The clinical utility of an *SCN1A* genetic diagnosis in infantile-onset epilepsy

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The availability of genetic sequencing has been limited worldwide by cost as well as the availability of technology and expertise, both in undertaking the test and in interpretation of results. It is envisaged that cost will decline significantly in the near future, so that the primary factor limiting testing will not be the availability of sequencing but rather the interpretation of results. Since its inception in November 2005, we have prospectively evaluated the clinical utility of testing for the sodium channel α1 subunit gene (*SCN1A*) in the Glasgow-based UK National Health Service clinical and laboratory diagnostic service. Mutations in the *SCN1A* gene are associated with several epilepsy syndromes, ranging from relatively mild phenotypes found in families with genetic epilepsy with febrile seizures plus to the severe infantile-onset epilepsy, Dravet syndrome.

Previously known as severe myoclonic epilepsy in infancy, Dravet syndrome typically presents in the first year of life with prolonged, febrile and afebrile, generalized clonic or hemi-clonic epileptic seizures in children with no pre-existing developmental problems. Other seizure types including myoclonic, focal, and atypical absence seizures may appear between the ages of 1 and 4 years. The epilepsy is usually not responsive to

AIM Genetic testing in the epilepsies is becoming an increasingly accessible clinical tool. Mutations in the sodium channel alpha 1 subunit (*SCN1A*) gene are most notably associated with Dravet syndrome. This is the first study to assess the impact of *SCN1A* testing on patient management from both carer and physician perspectives.

METHOD Participants were identified prospectively from referrals to the Epilepsy Genetics Service in Glasgow and contacted via their referring clinicians. Questionnaires exploring the consequences of *SCN1A* genetic testing for each case were sent to carers and physicians.

RESULTS Of the 244 individuals contacted, 182 (75%) carried a *SCN1A* mutation. Carers of 187 (77%) patients responded (90 females, 97 males; mean age at referral 4y 10mo; interquartile range 9y 1mo). Of those participants whose children tested positive for a mutation, 87% reported that genetic testing was helpful, leading to treatment changes resulting in fewer seizures and improved access to therapies and respite care. Out of 187 physicians, 163 responded (87%), of whom 48% reported that a positive test facilitated diagnosis earlier than with clinical and electroencephalography data alone. It prevented additional investigations in 67% of patients, altered treatment approach in 69%, influenced medication choice in 74%, and, through medication change, improved seizure control in 42%.

INTERPRETATION In addition to confirming a clinical diagnosis, a positive *SCN1A* test result influenced treatment choice and assisted in accessing additional therapies, especially in the very young.

Whilst acknowledging the recent major advances that have taken place in the understanding of the genetic mechanisms that underlie epilepsy, many neurologists and paediatricians do not regard genetic testing as contributing to patient care. The availability of genetic sequencing has been limited worldwide by cost as well as the availability of technology and expertise, both in undertaking the test and in interpretation of results. It is envisaged that cost will decline significantly in the near future, so that the primary factor limiting testing will not be the availability of sequencing but rather the interpretation of results. Since its inception in November 2005, we have prospectively evaluated the clinical utility of testing for the sodium channel α1 subunit gene (*SCN1A*) in the Glasgow-based UK National Health Service clinical and laboratory diagnostic service. Mutations in the *SCN1A* gene are associated with several epilepsy syndromes, ranging from relatively mild phenotypes found in families with genetic epilepsy with febrile seizures plus to the severe infantile-onset epilepsy, Dravet syndrome.

Previously known as severe myoclonic epilepsy in infancy, Dravet syndrome typically presents in the first year of life with prolonged, febrile and afebrile, generalized clonic or hemi-clonic epileptic seizures in children with no pre-existing developmental problems. Other seizure types including myoclonic, focal, and atypical absence seizures may appear between the ages of 1 and 4 years. The epilepsy is usually not responsive to...
to standard antiepileptic medication and affected children develop cognitive and behavioural impairment and a motor disorder. Seizure types such as status epilepticus may be life-threatening and sudden unexpected death in epilepsy may occur.7

There is some evidence supporting specific treatment regimes for the epileptic seizures associated with Dravet syndrome.8–11 As the encephalopathy is associated with cognitive decline and permanent neurological impairment, it has been suggested that aggressive, focused therapy should be commenced as soon as possible.12 The clinical diagnosis of Dravet syndrome is based on recognition of seizure types, clinical course, and electroencephalographic (EEG) features. Given the temporal evolution of these features, a definitive diagnosis is usually not made until 2–4 years of age, even by experienced clinicians.13 Most children present to general paediatricians in emergency departments, where it may be difficult to make a distinction between the first seizures in Dravet syndrome and ‘milder’ epilepsy phenotypes.

Because of the complexities in making an electroclinical diagnosis of Dravet syndrome, and with the potential to improve seizure control and implications for family counseling, molecular genetic testing may aid clinicians in making an early diagnosis of SCN1A-associated encephalopathies. This is the first study to assess the impact of SCN1A genetic testing on patient management from both carer and physician perspectives.

### METHOD

Cases were identified from referrals to the Epilepsy Genetics Service in Glasgow between November 2005 and February 2010. Referring clinicians including paediatric neurologists, general paediatricians, clinical geneticists, and adult neurologists completed a structured referral form for every patient. This detailed the epilepsy phenotype including age at first seizure, seizure types, imaging, EEG data, and developmental status. To maintain diagnostic consistency, phenotypes were assessed by the same child neurologist (SMZ), who was masked to the mutation type, and phenotypes were classified as either Dravet syndrome, genetic epilepsy with febrile seizures plus, febrile seizures plus, myoclonic ataxic epilepsy, or ‘without clear syndromic diagnosis’.

Diagnostic criteria for Dravet syndrome were seizure onset mainly in the first year of life and frequent hemiconic and/or generalized tonic-clonic/clonic seizures, mainly triggered by fever and often prolonged (>10 min) with status epilepticus frequently occurring in infancy. After the first year of life other seizure types (febrile and afebrile) can be seen, including focal seizures with impairment of awareness and atypical absences. Children have normal cognitive and motor development before seizure onset with subsequent slowing including plateauing or regression of skills. Consistent with previous reports, we regarded the presence of myoclonic seizures and ataxia as highly characteristic for Dravet syndrome; however, their absence did not exclude that diagnosis.14 Individuals were classified within the genetic epilepsy with febrile seizures plus group if they had phenotypes consistent with febrile seizures plus and a relevant family history.15

We designed an eight-item questionnaire on the consequences of SCN1A testing on their child and family for carers to complete. This included six questions with ‘yes’, ‘no’, or ‘not sure’ answers (Table I) and two open questions regarding positive and negative aspects of genetic testing. The questionnaire was sent to 244 parents/carers who had been contacted by their referring clinician. Those who responded gave consent for us to send a questionnaire to their physician. Physicians completed a 16-item questionnaire for each case, including 14 questions with ‘yes’, ‘no’, or ‘not sure’ answers (Table II) and two open questions regarding positive and negative aspects of genetic testing. Physicians were asked for each child whether the SCN1A testing result altered treatment or outcomes in that child. Physicians did not have access to carers’ responses.

This study was approved by the regional ethics committee and informed consent was obtained from each participant or his or her parent/carer.

### Statistical analysis

Patients for whom data were missing were excluded by case-wise deletion from the relevant analyses. Our primary hypotheses were that a positive SCN1A mutation result is (1) clinically more useful than a negative result and (2) more useful at a young age (<2y) than at an older age (≥5y). These hypotheses were tested using χ² statistics. Where assumptions for a χ² test are not fulfilled, Fisher’s exact test is given. Continuous variables are shown as median and interquartile ranges and differences analysed using the Mann–Whitney U test. Correlations between variables were calculated using Spearman’s correlation coefficient (rs). Analyses were performed using SPSS statistical software version 16.0 (SPSS Inc., Chicago, IL, USA) at a significance level of 5%. Qualitative data from open questions were transcribed and analysed using grounded theory.16,17 Following transcription, each comment was coded and printed as an individual script allowing the comments to be viewed simultaneously and physically manipulated. ‘Open coding’ was used to examine the scripts more closely and to generate themes.17 The themes were developed into conceptually meaningful categories and diagrams were then drawn to investigate the relationship between categories, illustrating that some were subthemes of more general categories. To reduce research bias, two independent researchers experienced in qualitative research coded the data and identified themes. These were then discussed and refined with a group of senior clinicians using an iterative process. The main themes and illustrative comments are presented within this paper.
Table I: Responders versus non-responders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders (n=187)</th>
<th>Non-responders (n=57)</th>
<th>( \chi^2 )</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/Females</td>
<td>97/90</td>
<td>34/23</td>
<td>0.9</td>
<td>1</td>
<td>0.321</td>
</tr>
<tr>
<td>Age at referral median (IQR), y</td>
<td>4y 10mo (9y 1mo)</td>
<td>4y 7mo (7y 11mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental status’ median (IQR)</td>
<td>3.0 (2.0)</td>
<td>3.0 (2.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenotype (percentage of Dravet syndrome cases)</td>
<td>87% (163/187)</td>
<td>86% (49/57)</td>
<td>5.6</td>
<td>4</td>
<td>0.465</td>
</tr>
</tbody>
</table>

\( ^a \)\( \chi^2 \) test. \( ^b \)Mann–Whitney U test – median with interquartile range. \( ^c \)Developmental status classified using a 5-point scale as 1 = ‘normal’, 2 = ‘mild learning disability’, 3 = ‘moderate’, 4 = ‘severe’, and 5 = ‘profound’. IQR, interquartile range.

Table II: Parent/carer questionnaire on usefulness of SCN1A genetic testing

<table>
<thead>
<tr>
<th>Genetic testing</th>
<th>Children who tested positive for a mutation (n=140), % (n)</th>
<th>Children who tested negative for a mutation (n=47), % (n)</th>
<th>( \chi^2 ), df=1</th>
<th>p</th>
<th>Children who tested positive for a mutation ( \leq 2y ) (n=39), % (n)</th>
<th>Children who tested positive for a mutation ( \geq 5y ) (n=72), % (n)</th>
<th>( \chi^2 ) (df=1)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was helpful in giving an explanation for your child’s epilepsy</td>
<td>87 (121/139)</td>
<td>19 (9/47)</td>
<td>76.9</td>
<td>&lt;0.001</td>
<td>100 (38/38)</td>
<td>90 (60/67)</td>
<td>0.047</td>
<td>b</td>
</tr>
<tr>
<td>2. Led to a change in medication to treat your child’s epilepsy</td>
<td>55 (76/139)</td>
<td>9 (4/47)</td>
<td>30.5</td>
<td>&lt;0.001</td>
<td>75 (27/36)</td>
<td>54 (37/69)</td>
<td>4.5</td>
<td>0.033</td>
</tr>
<tr>
<td>Medication change in detail</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commencing of new medication</td>
<td>79 (57/72)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>77 (17/22)</td>
<td>80 (28/35)</td>
<td>0.1</td>
<td>0.806</td>
</tr>
<tr>
<td>Discontinuation of lamotrigine/carbamazepine</td>
<td>21 (15/72)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>27 (6/22)</td>
<td>20 (7/35)</td>
<td>0.4</td>
<td>0.524</td>
</tr>
<tr>
<td>3. Medication change improved seizure control</td>
<td>69 (51/74)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>96 (21/22)</td>
<td>69 (22/32)</td>
<td>5.7</td>
<td>0.017</td>
</tr>
<tr>
<td>4. Medication change made a difference to your child’s developmental progress</td>
<td>34 (25/74)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>79 (11/14)</td>
<td>38 (11/29)</td>
<td>6.2</td>
<td>0.012</td>
</tr>
<tr>
<td>5. Led to other changes in treatment of your child’s epilepsy (PT, OT, SALT), change of goals and expectations, respite care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other change in detail</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access to therapies (PT, OT, SALT)</td>
<td>66 (29/44)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>82 (14/17)</td>
<td>57 (8/14)</td>
<td>0.233</td>
<td>b</td>
</tr>
<tr>
<td>Adjustment of goals</td>
<td>23 (10/44)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6 (1/17)</td>
<td>36 (5/14)</td>
<td>0.067</td>
<td>b</td>
</tr>
<tr>
<td>Access to respite care</td>
<td>9 (4/44)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6 (1/17)</td>
<td>7 (1/14)</td>
<td>1.000</td>
<td>b</td>
</tr>
<tr>
<td>6. Was helpful in caring for your child</td>
<td>61 (84/138)</td>
<td>19 (9/47)</td>
<td>24.4</td>
<td>&lt;0.001</td>
<td>88 (29/33)</td>
<td>60 (36/60)</td>
<td>7.9</td>
<td>0.005</td>
</tr>
</tbody>
</table>

\( ^a \)\( \chi^2 \) test between groups of children who tested positive for a mutation aged \( \leq 2y \) and children \( \geq 5y \) of age, including all those with either a positive or a negative response. \( ^b \)Fisher’s exact test. PT, physiotherapy; OT, occupational therapy; SALT, speech and language therapy.

RESULTS

Of the 244 individuals/families that were contacted, 182 (75%) carried a SCN1A mutation and 62 (25%) did not. The phenotypes of the 244 affected individuals were as follows: 212 (87%) Dravet syndrome, 14 (6%) genetic epilepsy with febrile seizures plus, two (1%) febrile seizures plus, three (1%) myoclonic astatic epilepsy, and 13 (5%) without clear syndromic diagnosis. The questionnaires were completed and returned by 187 out of 244 (77%) families.

Affected individuals of responding families did not differ significantly from those of non-responding families in sex distribution, age at referral, developmental status, and overall phenotypes (Table I). The proportion of individuals referred without a clear diagnosis was significantly higher in the younger age groups than in the older age groups. Sixty-four per cent (9/14) of all infants under 1 year and 42% (13/31) of all 1-year-olds did not have a clinical diagnosis, compared with 26% (17/66) of 2- to 4-year-olds, 22% (8/36) of 5- to 9-year-olds, and 15% (10/68) of those aged 10 years and older (\( \chi^2=16.5; \) df=1; \( p<0.001 \); Fig. 1).

Parent/carer views on genetic testing are summarized in Table II. Among the SCN1A mutation-positive group, 87% of carers reported genetic testing as helpful in giving an explanation for their child’s epilepsy and 55% said it led to a change in treatment, with 69% of this group reporting fewer seizures...
Physician questionnaires were returned by 163 out of 187 (87%) clinicians, of whom 119 were paediatric neurologists (73%), 35 paediatricians (22%), seven geneticists (4%), and two adult neurologists (1%). Their views on genetic testing are summarized in Table III. Physicians reported that testing confirmed an established clinical diagnosis in 45% of children who tested positive for a mutation and allowed a diagnosis to be made earlier than with clinical and EEG data alone in 48%. Additional investigations were avoided in 67% of cases, while in 69% testing altered the treatment approach and in 74% it helped medication choice. Improved seizure control was reported in 42% after medication change, and in 50% testing prevented prescription of drugs that could have worsened the epilepsy. Testing helped physicians manage the condition in 99% of cases and aided genetic counselling in 83%.

Both carers and physicians considered a positive test result significantly more useful than a negative test result (Tables II and III).

Table III: Physician questionnaire on usefulness of SCN1A genetic testing

| Genetic testing                                                                 | Children who tested positive for a mutation (n=124), % (n) | Children who tested negative for a mutation (n=39), % (n) | $\chi^2$ (df=1) | p-value | Children who tested positive for a mutation $\leq$2y (n=36), % (n) | Children who tested positive for a mutation $\geq$5y (n=61), % (n) | $\chi^2$ (df=1) | p
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</tr>
</thead>
<tbody>
<tr>
<td>1. Confirmed an established clinical diagnosis</td>
<td>45 (54/120)</td>
<td>5 (2/39)</td>
<td>20.5</td>
<td>&lt;0.001</td>
<td>55 (17/31)</td>
<td>45 (27/60)</td>
<td>0.8</td>
<td>0.373</td>
</tr>
<tr>
<td>2. Confirmed a suspected clinical diagnosis</td>
<td>83 (100/121)</td>
<td>8 (3/38)</td>
<td>70.8</td>
<td>&lt;0.001</td>
<td>89 (31/35)</td>
<td>78 (45/58)</td>
<td>1.8</td>
<td>0.184</td>
</tr>
<tr>
<td>3. Allowed a diagnosis to be made earlier than with clinical and EEG data alone</td>
<td>48 (59/123)</td>
<td>5 (2/38)</td>
<td>22.5</td>
<td>&lt;0.001</td>
<td>71 (24/34)</td>
<td>41 (24/58)</td>
<td>7.3</td>
<td>0.007</td>
</tr>
<tr>
<td>4. Prevented misdiagnosis</td>
<td>48 (59/123)</td>
<td>26 (10/38)</td>
<td>5.6</td>
<td>0.030</td>
<td>66 (21/32)</td>
<td>41 (24/59)</td>
<td>5.2</td>
<td>0.023</td>
</tr>
<tr>
<td>5. Saved the child additional investigations</td>
<td>67 (82/122)</td>
<td>8 (3/38)</td>
<td>40.9</td>
<td>&lt;0.001</td>
<td>81 (26/32)</td>
<td>66 (37/56)</td>
<td>2.3</td>
<td>0.129</td>
</tr>
<tr>
<td>6. Altered the treatment approach</td>
<td>69 (83/121)</td>
<td>18 (7/38)</td>
<td>29.6</td>
<td>&lt;0.001</td>
<td>83 (29/35)</td>
<td>65 (37/57)</td>
<td>3.4</td>
<td>0.063</td>
</tr>
<tr>
<td>7. Was helpful in choosing the most appropriate medication</td>
<td>74 (91/123)</td>
<td>18 (7/38)</td>
<td>37.6</td>
<td>&lt;0.001</td>
<td>94 (32/34)</td>
<td>66 (37/56)</td>
<td>9.3</td>
<td>0.002</td>
</tr>
<tr>
<td>8. Medication change improved seizure control</td>
<td>42 (35/83)</td>
<td>14 (1/7)</td>
<td>0.148</td>
<td>p&lt;0.01</td>
<td>57 (16/28)</td>
<td>56 (15/27)</td>
<td>0.01</td>
<td>0.906</td>
</tr>
</tbody>
</table>
| 9. Further decline of cognitive function was prevented after implementation of new treatment strategies | 10 (8/83) | 0/7 | 0.508 | p<0.01 | 25 (3/12) | 12 (3/25) | 0.367 | p
| 10. Prevented prescription of drugs that could have worsened the epilepsy | 50 (61/123) | 3 (1/37) | 26.3 | <0.001 | 63 (19/30) | 47 (26/55) | 2.0 | 0.156 |
| 11. Was helpful in providing an explanation of the underlying disease for the family | 98 (118/121) | 21 (8/39) | 104.5 | <0.001 | 100 (34/34) | 98 (58/59) | 1.000 | p
| 12. Aided genetic counselling | 83 (100/121) | 15 (6/39) | 59.6 | <0.001 | 97 (32/33) | 79 (44/56) | 5.6 | 0.018 |
| 13. Parents/carers expressed regret at knowing the underlying genetic diagnosis | 1 (1/120) | 0/33 | 0.784 | p<0.01 | 3 (1/34) | 0 (0/54) | 0.205 | p
| 14. Is considered helpful in managing patient | 99 (120/121) | 82 (31/38) | <0.001 | p<0.01 | 100 (35/35) | 98 (58/59) | 1.000 | p

* $\chi^2$ test between groups of children who tested positive for a mutation aged $\leq$2y and children $\geq$5y of age, including all those with either a positive or a negative response. **Fisher’s exact test. EEG, electroencephalogram.
In order to explore potential benefits of early genetic testing, we compared the following subgroups of children: children who tested positive for a mutation at the age of 2 years or below \( (n=39) \), in whom it is often difficult to make a clinical diagnosis as the whole clinical picture has not evolved yet, and children aged 5 years and older \( (n=72) \), in whom the core electroclinical features of the syndrome will have developed and there is less doubt about the clinical diagnosis. We included all those with a positive or a negative questionnaire response, and excluded those with a ‘not sure’ response. Parents of younger children receiving a positive test result were more likely than parents of older children to report that the test was helpful in giving an explanation for their child’s epilepsy (Table II) and/or led to a medication change that improved seizure control and developmental progress. Compared with the older age group, in young children a positive test result more often led to increased access to therapies (physiotherapy, occupational therapy, and speech and language therapy) and more parents said it helped them care for their child.

Physicians reported that a positive test result in those aged 2 years and younger allowed them to make a diagnosis earlier than with clinical and EEG data alone, helped prevent misdiagnosis, was helpful in choosing the most appropriate medication, and, compared with a positive result in older children, was more likely to aid genetic counselling (Table III).

Comparing carer and physician views on genetic testing in 99 out of 108 children who tested positive for a mutation (92%), there was agreement that genetic testing was helpful in giving an explanation for the disease. Positive correlations were also observed in responses to whether a positive test result led to a change in treatment \( (n=109; r_S=0.333; p<0.001) \). There was no concordance about whether the new treatment resulted in improved seizure control \( (n=61; r_S=0.232; p=0.071) \) or halted developmental decline \( (n=37; r_S=0.084; p=0.620) \).

The main themes and illustrative quotes drawn from the qualitative data are summarized in Figure 2. Significant concordance between carers and physicians is evident within major themes such as the importance of definitive diagnosis and improvements in treatment, although with different emphases (see Fig. 2). There were also some concerns unique to carers, for example regarding the importance of high-quality genetic counselling.

## DISCUSSION

A positive SCN1A test result not only confirmed a clinical diagnosis but enabled early diagnosis, reduced the need for further investigations, impacted on treatment choice, and facilitated access to additional therapies, especially in the very young.

A recent report from the International League Against Epilepsy Genetics Commission on genetic testing in the epilepsies emphasizes that ‘little is known about the impact of genetic testing on patients with epilepsy today’. Over the last 10 years there has been an explosion of knowledge relating to genetic science and epilepsy and an elucidation of the pathogenesis of seizure disorders. However, evidence of the clinical usefulness of genetic testing in epilepsy is sparse and the issue remains under debate. An important aspect of this discussion had been whether genetic testing in Dravet syndrome merely confirms a clinical diagnosis or whether it allows a diagnosis to be made earlier than with clinical tools alone. From our referral data and understanding of the typical course of Dravet syndrome, it is evident that a clear clinical diagnosis at the time of referral is often not available in children under 2 years. In 50% of very young patients we were able to establish a specific genetic diagnosis that consequently aided genetic counselling and influenced medication choice at an early stage in the evolution of the syndrome. Having a clear diagnosis spares affected children the burden of additional traumatic procedures and reduces expenditure on further tests. Clinicians reported that a positive test result allowed them to make a diagnosis earlier than with clinical and EEG data alone, particularly in those aged 2 years and younger.

We observed a significant proportion of individuals without a clear syndromic diagnosis, even in the older age groups, which could be explained by the heterogeneous background of referrers. In clinical practice there is doubt about diagnosis in older patients referred by non-specialists and adult neurologists, who may not have knowledge of Dravet syndrome or who may lack access to the early infantile and childhood history. SCN1A testing should be considered in adult patients with epilepsy and intellectual disability in whom the early history or clinical phenotype is suggestive.

It has been argued that genotyping does not influence patient management. However, our data suggest that in a substantial number of cases a positive SCN1A test result altered the treatment approach, particularly in those 2 years and younger. This included the choice of medication and, specifically, the introduction of antiepileptic medication known to be effective in Dravet syndrome and withdrawal (or prevention of initiation) of medication that may have exacerbated seizures. This perception was shared equally by carers and clinicians. It had been argued that, even if treatment changes were implemented as a consequence of a positive test result, seizure control and disease outcome would not be affected. Randomized controlled trials show that certain combinations of medication can improve seizure control in Dravet syndrome. Our results, although descriptive in nature, confirm that a substantial number of both carers and clinicians observed an improvement in seizure control following medication change.

It has been suggested that aggressive focused therapy should be commenced as soon as possible to prevent cognitive decline and permanent neurological impairment. Our data show that one-third of carers thought that a medication change made a difference to the child’s developmental progress; this is in contrast to clinicians, of whom only 10% shared this opinion. Further longitudinal studies are required to evaluate the effect of ‘optimal’ treatment on developmental outcome in these patients.

The ability to offer genetic counselling is one of the recognized advantages of genetic testing, and many carers highlighted the significance of knowing their child’s genotype.
Knowing that a condition is likely or unlikely to be inherited allows families to make informed reproductive choices. Genetic information might have ethical, legal, and social implications for the individual and wider family including the perceived stigma of a genetic diagnosis. Although these broader issues of the implications of genetic testing might exist, our own experience specific to SCN1A gene testing is different. Our data clearly show that parents and carers appreciated knowledge of the mutation results and physicians reported that only a small number of parents/carers expressed regret at knowing the underlying genetic diagnosis. The delivery of genetic counselling – ‘giving the news’ – was an important recurring theme among those carers who expressed negative experiences. In some cases, carers were presented with a genetic result without further explanation, thus increasing misunderstanding and anxiety. This illustrates that, if genetic testing is requested, adequate provisions should be in place to guarantee good delivery and counselling of genetic testing results. The International League Against Epilepsy Genetics Commission report stated that ‘post-test genetic

Figure 2: Parent and physician views on SCN1A genetic testing – themes and example statements. Identified themes were developed through analysis of transcribed parent/carer and physician comments.
counselling is crucial to help the patient understand the test result and begin to digest it in the context of his or her life circumstances.  

Critics have argued that the psychological and social help an individual with Dravet syndrome receives will not depend on the identification of a mutation.  

Our parental responses showed that knowledge of an underlying genetic diagnosis was associated with relief and positive adjustment, enabling them to readjust their goals and expectations.  

Often parents made contact with Dravet syndrome support organizations and other families who have a child with similar problems. In addition, and somewhat surprisingly, a substantial number of carers were able to access additional therapies such as physiotherapy, occupational therapy, and speech and language therapy more easily once a positive genetic diagnosis was made, an observation that we feel should be more formally appraised. Access to therapies should depend not on mutation status but on an assessment of clinical need, particularly in the UK National Health Service, where most of our patients were recruited. However, it appears that genetic testing facilitates a confident clinical diagnosis of Dravet syndrome and its prognosis, allowing for a more focused therapeutic approach to the comorbidities of the syndrome.  

Many parents and carers reported that having a clear 'label' helped access to multi-agency support. We know that 20–30% of Dravet cases are mutation negative, with the mutation status reflecting those mutations we are able to identify at present; cases are mutation negative, with the mutation status depending on the identification of a mutation.  

Our parental responses showed that genetic testing facilitates a confident clinical diagnosis of Dravet syndrome and its prognosis, allowing for a more focused therapeutic approach to the comorbidities of the syndrome.  

However, a negative test result should not prevent a diagnosis of Dravet syndrome in the appropriate clinical context. Not giving a clear diagnosis might have far-reaching implications for the support available for an individual and their family. Dravet syndrome remains a clinical diagnosis and all affected patients irrespective of mutation status should have access to appropriate therapies.  

Finally, genetic testing in the epilepsies is becoming an increasingly accessible and important diagnostic tool resulting in new challenges in epilepsy care. Our results demonstrate that carers and physicians report significant benefits from a confirmed SCN1A test result. Physicians need to understand the information resulting from testing and appreciate the limitations of the technology. Genetic information should be interpreted within the appropriate clinical context to allow physicians to counsel individuals and families appropriately.

Limitations
The study results are subject to sampling bias; however, responders and non-responders did not differ significantly in demographic and phenotypic features, and response rates of 77 and 87% are high for this type of study. To minimize the interrater bias associated with qualitative analysis, two independent researchers and a group of senior clinicians reviewed the data coding and verified themes. We were not able to perform a power calculation because of the lack of pilot data as this is the first study to evaluate the usefulness of genetic testing in Dravet syndrome. The International League Against Epilepsy Genetics Commission has highlighted how little is known about the impact of genetic testing on patients with epilepsy, and there are no standardized tools to assess the usefulness of genetic testing in epilepsy.  

Our study provides new data on how genetic testing is viewed from a patient and physician perspective and this work might contribute to how genetic testing in the epilepsies is evaluated in the future.

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REFERENCES


