379

Behind The Seizure™: A No-cost, 125-gene Epilepsy Panel for Pediatric Seizure Onset Between 2–4 Years

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Introduction

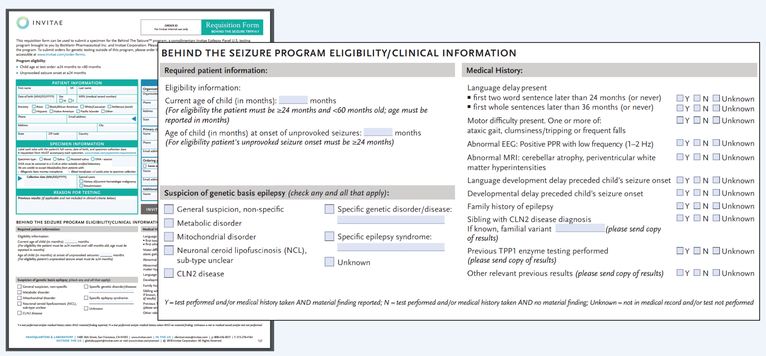
Epilepsy is a Common Childhood Neurological Disorder[1]

- >50% of pediatric-onset seizures have a genetic basis. Many epilepsies are still diagnosed based on seizure semiology (+/- EEG) and not with molecular genetic testing
- Epilepsy gene panels may uncover the etiology of pediatric seizures and expedite the time to treatment
- CLN2 disease, one form of Neuronal Ceroid Lipofuscinosis (NCL), commonly presents non-specifically with seizures and a history of language development delay at 2–4 years of age[3]
- Genetic testing may impact clinical management (e.g., choice of AED, targeted therapy), shorten diagnostic journey, avoid unnecessary testing, lead to clinical trial enrollment opportunity, and facilitate genetic counseling/family planning
- Behind the Seizure (*BTS*, www.invitae.com/en/behindtheseizure/) is a no-cost gene panel program for children aged 2 to 4 years, who experienced their first unprovoked seizure after the age of 2
- The BTS program provides a 125-gene panel with an average turnaround time of 10–14 days (Invitae Epilepsy Panel) with the option to add on preliminary-evidence genes
- CLN2 disease diagnoses occurs on average at 5 years old: a full 2 years after average seizure onset and after significant neurodegeneration[3,4]
- Our objective is to determine whether this testing approach (*BTS*) can decrease the age of diagnosis in CLN2 disease

Methods

- Data from BTS program tests reported between December 4, 2016 and January 24, 2018

Figure 1. Behind the Seizure (*BTS*) Requisition Form



- Variants classified according to ACMG standards[5]:
  - Pathogenic (PATH), Likely Pathogenic (LPATH), Variant of Uncertain Significance (VUS), Benign (BEN), Likely Benign (LBEN)
- Molecular diagnosis (MDx) defined as:
  - 1 variant in a gene (PATH or LPATH) with autosomal dominant inheritance, X-linked dominant, X-linked recessive (male) OR,
  - 2 variants (PATH or LPATH) in a gene with autosomal recessive inheritance
- Outcome groups: Data divided into 3 groups by outcome:

Outcome Group	Description
No MDx	No molecular diagnosis identified
All MDx	Any molecular diagnosis in a gene included in the Invitae Epilepsy Panel
CLN2 Disease MDx	Molecular diagnosis of CLN2 disease (biallelic TPP1 variants, PATH or LPATH)

BTS Data Collected:
- Patient Age
- Physician Suspicion of Genetic Basis
- Medical History

Next Best Action/Test:
(1) 1 PATH/LPATH for AR condition, OR
(2) 1 VUS for AD condition, with:
- No MDx identified
- Follow-up testing available or change in management for condition

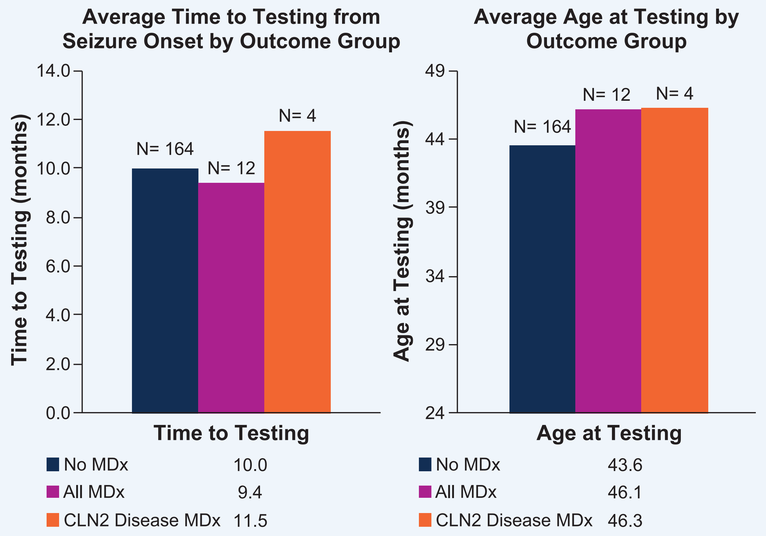
- Suspicion of genetic basis and medical history were optional on the requisition form — a blank item was not taken to be a negative
  - All proportions calculated based on this data used the total number of orders where "y" or "n" was selected

Results

Summary

- From December 4, 2016 to January 24, 2018, 176 tests have been reported to eligible patients through the *BTS* program with 12 molecular diagnoses **(Table 1)**
- Average age at testing, age at first seizure, and time to testing from seizure onset were similar between all outcome groups

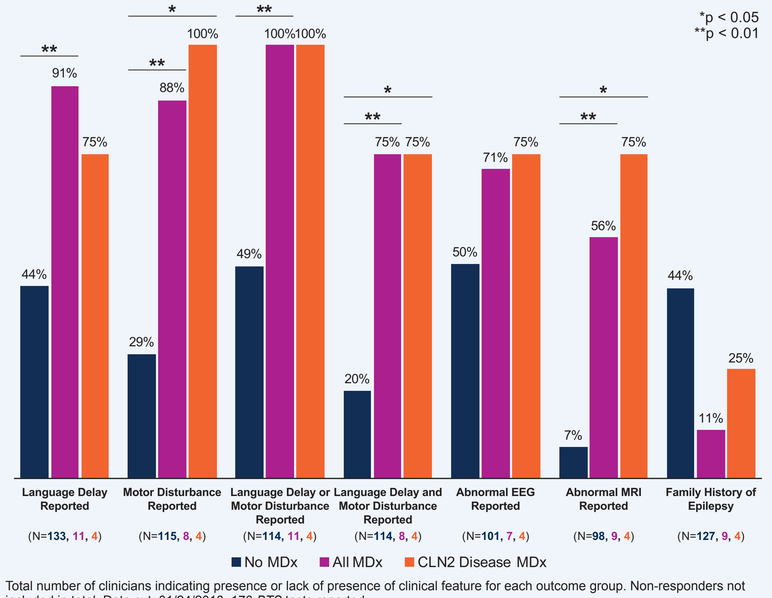
Figure 2. Age and Time to Testing



Data cut: 01/24/2018, 176 *BTS* tests reported.

- Diagnosis of CLN2 disease was 1–2 years earlier than reported average (11.5 months from seizure onset to diagnosis versus 2–3 years)[5]

Figure 3. Clinical Presentation by Outcome Group



Total number of clinicians indicating presence or lack of presence of clinical feature for each outcome group. Non-responders not included in total. Data cut: 01/24/2018, 176 *BTS* tests reported.

- Large differences in clinical features were seen between No MDx and All MDx Outcome Groups: Presence of language delay (44.4% vs. 90.9%, respectively) and motor disturbance (28.7% vs. 87.5% respectively)
- Language delay or motor disturbance was reported in 100% of patients in the All MDx group, versus 49% in the No MDx group. These features may be subtle
- Abnormal EEG and MRI higher in All MDx outcome groups
  - Use of EEG and MRI, as defined by clinician reporting, was similar between the two groups (58–61% vs. 58–75%)
- Family history of epilepsy was not a good predictor of molecular genetic testing outcome (11.1% of All MDx, 44.1% of No MDx)
  - Most conditions here are autosomal dominant **(Table 1)**
- Suspicion of a genetic etiology of epilepsy was not different between the No MDx and All MDx group (95% of ordering clinicians versus 75%, respectively)
- Where a molecular diagnosis of CLN2 disease was found, only 1 of 4 ordering physicians noted suspicion of CLN2 disease

Table 1. Molecular Diagnoses

Gene	Inheritance	Conditions	Possible Management Implication	Number of Diagnoses (n=12)
TPP1	AR	CLN2 disease (Ceroid lipofuscinosis, neuronal [NCL, CLN2]), 2	Approved therapy for eligible patients in the US and EU	4
SCN1A	AD	Epilepsy, generalized, with febrile seizures plus, type 2 Epileptic encephalopathy, early infantile, 6 (Dravet syndrome) Febrile seizures, familial, 3A Migraine, familial hemiplegic, 3	Pharmacogenomic information available (PharmGKB: Avoid sodium channel blockers) Interventional clinical trials open for enrollment (Stiripentol)	1
MECP2	XLD	Rett syndrome	Interventional clinical trials open for enrollment for Rett Syndrome, females only	1
SYNGAP1	AD	Mental retardation, autosomal dominant 5	No disease-altering treatment or pharmacogenomic information available (PharmGKB)	3
CHD2	AD	Epileptic encephalopathy, childhood-onset	No disease-altering treatment or pharmacogenomic information available (PharmGKB)	1
GPHN	AD/AR	Molybdenum cofactor deficiency C	No disease-altering treatment or pharmacogenomic information available (PharmGKB)	1
GRIN2A	AD	Epilepsy, focal, with speech disorder and with or without mental retardation	NMDA inhibitors (under proof of concept)[8] No disease-altering treatment or pharmacogenomic information available (PharmGKB)	1

Table 2. Next Best Action/Test Cases

Criteria	Gene	Associated Condition(s)	Next Test/Action	Number of Cases
1 1 PATH for AR condition with no MDx	*ALHD7A1*	Epilepsy, pyridoxine-dependent	Alpha-aminoadipic semi-aldehyde test	1
	PPT1	Ceroid lipofuscinosis, neuronal, 1	PPT1 enzyme activity test	1
2 1 VUS for AD condition with no MDx	*DEPDC5*	Numerous autosomal dominant epilepsies	Rapamycin (under proof of concept)[8]	2
	GRIN2A	Epilepsy-aphasia, West syndromes	NMDA inhibitors (under proof of concept)[8]	4
	GRIN2B	Lennox-Gastaut, West syndromes	NMDA inhibitors (under proof of concept)[8]	4
	KCNQ2	Early-onset epileptic encephalopathy, Benign familial neonatal seizures	Na+ channel blockers, K+ channel openers (under proof of concept[8]	4
	KCNT1	Seizures, Early-infantile epileptic encephalopathy, West syndrome	Quinidine (under proof of concept)[8]	4
	MTOR	Intractable epilepsy, focal epilepsy	Rapamycin (under proof of concept)[8]	1
	SCN1A	Dravet syndrome, Genetic epilepsy with febrile seizures plus	Pharmacogenomic information available (PharmGKB: Avoid sodium channel blockers) Interventional clinical trials open for enrollment (Stiripentol)	7
	SCN2A	Early-onset and early-infantile epileptic encephalopathy	Phenytoin or other Na+ channel blockers for GOF[8], Na+ channel blockers contraindicated for LOF[8]	1
	SCN8A	Infantile epilepsy with migrating focal seizures	Phenytoin or other Na+ channel blockers for GOF[8], Na+ channel blockers contraindicated for LOF[8]	5
	TSC1/TSC2	Tuberous sclerosis 1/2	Interventional clinical trials underway[9] Vigabitrin for infantile spasms. Review clinical criteria for tuberous sclerosis[11]	2

Change from VUS to PATH/LPATH for AD trait with new evidence, for example if determined to be de novo, would lead to a molecular diagnosis.

Conclusions

- The data set supports early testing of patients with language delay or motor disturbance as being associated with MDx
- Decreased time from seizure onset to diagnosis through *BTS* points to no-cost gene panel testing as an effective means to decrease time to diagnosis in CLN2 disease
- Next Best Actions/Tests illustrated here include subsequent testing or treatments which could be used to impact management
  - Epilepsy gene panels identifying cases where there is a VUS and a PATH or only 1 PATH/LPATH in a gene associated with an autosomal recessive trait can be followed by other types of testing when available; for example, inconclusive cases in *TPP1* can be followed up with a TPP1 enzyme activity test to rule out CLN2 disease
  - Consultation with genetic counselor/genetics teams may be of benefit as they may be well versed in next best test in such cases
- Suspicion of a genetic etiology and family history of epilepsy are not good predictors of genetic testing outcome in this dataset; language delay and motor disturbance are the best indicators of genetic testing outcome
- Time from seizure onset to testing does not appear to influence outcome of molecular genetic testing (molecular diagnosis vs. no molecular diagnosis). MDx can however decrease the time to the diagnosis of the etiology of seizures such as in diagnosis of CLN2 disease

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1. Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. Epileptic Disorders. 2015 Jun 1;17(2):117-23. **2.** Wang J, Lin ZJ, Liu L, Xu HQ, Shi YW, Yi YH, He N, Liao WP. Epilepsy-associated genes. Seizure-European Journal of Epilepsy. 2017 Jan 1;44:11-20. **3.** Nickel M, Jacoby D, Lezius S, et al. Natural history of CLN2 disease: quantitative assessment of disease characteristics and rate of progression. Poster session presented at: The 12th Annual WORLD Symposium; February – March 2016; San Diego, CA. **4.** Schulz, A., Miller, N., Mole, S.E., and Cohen-Pfeffer, J.L. Neuronal ceroid lipofuscinosis-2 (CLN2) natural history and path to diagnosis: International experts' current experience and recommendations on CLN2 disease, a type of Batten disease, resulting from TPP1 enzyme deficiency. Eur J Paediatr Neurol. 2015; 19: S119. **5.** Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine. 2015 May;17(5):405. **6.** Schulz et al., 2018. Manuscript submitted to Lancet Neurology. Under review. **7.** M. Whirl-Carrillo, E.M. McDonagh, J. M. Hebert, L. Gong, K. Sangkuhl, C.F. Thorn, R.B. Altman and T.E. Klein. "Pharmacogenomics Knowledge for Personalized Medicine" Clinical Pharmacology & Therapeutics (2012) 92(4): 414-417. **8.** Mei D, Parrini E, Marini C, Guerrini R. Mol Diagn Ther. 2017. **9.** Clinicaltrials.gov, accession 02/27/2018. **10.** Genetic Testing Registry. http://www.ncbi.nlm.nih.gov/gtr/. Accession 02/27/2018. **11.** Northrup H, Krueger DA, Roberds S, Smith K, Sampson J, Korf B, Kwiatkowski DJ, Mowat D, Nellist M, Povey S, de Vries P. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatric neurology. 2013 Oct 1;49(4):243-54.

http://www.biomarin.com/pdf/ACMG2018p3.pdf

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