Unexplained refractory and/or suspect familial epilepsy: All patients should have completed:
- Magnetic resonance imaging (MRI)
- Electroencephalogram
Consider metabolic or autoimmune testing based on clinical presentation (see metabolic and autoimmune testing tables)

Family history of epilepsy with known variant
- YES
  - Order: FMTT / Familial Mutation, Targetted Testing
  - Perform any metabolic confirmatory assays recommended in interpretation and consider family studies for segregation analyses
- NO
  - Does the identified epilepsy include:
    - Congenital anomalies
    - Developmental delay
    - Intellectual disability
    - Autism
    - NO
      - Order: CMACB / Chromosomal Microarray, Congenital, Blood
      - Is a mitochondrial epilepsy suspected?
        - YES
          - Mitochondrial epilepsy syndrome suspected
            - A positive GDF15 / Growth Differentiation Factor 15 (GDF15), Plasma or FAPM / Fatty Acid Profile, Mitochondrial (C8-C18), Serum result increases the likelihood of a mitochondrial disorder
          - Definitive cause found
          - NO
            - Mitochondrial epilepsy NOT suspected
              - Is a myopathy present?
                - YES
                  - Perform any metabolic confirmatory assays recommended in interpretation and consider family studies for segregation analyses
                  - Definitive cause found
                - NO
                  - Definitive cause found
      - Negative or Inconclusive
  - NO
    - Specific epilepsy syndrome suspected?
      - YES
        - Order as appropriate:
          - CSTB / CSTB Gene, Repeat Expansion Analysis, Varies
          - HMMP / Hemiplegic Migraine With or Without Epilepsy Gene Panel, Varies
          - TSCP / Tuberous Sclerosis Gene Panel, Varies
          - CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies*
          - Definitive cause found
        - NO
          - Mitochondrial epilepsy syndrome suspected
          - Definitive cause found
          - Consider WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies or whole genome sequencing
          - Diser-specific management
        - NO
          - No chromosomal cause found
          - Is a mitochondrial epilepsy suspected?
            - YES
              - Mitochondrial epilepsy NOT suspected
              - Consider WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies or whole genome sequencing
              - Definitive cause found
            - NO
              - Mitochondrial epilepsy suspected
              - Definitive cause found
        - Negative or Inconclusive
      - NO
        - Definitive cause found
        - Disorder-specific management
        - Perform any metabolic confirmatory assays recommended in interpretation and consider family studies for segregation analyses
  - Definitive cause found

Chromosomal cause found
- YES
  - Order: EPPAN / Comprehensive Epilepsy With or Without Encephalopathy Gene Panel, Varies
  - Definitive cause found
- NO
  - Definitive cause found

Disorder-specific management
- NO
  - NO
    - Definitive cause found
  - YES
    - Consider WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies or whole genome sequencing
    - Definitive cause found

Disorder-specific management

*CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies can be used to modify any epilepsy panel or test any single gene included on any epilepsy panel.
**Segregation studies can be performed to determine if a variant segregates with the condition in a family and/or occurred de novo, which may clarify the significance of a variant. For more information, contact the Laboratory Genetic Counselors at 800-533-1710.