### Proposal form for the evaluation of a genetic test for NHS Service Gene Dossier

#### Test – Disease – Population Triad

| **Disease – name and description** (please provide any alternative names you wish listed) | Dravet Syndrome and its clinical sub-types: Classical Dravet syndrome is also termed Severe Myoclonic Epilepsy of Infancy (SMEI). There are subtle variants of Dravet which may have all the features of the syndrome except one such as without myoclonic seizures or without generalised spike and wave on EEG. These have been termed borderline variants of SMEI. Rather than ascribing multiple different names to marginally different phenotypes the term Dravet Syndrome is now preferred by Epileptologists to describe the group of severe infantile onset epilepsies associated with mutations in SCN1A. |
| **OMIM number for disease** | #607208, #182389, #604403 |
| **Gene – name and description** (please provide any alternative names you wish listed) | SCN1A, Sodium channel, neuronal type 1, alpha subunit |
| **OMIM number for Gene** | *182389 |
| **Mutational spectrum for which you test** | Nonsense, missense and frameshift mutations in all coding exons and intron boundaries. Large scale rearrangements of the gene (deletions and duplications) |
| **Technical Method(s)** | • Bi-directional DNA sequencing  
  • Multiplex Ligation-dependent Probe Amplification (MLPA) |
| **Validation Process**  
Note please explain how this test has been validated for use in your laboratory) | Grade A Trainee project: 6/6 mutations were identified in “blind” analysis using confirmation sensitive capillary electrophoresis (CSCE). A further panel of 20 patients with varied infantile epileptic encephalopathies, referred from a consultant paediatric neurologist, were screened using CSCE and DNA sequencing.  

Diagnostic testing methodologies: (DNA sequencing) Mutation scanning in single direction confirmed in opposite direction and again in an exon specific separate assay. All primers SNP and BLAST alignment checked. All mutations identified in previous grade a project were confirmed using this methodology. This methodology is well established in the laboratory for many disorders.  

(MLPA) Use of an MLPA kit designed specifically for the SCN1A gene. Exon 21 deletion control identified amongst 10 normal control samples, assay repeated to validate results. This methodology is well established in the laboratory for other disorders. |
| **Are you providing this test already? If yes, how many reports** | Yes  
POSITIVE 159 (32%) |
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
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<tbody>
<tr>
<td>have you produced?</td>
<td>NEGATIVE 327</td>
</tr>
<tr>
<td>NB please give the number of mutation positive/negative samples you have reported</td>
<td>PENDING SAMPLES 122</td>
</tr>
<tr>
<td>For how long have you been providing this service?</td>
<td>Since December 2005</td>
</tr>
<tr>
<td>Is there specialised local clinical/research expertise for this disease?</td>
<td>Yes X No Please provide details Dr Sameer Zuberi, Consultant Paediatric Neurologist is Lead Clinician for the Scottish Managed Clinical Network for Paediatric Epilepsy and runs joint genetics/neurology clinics with clinical geneticists</td>
</tr>
<tr>
<td>Are you testing for other genes/diseases closely allied to this one? Please give details</td>
<td>No</td>
</tr>
<tr>
<td>Your Activity How many tests do you (intend to) provide annually in your laboratory?</td>
<td>250 (increased from 100 with the benefit of more experience!) of those 169 from UK outside Scotland</td>
</tr>
<tr>
<td>Based on experience how many tests will be required nationally? Please identify the information on which this is based</td>
<td>Based on the number of referrals in the 28 months of service we would expect to receive 22 (14 from UK outside Scotland) diagnostic referrals a month and on average 5 parental samples a month.</td>
</tr>
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</table>
## Epidemiology

### Estimated prevalence of disease in the general UK population

Please identify the information on which this is based

This is difficult to ascertain as historically this group of epilepsy syndromes have been excluded from epidemiological studies as they have been difficult to diagnose in electro-clinical terms (Jallon and Latour, 2005. Epidemiology of Idiopathic Generalized Epilepsy. *Epilepsia* 46: 10-14).

1:20,000 is suggested in Yakoub *et al* (Brain and Development 14, 299-303, 1992) for classical SMEI but this may well be an underestimate.

More will be revealed regarding prevalence with the aid of molecular genetic diagnosis.

### Estimated gene frequency

(Carrier frequency or allele frequency) Please identify the information on which this is based

Autosomal dominant, mostly *de novo*. Familial cases arise in GEFS+

### Estimated penetrance

Please identify the information on which this is based

The majority of cases are sporadic and the great value of this test is providing an early diagnosis and allowing appropriate treatment. Penetrance is difficult to estimate.

### Target Population

The essential clinical or family history features defining the target population must be described.

(C)-Testing Criteria

| Clinical<br> Epilepsy phenotype: | Prolonged febrile seizures<br> Status epilepticus<br> Febrile seizures<br> Generalised tonic-clonic / clonic seizures<br> Focal seizures with impairment of awareness/atypical absences<br> Epileptic encephalopathy<br> Development: | Cognitive decline following epilepsy onset<br> Some aquired motor/movement disorder<br> Learning difficulties<br> EEG Features: | Generalised spike & wave activity<br> Photosensitivity<br> Family History | A family history with some of the features outlined above is indicative of GEFS+ in which SCN1A mutations are found

### Estimated prevalence of disease in the target population

~95-99%
**Intended Use** (Please use the questions in Annex A to inform your answers)

<table>
<thead>
<tr>
<th>Please tick the relevant clinical management criteria that this test effects.</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Prognosis &amp; Management</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Presymptomatic testing</td>
<td></td>
<td>X</td>
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<tr>
<td>Risk Assessment</td>
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<td>X</td>
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### Test Characteristics

#### Analytical sensitivity and specificity

This should be based on your own laboratory data for the specific test being applied for or the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up.

- Sensitivity of >98% for bi-directional sequencing, 99.5% when MLPA included.

#### Clinical sensitivity and specificity of test in target population

The *clinical sensitivity* of a test is the probability of a positive test result when disease is known to be present; the *clinical specificity* is the probability of a negative test result when disease is known to be absent. The denominator in this case is the number with the disease (for sensitivity) or the number without disease (for specificity).

- Where SMEI and associated syndromes are indicated the clinical sensitivity is around 80%. (Previous studies have had a clinical sensitivity of 40-98%, the variances in these figures is likely to be due to selection criteria i.e. SMEI only or inclusion of other infantile epileptic encephalopathies).
- Specificity for SMEI cases alone would be 95% due to classical features of the syndrome.
- Our results are slightly at odds with this estimate as many patients who do not fit *all* clinical criteria have been tested in the early stages of this service.

*Positive predictive value* and *penetrance* are notionally equivalent for any single genetic allele – the probability of developing disease given a positive test. The relationship is much more complex if more than one gene is responsible for the disease (locus heterogeneity), or if in any one gene there are multiple alleles (allelic heterogeneity), unless all the alleles are tested. In these cases, there are implications for the *clinical sensitivity* of the test and for its *negative predictive value*. For example, for a disease (such as APKD) that may be caused by either of two separate genes, even if each is 100 percent penetrant, the *clinical sensitivity* and the *negative predictive value* (and *clinical validity*) will both be reduced: *clinical sensitivity* since its maximum value can be no greater than the proportion of the disease that is caused by that particular gene, and *negative predictive value* since a negative test on Gene A will be no guarantee that the patient will not develop the phenotype, because the disease may be caused by Gene B. A similar form of analysis may be applied to genes with multiple alleles unless the “test” measures all the alleles.
**Clinical validity (positive and negative predictive value in the target population)**

The *clinical validity* of a genetic test is a measure of how well the test predicts the presence or absence of the phenotype, clinical disease or predisposition. It is measured by its positive predictive value (the probability of getting the disease given a positive test) and negative predictive value (the probability of not getting the disease given a negative test). The denominator in this case is the number of people with a positive or a negative test respectively - not the number with or without the disease. The clinical validity may be calculated knowing the sensitivity and the specificity and the prevalence of the disease in the population being studied. Positive and negative predictive values depend critically on the prevalence of the disease in the test population.

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Positive predictive value is high ~99% particularly in SMEI. The value is predicted to be lower in GEFS+ families as some symptoms of this disease can be so mild.

The negative predictive value is estimated to be low. Approximately 1/100 of our patients thought to have SMEI/related syndrome (based on clinical, and electro-clinical data) were found not to have an SCN1A mutation, this is most likely due to allelic heterogeneity particularly for the related syndromes.
Clinical utility of test in target population
(Please refer to Appendix A)

Please provide a full description of the clinical care pathway for those individuals undergoing testing. This should include details of which medical specialties will be able to refer for testing.

(B)-Testing Criteria

How will the test add to the management of the patient or alter clinical outcome?

What impact will this test have on the NHS i.e. by removing the need for alternative management and/or investigations for this clinical population?

Is there an alternative means of diagnosis or prediction that does not involve molecular diagnosis? If so (and in particular if there is a biochemical test) please state the added advantage of the molecular test.

Suspected diagnosis of:

- Dravet Syndrome and it’s clinical subtypes including severe myoclonic epilepsy of infancy and borderline severe myoclonic epilepsy of infancy.

Referrals made by paediatric neurologists, neurologists, paediatricians, clinical geneticists.

Sample processed for SCN1A mutation screening.

When a pathogenic mutation is identified the diagnosis can be made and/or confirmed (i.e. some patients are so young that their epilepsy phenotype has not fully evolved enough for a clinical diagnosis to be made).

A confirmed diagnosis has implications for treatment strategies and overall prognosis for the patient. With a confirmed diagnosis Stiripentol, an anti-convulsant drug that is currently un-licensed in the UK, can be prescribed and administered. This drug has helped many patients remain seizure free which in turn prevents/slowes developmental regression and other associated symptoms of the disorder. It removes the need for trialling different anti-convulsant drug therapies which is costly and time consuming for the NHS and may have a negative impact on the patients health.

The only other means of diagnosing SMEI or related disorders is clinically. A detailed history of all seizures and seizure types are required along with history of medications given and their affect on patient’s health, EEG data, developmental status and family history. Gathering such data to the extent that would enable a clear clinical diagnosis can take years by which point the patient may be so badly affected by the seizures that they are very developmentally regressed or even terminally ill.

The added advantage this molecular test provides is for very young patients who present with prolonged febrile seizures. If such patients can be diagnosed with SMEI early their drug therapy can be targeted specifically to treat SMEI. This may prevent the developmental problems associated with the syndrome appearing as the brain may avoid damage due to seizure control.

Please complete the referral pathway diagram on the following page and the testing criteria form.
TARGET POPULATION
Majority of target population made up of severe infantile onset epilepsies. Remainder constitutes patients of varying ages who fulfil criteria as outlined in clinical proforma (attached)

WHAT TYPE AND LEVEL OF PROFESSIONAL OR REFERRER DO YOU ACCEPT SAMPLES FROM?
Consultant physician with expertise in epilepsy: Paediatric Neurologists, Adult Neurologists, Clinical Geneticists

PLEASE PROVIDE DETAILS OF HOW REFERRALS WILL BE ASSESSED FOR APPROPRIATENESS?
Consultant Paediatric Neurologist gate kept service; referrals are monitored by testing criteria (see next page).

HOW MANY TESTS DO YOU EXPECT TO PERFORM ANNUALLY?
~250
**UKGTN Testing criteria:**

| Name of Disease(s): | SEVERE MYOCLONIC EPILEPSY OF INFANCY; SMEI (607208)  
SODIUM CHANNEL, NEURONAL TYPE I, ALPHA SUBUNIT; SCN1A (182389)  
FEBRILE CONVULSIONS, FAMILIAL, 3; FEB3 (604403) |
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<tbody>
<tr>
<td>Name of gene(s):</td>
<td>sodium channel, voltage-gated, type I, alpha subunit; SCN1A (182389)</td>
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</tbody>
</table>

### Patient Information

- **Patient name:**
- **Date of birth:**
- **Patient postcode:**
- **NHS number:**
- **Name of referrer:**
- **Title/Position:**
- **Lab ID:**

### Referrals

Referrals will only be accepted from one of the following:

<table>
<thead>
<tr>
<th>Referrer</th>
<th>Tick if this refers to you.</th>
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<tbody>
<tr>
<td>Clinical Geneticists</td>
<td></td>
</tr>
<tr>
<td>Paediatric neurologists</td>
<td></td>
</tr>
<tr>
<td>Adult neurologists</td>
<td></td>
</tr>
<tr>
<td>Consultant epileptologist</td>
<td></td>
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### Minimum criteria

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tick if this patient meets criteria</th>
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| Electroclinical Phenotype of Dravet Syndrome or clinical subtypes – several seizure types in one individual with onset in infancy, refractory to medication and with generalised spike and wave on EEG **OR**  
Infants less than 1 year with 2 or more prolonged hemiclonic febrile seizures in early infancy |                                      |

If the sample does not fulfill the clinical criteria or you are not one of the specified types of referrer and you still feel that testing should be performed please contact the laboratory to discuss testing of the sample.