffic and trees
Prematurity	++	++		Paraquat/OP/warfarin	++	-	Agricultural society with ready access
Post anoxic encephalopathy	+++	+	Poor perinatal monitoring, risk assessment	FND: PNEA	++	+	Minimal 1 <sup>st</sup> line healthcare with stigma on MH
Epilepsy	+++	+	Generic outcome of all of above	Chronic daily headache	++	++	No pharmacovigilance
Metabolic disorders	?	+	Unknown	Sydenham Chorea	+	+/-	Steady incidence, mild decrease
Major neurogenetic or neurodevelopmental dis	++	+	No prenatal screening and religious objection	Rabies, tetanus	+	-	Neglected tropical diseases which continue
Vitamin deficiencies	++	+/-	Supplementation is not standard care but incidence is decreasing	ADHD, dyslexia	-	-	Query ADHD: <10 times in 13y. Dyslexia: never.

Cerebral Palsy: tip of the iceberg  
 Marieke Dekker  
 KCMC, Moshi Kilimanjaro  
 Tanzania (East Africa)

**The majority of cerebral palsy cases (94%) involve brain injury or abnormalities occurring during the prenatal or perinatal period, with only 6% arising postnatally. [1]**

**However, for many individuals, the specific cause remains unknown because of poor access to genetic tests as in East Africa and many medical centers in the USA, as discussed above for BRAT1 & TSPYL. In some cases, despite thorough clinical & genetic investigations. New causes of acquired**

**& genetic disorders of brain that cause the collective disabilities called “cerebral palsy” are continuously being recognized through thoughtful caring for patients & basic research.**

1. [Cerebral Palsy](#). Lancet. 2025. Novak I, Jackman M, Finch-Edmondson M, Fahey M. **New**
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4. [Molecular Diagnostic Yield of Exome Sequencing and Chromosomal Microarray in Cerebral Palsy: A Systematic Review and Meta-analysis](#). JAMA Neurology. 2022. Srivastava S, Lewis SA, Cohen JS, et al.
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