Topic Brief: Whole Genome Sequencing for Epilepsy

Date: 10/31/2022
Nomination Number: 1006

Purpose: This document summarizes the information addressing a nomination submitted on June 3, 2022, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: Whole genome sequencing for diagnosis of genetic-based epilepsy has the potential to lead to efficient and effective treatment, but its clinical utility has not been established, and insurers do not cover the cost of tests. A new systematic review on the effectiveness of whole genome sequencing in epilepsy could ultimately contribute to practice and policy change.

Findings: The EPC Program will not develop a new systematic review because we did not find enough primary studies addressing the concerns of this nomination.

Background

Epilepsy is a brain disorder that causes seizures. In 2015, 1.2 percent (about 3.4 million) of the total United States population had active epilepsy. There are varied etiologies for seizures including stroke, brain tumor, traumatic brain injury, and central nervous system infection.[1] Epilepsy can also be genetic in origin, and this type accounts for 30 percent of all epilepsies.[2]

Developmental and epileptic encephalopathies (DEEs) are a group of severe, early onset epilepsies characterized by refractory seizures, developmental delay or regression associated with ongoing epileptic activity, and generally poor prognosis. Some of the most well-studied DEEs include infantile spasms as well as Dravet, Lennox-Gastaut, and West syndromes. The incidence of severe epilepsies that begin before 18 months is one in 2,000 births.[3]

The most common types of genetic causes of DEE are sequence changes (30-40% of cases) and chromosomal deletions or duplications (5-10% of cases).[3] Single gene defects in ion channels or neurotransmitter receptors have been associated with most inherited forms of epilepsy, including some focal and lesional forms as well as specific epileptic developmental encephalopathies. Genetic tests are available, including targeted assays and revolutionary tools that sequence all coding (whole exome) and non-coding (whole genome) regions of the human genome.[4] Treatment may include anti-epileptic medications, therapies involving brain stimulation, diet modification, and, in some cases, surgery.[5]

Scope

What is the clinical utility of whole genome sequencing in children with epilepsy?

Table 1. Questions and PICOTS (population, intervention, comparator, outcome)

Questions	Whole genome sequencing in pediatric epilepsy
Population	Individuals 18 years and younger with epilepsy
Interventions	Whole genome sequencing
Comparators	No genetic testing Other type of genetic testing
Outcomes	Treatment change, redirection of care, prognostic information, reproductive information, subspecialty referral, personal utility (patient-reported benefits), utility of negative or uncertain results, harms

Assessment Methods

See Appendix A.

Summary of Literature Findings

We did not find any systematic reviews and found only one primary study addressing the key question. The one primary study reported on immediate treatment changes following whole genome sequencing in pediatric neurology patients, 47.5 percent of whom had epilepsy.

Table 2. Literature identified for each question

Question	Systematic reviews (10/2019-10/2022)	Primary studies (9/2017-9/2022)
Question 1: Whole genome sequencing in pediatric epilepsy	Total: 0	Total: 1 • Prospective cohort: 1[6]

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

While whole genome sequencing may assist with diagnosis of genetic forms of epilepsy, which could lead to improved outcomes for patients, this has not been established and the literature is too sparse for a systematic review that could ultimately be used to influence practice and policy.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

References

1. Epilepsy Fast Facts. Centers for Disease Control and Prevention. doi: https://www.cdc.gov/epilepsy/about/fast-facts.htm#:~:text=Active%20Epilepsy&text=This%20is%20about%203.4%20million,million%20adults%20and%20470%2C000%20children.
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7. Begley CE, Durgin TL. The direct cost of epilepsy in the United States: A systematic review of estimates. Epilepsia. 2015 Sep;56(9):1376-87. doi: https://doi.org/10.1111/epi.13084. PMID: 26216617.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years October 26, 2022 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
    - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
    - EHC Program https://effectivehealthcare.ahrq.gov/
    - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
    - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
    - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
    - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- University of York Centre for Reviews and Dissemination database https://www.crd.york.ac.uk/CRDWeb/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/
- Joanna Briggs Institute http://joannabriggs.org/
- Epistemonikos https://www.epistemonikos.org/

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed for the last five years, October 26, 2017-October 26, 2022. We reviewed all studies identified titles and abstracts for inclusion. We classified identified studies by question and study design to estimate the size and scope of a potential evidence review.

Search strategy

Ovid MEDLINE ALL <1946 to October 25, 2022>
Date searched: October 26, 2022
1 exp *Epilepsy/ (102962)
2 (BECCT or BECTS or BRE or CAE or CECTS or Dravet or epilep* or "infantile spasms" or "Landau-Kleffner" or "Lennox Gastaut" or "nodding syndrome" or panayiotopoulos or rolandic or seizure$1 or west).ti,ab,kf. (321241)
3 or/1-2 (328759)
4 Whole Genome Sequencing/ (9067)
5 (NGS or WGS or ((complete or entire or full or next-generation or whole) adj3 genom*) or (genom* adj2 (sequenc* or test*))).ti,ab,kf. (181360)
6 or/4-5 (182822)
7 and/3,6 (2085)
8 7 and (baby or babies or "early onset" or infan* or ((month* or year*) adj2 (age or old or olds)) or neonat* or newborn* or toddler* or nursery or nurseries or preschool* or pre-school or child* or girl$1 or boy$1 or pediatric* or paediatric* or adolesc* or young* or school* or postnatal* or post-natal* or postpartum or post-partum or puerper* or preteen* or pre-teen* or teen* or juvenile$1 or youth*).ti,ab,kf. (525)
9 8 not ((exp animals/ not humans/) or (animal model* or bovine or canine or capra or cat or cats or cattle or cow or cows or dog or dogs or equine or ewe or ewes or feline or foal$1 or goat or goats or horse or hamster* or horses or invertebrate or invertebrates or macaque or macaques or mare or mares or mice or monkey or monkeys or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate or primates or rabbit or rabbits or rat or rats or rattus or rhesus or rodent* or sheep or simian or sow or sows or vertebrate or vertebrates or zebrafish).ti.) (491)
10 limit 9 to english language (468)
11 limit 10 to yr="2019 -Current" (259)
12 11 and ((meta-analysis or "systematic review").pt. or (meta-anal* or metaanal* or ((evidence or scoping or systematic or umbrella) adj4 (review or synthesis))).ti.) (2)
13 limit 10 to yr="2017 -Current" (338)
14 13 and ((controlled clinical trial or randomized controlled trial).pt. or (control$3 or group$1 or random* or trial).ti.) (6)
15 13 and (exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or (cohort$1 or comparative stud* or evaluation studies or follow-up* or longitudinal$3 or prospective$3 or retrospective$3 or "time series").ti,ab,kf.) (95)
16 or/12,14-15 (100)

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials
Date searched: October 26, 2022
1Epilepsy/ or Drug Resistant Epilepsy/ or Epilepsies, Partial/ or Epilepsy, Complex Partial/ or Epilepsy, Frontal Lobe/ or Epilepsy, Partial, Motor/ or Epilepsy, Partial, Sensory/ or Epilepsy, Rolandic/ or Epilepsy, Temporal Lobe/ or Epilepsy, Benign Neonatal/ or Epilepsy, Generalized/ or Epilepsy, Absence/ or Epilepsy, Tonic-Clonic/ or Nodding Syndrome/ or Spasms, Infantile/ or Epilepsy, Post-Traumatic/ or Epilepsy, Reflex/ or Epileptic Syndromes/ or Epilepsies, Myoclonic/ or Myoclonic Epilepsies, Progressive/ or Lafora Disease/ or MERRF Syndrome/ or Unverricht-Lundborg Syndrome/ or Myoclonic Epilepsy, Juvenile/ or Landau-Kleffner Syndrome/ or Lennox Gastaut Syndrome/ (2551)
2 (BECCT or BECTS or BRE or CAE or CECTS or Dravet or epilep* or "infantile spasms" or "Landau-Kleffner" or "Lennox Gastaut" or "nodding syndrome" or panayiotopoulos or rolandic or seizure$1 or west).ti,ab. (17592)
3 or/1-2 (17778)

4 Whole Genome Sequencing/ (21)
5 (NGS or WGS or ((complete or entire or full or next-generation or whole) adj3 genom*) or (genom* adj2 (sequenc* or test*))).ti,ab. (2103)
6 or/4-5 (2107)
7 and/3,6 (16)
8 7 and (baby or babies or "early onset" or infan* or ((month* or year*) adj2 (age or old or olds)) or neonat* or newborn* or toddler* or nursery or nurseries or preschool* or pre-school or child* or girl$1 or boy$1 or pediatric* or paediatric* or adolesc* or young* or school* or postnatal* or post-natal* or postpartum or post-partum or puerper* or preteen* or pre-teen* or teen* or juvenile$1 or youth*).ti,ab. (7)

Ovid APA PsycInfo <1806 to October Week 3 2022>
Date searched: October 25, 2022
1 exp Epilepsy/ (30058)
2 (BECCT or BECTS or BRE or CAE or CECTS or Dravet or epilep* or "infantile spasms" or "Landau-Kleffner" or "Lennox Gastaut" or "nodding syndrome" or panayiotopoulos or rolandic or seizure$1 or west).ti,ab. (77525)
3 or/1-2 (78255)
4 Genomic Sequencing/ (123)
5 (NGS or WGS or ((complete or entire or full or next-generation or whole) adj3 genom*) or (genom* adj2 (sequenc* or test*))).ti,ab. (2354)
6 or/4-5 (2399)
7 and/3,6 (109)
8 7 and (baby or babies or "early onset" or infan* or ((month* or year*) adj2 (age or old or olds)) or neonat* or newborn* or toddler* or nursery or nurseries or preschool* or pre-school or child* or girl$1 or boy$1 or pediatric* or paediatric* or adolesc* or young* or school* or postnatal* or post-natal* or postpartum or post-partum or puerper* or preteen* or pre-teen* or teen* or juvenile$1 or youth*).ti,ab. (49)
9 limit 8 to yr="2019 -Current" (18)
10 limit 9 to ("0830 systematic review" or 1200 meta analysis) (0)
11 limit 8 to yr="2017 -Current" (23)
12 limit 11 to "0300 clinical trial" (0)
13 limit 11 to ("0400 empirical study" or "0430 followup study" or "0450 longitudinal study" or "0451 prospective study" or "0453 retrospective study" or 1800 quantitative study) (9)

EPISTEMONIKOS
Date searched: October 26, 2022
(title:((title:(Epilepsy OR epileptic OR BECCT OR BECTS OR BRE OR CAE OR CECTS OR Dravet OR "infantile spasms" OR "Landau-Kleffner" OR "Lennox Gastaut" OR "nodding syndrome" OR panayiotopoulos OR rolandic OR seizure* OR "west syndrome") OR abstract:(Epilepsy OR epileptic OR BECCT OR BECTS OR BRE OR CAE OR CECTS OR Dravet OR "infantile spasms" OR "Landau-Kleffner" OR "Lennox Gastaut" OR "nodding syndrome" OR panayiotopoulos OR rolandic OR seizure* OR "west syndrome")) AND (title:(NGS OR WGS OR ((complete OR entire OR full OR next-generation OR whole OR sequenc* OR test*) AND genom*)) OR abstract:(NGS OR WGS OR ((complete OR entire OR full OR next-generation OR whole OR sequenc* OR test*) AND genom*)))) OR abstract:((title:(Epilepsy OR epileptic OR BECCT OR BECTS OR BRE OR CAE OR CECTS OR Dravet OR "infantile spasms" OR "Landau-Kleffner" OR "Lennox Gastaut" OR "nodding syndrome" OR panayiotopoulos OR rolandic OR seizure* OR "west syndrome") OR abstract:(Epilepsy OR epileptic OR BECCT OR BECTS OR BRE OR CAE OR CECTS OR

Dravet OR "infantile spasms" OR "Landau-Kleffner" OR "Lennox Gastaut" OR "nodding syndrome" OR panayiotopoulos OR rolandic OR seizure* OR "west syndrome")) AND (title:(NGS OR WGS OR ((complete OR entire OR full OR next-generation OR whole OR sequenc* OR test*) AND genom*)) OR abstract:(NGS OR WGS OR ((complete OR entire OR full OR next-generation OR whole OR sequenc* OR test*) AND genom*))))) (8)

PROSPERO
Date searched: October 26, 2022
((Epilep* OR Dravet OR "infantile spasms" OR "Landau-Kleffner" OR "Lennox Gastaut" OR "nodding syndrome" OR panayiotopoulos OR rolandic OR seizure* OR "west syndrome") AND genom*) WHERE CD FROM 26/10/2019 TO 26/10/2022 (0)

ClinicalTrials.gov

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes. Severe epilepsies that begin before 18 months have an incidence of one in 2,000 births.[3]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the United States population or for a vulnerable population	Yes. An early diagnosis that could influence the course of treatment has the potential to affect overall costs associated with the condition.
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. A systematic review from 2015 reported epilepsy-specific annual cost estimates ranging from $8,412- $11,354 per year.[7]
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	Yes. We did not find any recent systematic reviews that address the nomination.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. The clinical utility of whole genome sequencing for epilepsy has not been established, so it is not standard practice and is not covered by insurers.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. The clinical utility of whole genome sequencing for epilepsy has not been established, so it is not standard practice and is not covered by insurers.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	Size/scope of review: we found only one primary study. A new systematic review would be limited