In conclusion, atypical benign partial epilepsy of childhood should be recognized as a unique and distinct epileptic syndrome, characterized by an onset with focal motor seizures and localized centro-parieto-temporal electroencephalogram spike discharges, followed by negative motor seizures and diffuse, semicontinuous epileptic aggravations on electroencephalograms, and remission before adolescence. An inappropriate treatment strategy may prolong the catastrophic state, erroneously turning patients into potential surgical candidates.

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小児てんかんの治療

―Expert Consensus 研究結果の日米欧比較―

小国　弘量　　平野　嘉子　　加藤　郁子

要旨　小児てんかんにおける各種抗てんかん薬（AED）の選択順位に関して日米欧の差異を明らかにする目的で，米欧において施行された Expert Consensus（EC）研究を参考としたアンケート調査を行った．対象はてんかん専門医資格を取得して 5 年以上たつ小児科医師 41 名である．方法は各種てんかん症候群の治療に使用する AED を 9 点評価（適切さの評価）し，その結果を統計処理して最適薬，第 1 ～ 3 選択薬まで求めた．結果として，carbamazepine，valproate sodium 以外の AED の選択順位は米欧で日本と大きく異なり benzodiazepine 系の AED の使用が少なく oxcarbamazepine，lamotrigine，topiramate，levetiracetam などの新規 AED が早期に導入されていた．米欧の EC 研究の結果は，今後，日本において新規 AED の使用の参考となろう．

見出し語　抗てんかん薬治療，小児てんかん，新規抗てんかん薬，Expert Consensus 研究

はじめに

小児てんかんあるいはてんかん症候群に対する治療の主体は，抗てんかん薬（antiepileptic drug；AED）である．世界的に新規抗てんかん薬の導入が進み，各てんかん症候群に対する推奨薬剤の選択順位に変化が起きている[1,2]．AED 治療の選択に関して，無作為プラセボ比較研究やそのメタ分析研究が重要視されているが，必ずしもこれらの方法で最適な抗てんかん薬が選択できるわけではない．無作為プラセボ比較研究は最も実証的価値は高いが，対象となる群は主として治療抵抗性てんかんか，逆に軽症のてんかんとなり，偏りがでる，また，複数の薬物について比較研究されることは少ない．特に小児においては倫理的な問題もあり，この無作為プラセボ比較研究すら世界的に少ない[3]．このような経過により最近，実際の臨床現場で役立つ Expert Consensus（EC）研究が神経・精神疾患に応用されている[4]．これは，長い臨床経験に基づいた専門医の意見を集め，統計的手法を用いて集約する方法である．すでに小児てんかん治療の EC 研究結果が米国では 2005 年に，その欧州版が 2007 年に報告された．両者の研究結果はほぼ同等となっており興味深い．日本で導入されたばかりの新規 AED や今後導入予定の AED が従来のものに代わって使用されている例も多く，これから使用し始める我々にとって示唆に富む研究である[5,6]．日本においてもすでに 2006 年に gabapentin（GBP）が，2007 年に topiramate（TPM）が，そして 2008 年には lamotrigine（LTG）が導入されている．さらに levetiracetam（LEV）も治験は終了して承認待ちの状況であるし，いくつかの抗てんかん薬は治験準備中とされている．これらの新規抗てんかん薬の選択基準や従来の AED との比較等，早急に検討することが治療上重要な課題と考えられる．今回，小児てんかん並びにてんかん症候群に対する日米欧の小児てんかんの治療薬選択基準の差異を明らかにするために，日本の小児てんかん専門医に対して米欧で施行された EC 研究に準じたアンケート調査を施行し，比較検討したので，その結果を報告する．

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I　対象・方法

対象は，てんかん専門医を取得して 5 年以上たつ小児科医師 123 名である．方法として米国で施行された Wheless JW らの "Treatment of Pediatric Epilepsy：Expert Opinion, 2005"[5] に準じ，様々なてんかん症候群の治療選択薬順位についてアンケート調査を行った．治療選択としては，各てんかん症候群の治療に使用する薬剤を 9 点評価（適切さの評価）で記載すること，および最初に使用する薬剤が無効の場合に選択する薬剤名の記載を 9 点評価で求めた．点数評価方法は下記の記載を参考とした．

9 点：極めて適切，選んだ人の第 1 推奨薬（ひとつ以上あってもよい）
7 ～ 8 点：通常は適切，（この例の場合，たびたび使用する薬剤である）
4 ～ 6 点：どちらともいえない（時に使用する薬剤）
2 ～ 3 点：通常は不適切（稀にしか使用しない薬剤）
1 点：極めて不適切（使用してはいけない薬剤）

解析では各設問において AED に付与された点数の平均，標準偏差，95%信頼区間を求めた．各 AED ごとにコンセンサスの有無を実際の AED 点数分布と第 1，2，3 選択薬の理論値の分布を χ^2 乗検定で検定し，決定した．$p<0.05$ を有意とした．

平均が 6.5 点以上を第 1 選択薬，3.5 点以上 6.5 点未満を第 2 選択薬，3.5 点未満を第 3 選択薬とした．さらに回答者が 9 点と評価した割合を算出し，50%以上の回答者が一致して「極めて適切」と推奨した薬物を「最適薬」とした．治療薬として日本で使用されていない薬剤は省略したが，日本で使用されているが米国にない薬剤は調査に含めた．

Wheless らの設問内容は多岐にわたるため，今回は主なてんかん症候群を網羅する 16 の設問に限定した（設問内容は結果に記載）．治療薬とその略語に関しては下記の薬剤を挙げた．VPA（valproate sodium），PB（phenobarbital），ESM（ethosuximide），PRM（primidone），CZP（clonazepam），NZP（nitrazepam），DZP（diazepam），CLB（clobazam），CBZ（carbamazepine），ZNS（zonisamide），PHT（phenytoin），ST（sulthiame），AZM（acetazolamide），GBP（gabapentin），vitamin B6，臭化物（bromide），ACTH，ケトン食，その他（clorazepate，fludiazepam，ethylloflazepate，名称記入）とした．また，米欧で使用されている新規 AED に関して TPM（topiramate），LTG（lamotrigine），LEV（levetiracetam），OCBZ（oxcarbamazepine）とした．

表 1　日米欧 Expert consensus 研究回答者の比較

	日本	米国[5]	欧州[6]
小児てんかん専門医（n）	127	41	53
回答率（%）	34	95	74
N（男／女）	41（36/5）	39（31/8）	42
平均臨床経験（年）	24	21	未記載
平均年齢（歳）	53	53	未記載
50%以上の時間てんかん診療に費やす専門医比率（%）	80	90	未記載

Ⅱ 結　　果

てんかん専門医 123 名中 41 名（34%，男 36 名，女 5 名）から有効回答をえた．回答者の年齢は平均 53 歳（42 ～ 65 歳），治療経験は 24 年（12 ～ 38 年），全労働時間のてんかん診療が占める時間は約 80%で月平均 180 名の患者を診療していた．これは米国，欧州の EC 研究の総回答者人数，平均年齢，平均てんかん臨床経験年数と比較してほぼ同等であった（表 1）．

16 設問（合計 20 項目）において，日米欧で選択された最適薬，第 1 選択薬を表 2，3 に示す．具体的な設問内容は，下記設問 1 のように文章題であるため，表 2，3 では具体的なてんかん症候群名のみで表した．

設問 1．発達の遅れはあるが，健康な 2 歳児がミオクロニー発作（myoclonic seizures；MS）と全般性強直間代発作（generalized tonic-clonic seizures；GTCS）を持つ症候性てんかんと診断され，まだ未治療です．設問の対象の家族はできる限りの治療を希望し，協力的であり，各抗てんかん薬は有効濃度以上まで増量すると仮定して下さい（本設問は表 2 では 2 歳，MS＋GTCS 主徴の症候性全般てんかんとしている）．

設問 1 の解析結果：日本では本設問に対する回答として最適薬が VPA，第 1 選択薬が CZP と CLB であった（図 1，表 2）．それに対し米国ではそれぞれ VPA，TPM と ZNS であっ

表 2　日米欧の潜因性，症候性てんかんにおける最適薬，第 1 選択薬の比較

		日本	米国[5]	欧州[6]
設問	てんかん症候群			
1	2 歳　MS＋GTCS 主徴の SGE	VPA＊，CZP，CLB	VPA＊，TPM，ZNS	VPA＊
2	12 歳　MS＋GTCS 主徴の SGE	VPA＊，CZP，CLB	VPA＊，TPM，ZNS，LTG	VPA＊
3（1）	1 歳　GTCS 主徴の SGE	VPA＊，PB	TPM，LTG	VPA＊
3（2）	12 歳　GTCS 主徴の SGE	VPA＊	VPA＊，LTG，TPM	VPA＊
4	6 歳　潜因性 CPS	CBZ＊，ZNS	OCBZ＊，CBZ＊，LTG，LVC	CBZ＊，OCBZ＊，VPA
5（1）	CBZ が無効の場合の選択	ZNS＊，VPA	LTG＊，LVC，TPM	VPA＊
5（2）	ZNS が無効の場合の選択	CBZ＊，ZNS		
5（3）	PHT が無効の場合の選択	CBZ＊，ZNS	OCBZ＊，LTG，CBZ，LVC	CBZ＊，OCBZ，VPA
6	生後 6 カ月　結節性硬化症 West 症候群	VPA＊，ACTH，CZP，ZNS	VGB＊，ACTH	VGB＊
7	生後 8 カ月　症候性 West 症候群	VPA＊，ACTH，CZP，ZNS，vitamin B6	ACTH＊，TPM，ZNS，VGB	VGB＊，ACTH，predonine
8	6 歳　Lennox-Gastaut 症候群＋類回の失立転倒発作	VPA＊，CZP，CLB	VPA＊，TPM，LTG	VPA＊，LTG
9	VPA が無効の場合の選択	CZP，CLB，ESM，NZP	TPM，LTG，ZNS，LVC	LTG，TPM，CLB，CZP

抗てんかん薬略語は本文参照，＊：50% 以上の回答者が一致して「極めて適切」と推奨した「最適薬」
MS：myoclonic seizures，GTCS：generalized tonic-clonic seizures，SGE：symptomatic generalized epilepsy，CPS：complex partial seizure

表3 日米欧の特発性てんかんにおける最適薬と第一選択薬の比較

		日本	米国[5]	欧州[6]
設問	てんかん症候群			
10	8歳 BECT	CBZ＊, VPA	OCBZ＊, CBZ＊, LTG, LVC	VPA＊
11	6歳 小児欠神てんかん	VPA＊, ESM	ESM＊, VPA, LTG	VPA, ESM, LTG
12	ESMが無効の場合	VPA, CZP, CLB	VPA, LTG	VPA, LTG
13	12歳 若年欠神てんかん	VPA＊	VPA＊, LTG	VPA＊, LTG
14	VPAが無効の場合	ESM, CZP, CLB, PB	LTG, TPM, ZNS, LVC	LTG, ESM, LVC, TPM, CZP, CLB
15	6歳 救急患者	VPA＊	CBZ＊	
16（1）	15歳 JME男児	VPA＊, CZP	VPA＊, LTG＊, TPM	VPA＊, LTG
16（2）	15歳 JME女児	VPA＊, CZP	LTG＊, TPM, VPA	LTG＊, VPA

抗てんかん薬略語は本文参照，＊：50% 以上の回答者が一致して「極めて適切」と推奨した「最適薬」
BECT：benign childhood epilepsy with centrotemporal spikes，JME：juvenile myoclonic epilepsy

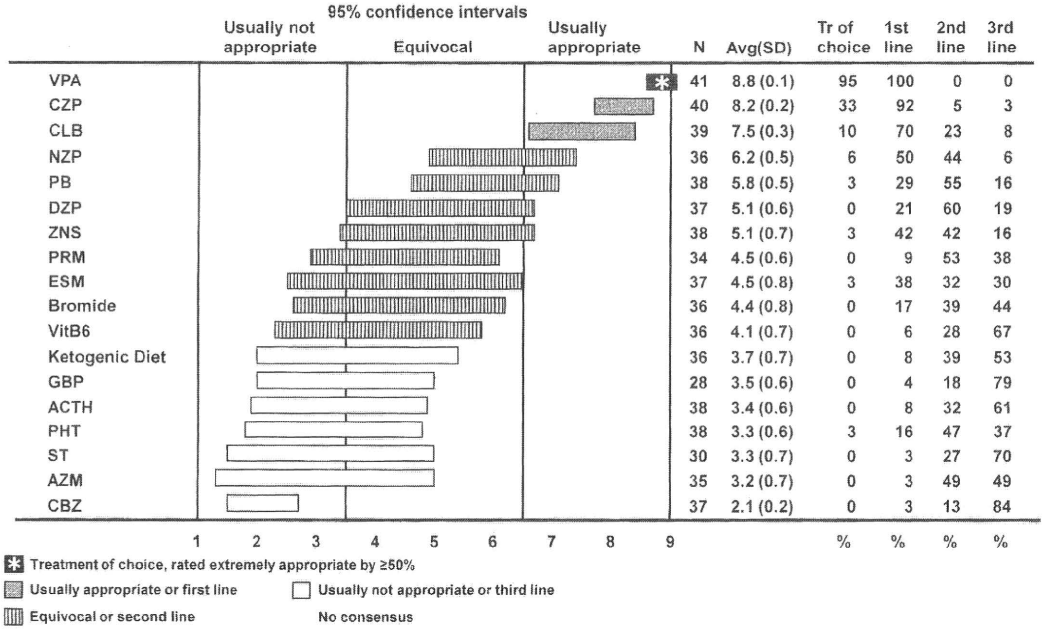

図1 2歳のミオクロニー発作＋全般性強直間代発作を主徴とする症候性全般てんかんの治療についての抗てんかん薬選択順位

VPA が平均 8.8 点，41 人すべての回答者が選択し，さらに 95%の回答者が 9 点をつけている（よって最適薬となる）．次に CZP，CLB がそれぞれ平均 8.2 点，7.5 点と 6.5 点以上を獲得し，第 1 選択薬となる．以下 NZP から VitB6 までが 3.5 点～6.5 点未満で第 2 選択薬となる．
上段左より治療薬（平均点の高い順），Usually not appropriate（第 3 選択薬），Equivocal（第 2 選択薬），Usually appropriate（第 1 選択薬），N（点数をつけた総人数），Avg（SD）（総合点の平均値で 9 点に近いほど適切な AED），Tr of choice（本剤が最も適切とした専門医の%，50%以上で最適薬）を表す．

た[5]．欧州では最適薬が VPA のみで，続いて第 2 選択薬として LTG，LEV，TPM，CLB を使用していた[6]．

1．治療選択の解析結果

表 2 に示すように日米欧の全 16 設問に示されるてんかん症候群の最適薬，第 1 選択薬の差異をまとめると，特発性全般てんかん症候群（設問 11 ～ 14，16）の第 1 選択薬は米欧では VPA 以外に LTG 使用頻度が高く，日本では VPA と CZP が中心であった．潜因性複雑部分発作（complex partial seizure；CPS）てんかん（設問 4，5），benign childhood epilepsy with centrotemporal spikes（BECT）（設問 10）において CBZ（一部 VPA）は共通していたが，米欧では OCBZ，LTG，LEV が加わり，日本では ZNS であった．症候性全般てんかん（設問 1 ～ 3），West 症候群（設問 6，7），Lennox-Gastaut 症候群（設問 8，9）では VPA，ACTH は共通していたが，米欧では TPM，LTG が多く使用され，日本では CZP，CLB が中心であった．日米欧の EC 研究を比較すると，米欧では benzodi-

azepine（BZD）系のAEDの使用が少なく，OCBZ，LTG，TPM，LEVなどの新規抗てんかん薬の導入が進み，CBZ，VPA以外のAEDの選択が異なっていた．

Ⅲ 考 察

世界的に新規AEDの導入が進んでいるが，日本においても欧米に10年遅れてGBP，TPM，LTGが次々と導入されている．しかし，まだこれらの新規AEDの経験も少なく，AED数が増加することにより逆にその使い分けをどうするか迷う場合もでてくる．成人てんかんにおいては，多くのエビデンスレベルの高い研究の結果をもとに選択薬が決定されてきているが，小児の場合には成人に比較してエビデンスレベルの高い研究結果は乏しい[3][7][8]．そのため，長い臨床経験に基づいた専門家の意見は有益な情報であろう．

今回の治療薬の選択順位に関して米欧において臨床に即したEC研究の結果が報告されており，その中ではてんかん症候群分類が採用されている[5][6]．今回，この方法を用いて日本の小児てんかん専門医の意見を集約して米欧のそれと比較した．偶然ではあるが，回答者の数，臨床経験など米欧と一致するところが多く，参考となろう．日本におけるAEDの選択順位は，今までの様々な論文などからみると非常に妥当な選択と考えられる[9]～[11]．MSとGTCSを合併する症候性全般てんかんでは，年齢にかかわらず日米欧ともVPAが最適薬であった．しかし，次選択薬となると日本ではCZP，CLBのBZD系薬剤が主体であるが，米欧ではTPM，LTG，LEVが選択されていた．また，これはGTCSを主徴とする症候性全般てんかんでも同じ傾向であった．

潜因性CPSてんかんでは，3者とも最適薬としてCBZは同じであったが，日本ではZNSが，米欧ではOCBZが同等に使用されていた．それ以外，米国ではLTG，LEVが，欧州ではLTGとVPAが第1選択薬として使用されていた．これは，ZNSが日本で最初に発売されたという経緯があるので当然かもしれない．また，欧州ではVPAが部分発作によく使用されるという傾向が認められた．症候性West症候群では，米国でもVGBとTPM，ZNSが上位候補に，欧州ではVGBが最適薬として使用されているが，日本ではいまだにVPAが最適薬として頻用されていることがわかる．Lennox-Gastaut症候群では，VPAが無効の場合，日本ではBZD系薬剤が選択され，米欧ではTPM，LTGが選択されている．TPMでは無作為プラセボ比較試験で本てんかん症候群の失立転倒発作に対する有効性が証明されている[12]．良性てんかんであるBECTにおける治療薬は，潜因性CPSてんかんと同様に日本ではCBZが，米国ではOCBZ，LTG，LEV，欧州ではむしろVPAが最適薬として選択されている．小児欠神発作てんかん，若年性欠神発作てんかんでは，米欧においてVPA，ESM以外にLTGが選択されている．この傾向は若年性ミオクロニーてんかんでも同様であり，3者ともVPAは最適薬に入っているが，すでに女性の場合には米欧ともLTGが最適薬となっている．これはLTGがVPAに比較して催奇形性，女性ホルモン系への副作用が少ないという理由からである[13]．以上より，米欧では最近，BZD系AEDの順位が低く，TPM，LTG，OCBZ，LEVなどの新規AEDが選択されていることが特徴であった．日本ではOCBZ，LEVに関しては治験準備中あるいは治験中であり，また，TPMは部分てんかんのみの保険適応であるので，まだまだ選択範囲としては米欧と比べて大きな差がある．これらの結果は，井上らの全年齢を対象としたてんかん治療のEC研究における日米の差とほぼ同様であった[14]．TPM，GBP，LTG，LEVに関して，数は少ないがすでに米欧で成人はもちろん小児においてもプラセボ比較研究が行われており，その有効性が示されている[3]．また，副作用においても，他のAEDとの相互作用が少ない，重篤な副作用も一部を除いて稀であり，従来のAEDに代わり，頻用されている傾向にあろう．しかしながら，その効果に関しては必ずしも従来のAEDに勝るという事実はなく，CBZ，VPAの両者は米欧でも最適薬として未だ多くのてんかんに使用されているのは特筆すべきである．また，CLBは，米国で未発売のために米国での選択順位が低いが，欧州ではLennox-Gastaut症候群や症候性全般てんかんでは第2選択薬としてよく使用されている[6]．EC研究は，無作為プラセボ比較研究のようにバイアスの入らないエビデンスレベルの高い研究結果ではないが，日常臨床で実際にAEDを選択する場面では非常に役立つ研究である．特に，日本において新規AEDが次々と導入されている現状においては米欧での経験を参考として使用できる利点もある．今後日本における経験の蓄積をも併せて，これらの新規AEDの選択順位や基準の確立が望まれる．

本研究は，厚生労働省精神・神経疾患研究委託費「19指―6 てんかんに対する新たな治療法開発と標準化に関する研究」（主任研究者：井上有一）の援助を受けて行われた．本研究に協力していただいた下記てんかん専門医各位に深謝いたします．

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Treatment of Childhood Epilepsies — Japanese Expert Consensus Study and a Comparison of the Results with Those of the USA and EU —

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We conducted a Japanese Expert Consensus (EC) study for the treatment of childhood epilepsies following the method reported from the USA and EU (Wheless JW, et al., 2005, 2007), and compared the results to reveal differences in the choice of antiepileptic drugs (AEDs). The subjects were 41 pediatric board-certified epileptologists who responded to the 23 questionnaires. A 9-point scale was used to grade each AED, in which 9 was the best whereas 1 was the worst for appropriateness of choice for each epileptic syndrome.

Lamotrigine (LTG) is frequently used for idiopathic generalized epilepsy except for valproate sodium (VPA) in both the USA and EU, while VPA and clonazepam were the main AEDs in Japan. For cryptogenic complex partial epilepsy and benign focal epilepsy, carbamazepine was a first-line AED among the USA, EU, and Japan, although other first-line AEDs were oxcarbamazepine (OCBZ), LTG, and levetiracetam (LEV) in both the USA and EU, while it was zonisamide in Japan. Regarding the treatment for symptomatic generalized epilepsy, West syndrome and Lennox-Gastaut syndrome, VPA and ACTH were first-line AEDs commonly used in the USA, EU, and Japan, while the other first-line AEDs were topiramate (TPM) and LTG in the USA and EU, and CZP and clobazam in Japan.

This Japanese EC study demonstrated the difference in the selection of AEDs for epileptic syndromes between the USA and EU, which use more newly-introduced AEDs including TPM, LTG, OCBZ and LEV as first-and second-line AEDs, and Japan.

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SPECIAL REPORT

Genetic testing in the epilepsies—Report of the ILAE Genetics Commission

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Summary

In this report, the International League Against Epilepsy (ILAE) Genetics Commission discusses essential issues to be considered with regard to clinical genetic testing in the epilepsies. Genetic research on the epilepsies has led to the identification of more than 20 genes with a major effect on susceptibility to idiopathic epilepsies. The most important potential clinical application of these discoveries is genetic testing: the use of genetic information, either to clarify the diagnosis in people already known or suspected to have epilepsy (diagnostic testing), or to predict onset of epilepsy in people at risk because of a family history (predictive testing). Although genetic testing has many potential benefits, it also has potential harms, and assessment of these potential benefits and harms in particular situations is complex. Moreover, many treating clinicians are unfamiliar with the types of tests available, how to access them, how to decide whether they should be offered, and what measures should be used to maximize benefit and minimize harm to their patients. Because the field is moving rapidly, with new information emerging practically every day, we present a framework for considering the clinical utility of genetic testing that can be applied to many different syndromes and clinical contexts. Given the current state of knowledge, genetic testing has high clinical utility in few clinical contexts, but in some of these it carries implications for daily clinical practice.

KEY WORDS: Epilepsy, Seizures, Genetics, Genetic testing, SCN1A.

The identification of genes that influence risk for the epilepsies has extremely important implications for both research and clinical practice. In a research context, study of the neurophysiologic and neurodevelopmental effects of mutations in identified genes can elucidate the basic processes underlying seizure susceptibility. This information may lead to the development of new treatments targeted to specific mechanisms, or even to ways of preventing epileptogenesis. In clinical practice, another important potential application of gene identification is genetic testing: the use of genetic information, either to clarify the diagnosis in people already known or suspected to have epilepsy (diagnostic testing), or to predict onset of epilepsy in people at risk of developing epilepsy because of a family history (predictive testing) (Table 1).

Herein we discuss the essential issues to be considered in the application of clinical genetic testing in the epilepsies. This discussion is important because assessment of the potential benefits and harms of testing in particular situations is complex, and many epileptologists and other clinicians are unfamiliar with the types of tests available, where to access them, how to decide whether they should be offered, and what procedures should be used to maximize benefit and minimize harm to their patients if they are offered.

One of the most promising areas of epilepsy genetics research is pharmacogenomics: the search for genetic variants associated with treatment response (efficacy or tolerability) (Kasperaviciute & Sisodiya, 2009; Loscher

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Table 1. Clinical contexts of genetic testing

Clinical context	Definition
Diagnostic testing	Testing used to confirm or exclude a known or suspected genetic disorder in an affected individual
Predictive testing	Testing used to predict development of a disorder in an unaffected individual at risk of developing the disorder because of a family history
Prenatal diagnosis	A special type of predictive testing used to confirm or exclude a disorder in a fetus at risk for the disorder
Carrier testing (also called carrier detection)	Testing used to identify usually asymptomatic individuals who have a gene mutation for an autosomal recessive or X-linked disorder

Table 2. Molecular methods for genetic testing

Molecular testing method	Definition
Sequencing	The nucleotide sequence of the DNA is determined for either the entire gene or selected regions of the gene.
Mutation scanning	Two-step process in which a segment of DNA is screened by one of a several techniques (e.g., SSCP, DHPLC, CSGE, DGGE[a]) to identify variant gene region(s), and then the variant regions are further analyzed (usually by sequencing) to identify the sequence alteration
Targeted mutation analysis	Evaluation of a DNA segment for the presence of one of a selected number of specific mutations (as opposed to complete gene sequencing, which detects any mutation). May refer to a panel of mutations tested or the use of a technique to identify deletions.
Fluorescent in situ hybridization (FISH)	A technique used to identify the presence of specific chromosomes or chromosomal regions through hybridization of fluorescently labeled DNA probes to denatured chromosomal DNA
Array-Comparative Genomic Hybridization (Array-CGH)	A technique used to detect DNA submicroscopic chromosomal rearrangements (deletions or duplications; also called copy number variations, or CNVs) at multiple loci simultaneously. May be carried out across the whole genome or in specific chromosomal regions
Single nucleotide polymorphism arrays (SNP arrays)	A technique used for genome-wide assessment of known SNPs and allowing detection of CNVs throughout the genome
Multiplex ligation-dependent probe amplification (MPLA)	A technique used to detect small intragenic rearrangements (deletions and duplications)
Other	Examples: linkage analysis, methylation analysis, protein truncation testing (PTT), uniparental disomy (UPD) study, Southern blot analysis

[a]SSCP, single strand conformational polymorphism analysis; DHPLC, denaturing high-performance liquid chromatography; CSGE, conformation-sensitive gel electrophoresis; DGGE, denaturing gradient gel electrophoresis.

et al., 2009). Genetic tests for variants associated with treatment response would have obvious clinical benefit, and are very likely to be introduced into clinical practice once identified and confirmed. In this report we have not addressed the issues related to testing for pharmacogenomic variants because they are likely to differ from those related to tests for genes that influence risk for developing epilepsy.

Testing Contexts and Methods

Genetic testing can be carried out either in a clinical laboratory or a research laboratory. A clinical laboratory performs analyses and gives results to providers and/or patients for the purpose of diagnosis, prevention, or treatment, usually for a fee. In the United States, the Clinical Laboratory Improvement Act (CLIA) requires that clinical laboratories be certified to meet certain federal quality and proficiency standards. A research laboratory performs analyses for research only; test results are not given to patients or providers, and CLIA certification is not required. In this article we discuss molecular genetic testing carried out in a clinical laboratory. The clinical contexts for clinical genetic testing are summarized in Table 1, and the molecular methods for testing in Table 2.

Previously, genetic tests could be ordered only by health care providers, but recently direct-to-consumer (DTC) genetic testing for disease susceptibility or ancestry has become available through commercial enterprises that market testing to the public, primarily over the Internet, for prices of several hundred dollars (Hauser & Johnston, 2009). Advocates of DTC testing say it provides increased autonomy, better access, and more privacy than testing through a health care provider. However, concerns have been raised about DTC testing because laboratories are not subject to the same quality control standards as in other types of testing; interpretations of the results and claims of benefit presented to consumers may not have a strong scientific basis; and genetic counseling is seldom included in the process of either choosing whether or not to obtain a test or interpreting the results. Because of these concerns, the American Society of Human Genetics has issued a position statement about DTC testing in the United States, calling for greater transparency, regulation, and provider education about DTC tests (Hudson et al., 2007).

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Potential Benefits and Harms

The potential benefits of genetic testing are many. With regard to diagnostic testing, a positive test result can clarify the diagnosis, provide important prognostic or treatment information, and possibly save the patient and family from expensive and uncomfortable or even invasive tests. Some patients might be relieved or comforted to have a genetic explanation for their seizures or those of their family members. Either a positive or a negative test result could have implications for reproductive decisions.

With regard to predictive testing, a negative test result can relieve anxiety and reduce the need for monitoring to detect seizures. A positive test result is likely to raise anxiety but could also enable a person to prepare for possible onset of seizures, and possibly take precautions to prevent accidents in case seizure onset should occur. It could also guide clinicians regarding the need for further investigations when seizures begin, depending on the clinical setting. In the future, prophylactic medication could theoretically be considered in some cases (although this approach has not been tested).

On the other hand, genetic testing also has potential harmful effects. As with other disorders, genetic information in epilepsy can contribute to psychological distress, adverse labeling, and discrimination in health insurance, life insurance, and employment (Billings et al., 1992; Burke et al., 2001). In the United States, legislation called the Genetic Information Nondiscrimination Act (GINA) was enacted in 2008 (Hampton, 2008), providing new protections by prohibiting discriminatory use of genetic information by health insurers and employers. The impact of this legislation remains to be seen.

For some patients with epilepsy, a genetic explanation might be disturbing rather than comforting. In addition, the identification of a genetic etiology could affect the family communication dynamics and social relationships of persons with epilepsy, and exacerbate the stigma, discrimination, and social isolation already associated with epilepsy in some cases (Phelan, 2005; Shostak & Ottman, 2006). Recent research also suggests that unlike the stigma associated with epilepsy per se, the stigma arising from the perception that a disorder is genetic may extend to the family members of an affected individual (Phelan, 2005). In what follows, we summarize considerations that should be used to minimize harm while maximizing the potential benefit of clinical genetic testing in the epilepsies. This is an area where more research is needed; little is known about the impact of genetic testing on patients with epilepsy today.

Criteria for Evaluating the Utility of a Genetic Test

Proven mutations have already been discovered in a large number of genes with a major effect on susceptibility to various forms of Mendelian idiopathic epilepsy, and Table 3 lists the most well-accepted and validated findings at this time. In addition to the genes listed in Table 3, mutation screening of candidate genes such as *CACNA1H* (Chen et al., 2003; Heron et al., 2004; Khosravani et al., 2005; Vitko et al., 2005; Chioza et al., 2006; Heron et al., 2007), *CACNB4* (Escayg et al., 2000a), *GABRD* (Dibbens et al., 2004), *CLCN2* (D'Agostino et al., 2004; Everett et al., 2007; Saint-Martin et al., 2009), and *MASS1* (Nakayama et al., 2002) has led to the identification of variants in some small families with complex inheritance, but the effects of these variants on disease risk largely await confirmation. In the case of *CLCN2*, mutations in families that appeared to have Mendelian inheritance were originally reported in error, and these findings were subsequently corrected (Kleefuss-Lie et al., 2009). Other potential epilepsy genes not included in Table 3 have been discovered through genetic linkage studies followed by association analysis in the linked regions, including *BRD2* (Pal et al., 2003), *ME2* (Greenberg et al., 2005), and *ELP4* (Strug et al., 2009), but some studies have not confirmed these findings (Lenzen et al., 2005; Cavalleri et al., 2007a) and causative mutations have not yet been reported in these genes.

Genes have also been identified in Mendelian symptomatic epilepsy syndromes where seizures are a symptom of a more widespread central nervous system disorder. These include many genes underlying malformations of cortical development (Leventer et al., 2008) and progressive myoclonus epilepsies such as Unverricht Lundborg disease, Lafora disease, and the neuronal ceroid lipofuscinoses (Shahwan et al., 2005). The genes in these symptomatic epilepsy syndromes are an important domain of genetic testing, although they are not reviewed in detail here.

Establishment of recommendations for genetic testing in all of these epilepsies would be extremely difficult because of their different clinical contexts; genetic contributions; and individual, familial, and social ramifications. In addition, genetic research is moving at such a rapid pace that recommendations at any single point in time could soon be changed with the emergence of new information. Therefore, rather than making specific recommendations, we wish to provide a framework for considering the utility of testing that can be applied to many different syndromes and contexts. In this section, we summarize the questions that need to be addressed in evaluating whether or not a genetic test is likely to provide useful information for clinical care. In the next section, we present examples where testing appears to have high utility, and others where it appears less useful at the present time (see Table 4 for diagnostic testing and Table 5 for predictive testing). Finally, for navigating this complex area, we provide a set of frequently asked questions (FAQs) and their answers (Table 6).

A useful framework for the evaluation of genetic testing has been developed in a model project carried out by the National Office of Public Health Genomics, U.S. Centers

Table 3. Genes identified in idiopathic epilepsy syndromes

	Locus	Gene	Product	References
Syndromes beginning in the first year of life				
Benign familial neonatal seizures	20q13.3	*KCNQ2*	$K_V7.2$ (K^+ channel)	(Biervert et al., 1998; Singh et al., 1998)
	8q24	*KCNQ3*	$K_V7.3$ (K^+ channel)	(Charlier et al., 1998)
Benign familial neonatal-infantile seizures	2q23-q24.3	*SCN2A*	$Na_V1.2$ (Na^+ channel)	(Heron et al., 2002; Berkovic et al., 2004; Striano et al., 2006; Herlenius et al., 2007)
Ohtahara syndrome	9q34.1	*STXBP1*	Syntaxin binding protein 1	(Saitsu et al., 2008)
	Xp22.13	*ARX*	Aristaless-related homeobox protein	(Kato et al., 2007; Fullston et al., 2009)
Early onset spasms	Xp22	*STK9/CDKL5*	cyclin-dependent kinase-like 5	(Kalscheuer et al., 2003)
X-linked infantile spasms	Xp22.13	*ARX*	Aristaless-related homeobox protein	(Stromme et al., 2002; Gecz et al., 2006)
Syndromes with prominent febrile seizures				
Dravet syndrome (severe myoclonic epilepsy of infancy)	2q24	*SCN1A*	$Na_V1.1$ (Na^+ channel)	(Claes et al., 2001; Nabbout et al., 2003; Wallace et al., 2003; Harkin et al., 2007)
Genetic (generalized) epilepsy with febrile seizures plus (GEFS+)	2q24	*SCN1A*	$Na_V1.1$ (Na^+ channel)	(Escayg et al., 2000b; Sugawara et al., 2001; Wallace et al., 2001b)
	19q13.1	*SCN1B*	β_1 subunit (Na^+ channel)	(Wallace et al., 1998, 2002; Audenaert et al., 2003; Scheffer et al., 2007)
	5q34	*GABRG2*	γ_2 subunit ($GABA_A$ receptor)	(Baulac et al., 2001; Harkin et al., 2002)
Childhood absence epilepsy with febrile seizures	5q34	*GABRG2*	γ_2 subunit ($GABA_A$ receptor)	(Wallace et al., 2001a; Kananura et al., 2002)
Epilepsy and mental retardation limited to females	Xq22	*PCDH19*	protocadherin	(Dibbens et al., 2008)
Idiopathic generalized epilepsies				
Early-onset absence epilepsy	1p35-p31.1	*SLC2A1*	GLUT1 (glucose transporter type 1)	(Suls et al., 2009)
Juvenile myoclonic epilepsy	5q34-q35	*GABRA1*	α_1 subunit ($GABA_A$ receptor)	(Cossette et al., 2002)
	6p12-p11	*EFHC1*	EF hand motif protein	(Suzuki et al., 2004)
Focal epilepsies				
Autosomal dominant nocturnal frontal lobe epilepsy	20q13.2-q13.3	*CHRNA4*	α_4 subunit (nACh receptor)	(Steinlein et al., 1995; Phillips et al., 2000)
	1q21	*CHRNB2*	β_2 subunit (nACh receptor)	(De Fusco et al., 2000; Phillips et al., 2001)
	8p21	*CHRNA2*	α_2 subunit (nACh receptor)	(Aridon et al., 2006)
Autosomal dominant partial epilepsy with auditory features (Autosomal dominant lateral temporal epilepsy)	10q24	*LGI1*	Leucine-rich repeat protein	(Gu et al., 2002; Kalachikov et al., 2002; Morante-Redolat et al., 2002)
Epilepsies associated with other paroxysmal disorders				
Generalized epilepsy and paroxysmal dyskinesia	10q22	*KCNMA1*	$K_{Ca}1.1$ (K^+ channel)	(Du et al., 2005)
Epilepsy with paroxysmal exercise-induced dyskinesia	1p35-p31.3	*SLC2A1*	GLUT1 (glucose transporter type 1)	(Suls et al., 2008; Weber et al., 2008)
Absence epilepsy and episodic ataxia	19p13	*CACNA1A*	$Ca_V2.1$ (Ca^{2+} channel)	(Jouvenceau et al., 2001; Imbrici et al., 2004)
Focal epilepsy and episodic ataxia	12p13	*KCNA1*	Kv1.1 (K^+ channel)	(Spauschus et al., 1999; Zuberi et al., 1999; Eunson et al., 2000)
Familial hemiplegic migraine and epilepsy	1q21-23	*ATP1A2*	Sodium-potassium ATPase	(Vanmolkot et al., 2003; Deprez et al., 2008)

Table 4. Examples of assessment of clinical validity and clinical utility for diagnostic testing in an affected individual[a]

	Gene(s)	Proportion of patients/families with mutations[b]	How accurate is a positive mutation test for confirming the diagnosis?	Clinical utility: In an affected individual, how useful is knowledge of mutation status for clinical management?
Syndromes beginning in first year of life				
Benign familial neonatal seizures	*KCNQ2* *KCNQ3*	>50% of families ~7% of families	Highly accurate in correct clinical context (but most cases have clear AD inheritance so diagnosis is usually clear without testing)	*Somewhat useful* Outcome usually benign (although severe outcome has been reported) Mutation status predicts favorable outcome; hence less aggressive management may be warranted De novo *KCNQ2* mutations reported in rare isolated cases. Finding of de novo mutation informs diagnosis and has management implications Genetic counseling implications
Benign familial neonatal-infantile seizures	*SCN2A*	unknown	Highly accurate in correct clinical context (but most cases have clear AD inheritance so diagnosis is usually clear without testing)	*Somewhat useful* Outcome is usually benign Mutation status predicts favorable outcome, hence less aggressive management may be warranted Genetic counseling implications
Ohtahara syndrome	*STXBP1* *ARX*	~35% of patients unknown	Highly accurate in correct clinical context	*Very useful* Establishes etiology so avoids further diagnostic test procedures Genetic counseling implications Usually de novo
Early onset spasms	*STK9/CDKL5*	10–17% of patients	Highly accurate in correct clinical context	*Very useful* Establishes etiology so avoids further diagnostic test procedures Genetic counseling implications Usually de novo
X-linked infantile spasms (usually in boys)	*ARX*	<5% of male patients	Highly accurate in correct clinical context	*Very useful* Establishes etiology so avoids further diagnostic test procedures Genetic counseling implications De novo cases reported in rare isolated cases. Finding of de novo mutation informs diagnosis and may alter clinical management
Syndromes with prominent febrile seizures				
Dravet syndrome (Severe myoclonic epilepsy of infancy)	*SCN1A*	70–80% of patients	Truncation mutations: highly accurate in correct clinical context Missense mutations: less clear and depends on electroclinical context	*Very useful* Establishes etiology so avoids further diagnostic test procedures Allows early optimization of antiepileptic therapy Most mutations de novo Mutations rarely identified in parent, sometimes with somatic mosaicism Genetic counseling implications

Continued

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Table 4. Continued

	Gene(s)	Proportion of patients/families with mutations[b]	How accurate is a positive mutation test for confirming the diagnosis?	Clinical utility: In an affected individual, how useful is knowledge of mutation status for clinical management?
Genetic (formerly Generalized) epilepsy with febrile seizures plus	*SCN1A* *SCN1B* *GABRG2*	5–10% of families <5% of families <1% of families	Missense mutations: highly accurate in correct clinical context	*Not useful* Because of extensive phenotypic heterogeneity, mutation status does not predict prognosis or treatment
Epilepsy and mental retardation limited to females	*PCDH19*	Unknown	Highly accurate in correct clinical context	*Very useful* Establishes etiology, especially in isolated cases or smaller families where mode of inheritance is unclear Genetic counseling implications
Idiopathic generalized epilepsy				
Early onset absence epilepsy	*SLC2A1*	~10% of patients	Highly accurate in correct clinical context	*Very useful* Establishes etiology so avoids further diagnostic test procedures May alter clinical management decisions (ketogenic diet found to be effective) Genetic counseling implications
Focal epilepsies				
Autosomal dominant nocturnal frontal lobe epilepsy	*CHRNA4* *CHRNB2* *CHRNA2*	<10% of families <5% of families unknown, probably rare	Highly accurate in correct clinical context	*Very useful* Variable outcome; some cases highly refractory Establishes etiology so no need to pursue structural lesion with repeated imaging Not known if optimal antiepileptic drug therapy or outcome of surgery will differ by mutation status Genetic counseling implications De novo mutations reported in rare isolated cases. Finding of de novo mutation informs diagnosis, and may alter clinical management if surgery is being considered
Autosomal dominant partial epilepsy with auditory features	*LGI1*	~50% of families	Highly accurate in correct clinical context	*Not very useful* Most cases have favorable course Establishes etiology so no need to pursue structural lesion with repeated imaging in rare severe cases Mutation status unlikely to alter management decisions (unknown if optimal antiepileptic drug therapy or surgery outcome will differ by mutation status) Genetic counseling implications De novo cases reported in rare isolated cases. Finding of de novo mutation informs diagnosis, but is unlikely to alter clinical management unless surgery is being considered

Continued

for Disease Control and Prevention, in collaboration with the Foundation for Blood Research, a nonprofit research organization (Haddow & Palomaki, 2004). This project, called "ACCE," takes its name from the four essential components of evaluation—analytic validity; clinical validity; clinical utility; and associated ethical, legal, and social

Table 4. Continued

	Gene(s)	Proportion of patients/families with mutations[b]	How accurate is a positive mutation test for confirming the diagnosis?	Clinical utility: In an affected individual, how useful is knowledge of mutation status for clinical management?
Epilepsies associated with other paroxysmal disorders				
Epilepsy with paroxysmal exercise-induced dyskinesia	*SLC2A1*	unknown	Highly accurate in correct clinical context	*Very useful* Establishes etiology so avoids further diagnostic test procedures May alter clinical management decisions (ketogenic diet found to be effective) Genetic counseling implications

[a]AD, autosomal dominant; Clinical context: includes syndrome, age at onset, seizure types and frequency, clinical course, electroencephalography (EEG), neuroimaging, and family history.
[b]Estimates of mutation frequency from Combi et al., 2004; Ottman et al., 2004; Deprez et al., 2009.

implications. A series of questions targeted to different aspects of the evaluation process is provided on the ACCE website: http://www.cdc.gov/genomics/gtesting/ACCE/acce_proj.htm (Accessed September 28, 2009).

Analytic validity

The analytic validity of a test refers to the laboratory component of testing. Does the test accurately identify the genotype of interest? Accuracy involves analytic sensitivity (the ability of the test to identify a positive sample correctly), analytic specificity (the ability of the test to identify a negative sample correctly), laboratory quality control (procedures for assuring the test results fall within specified limits), and reliability (the ability of the test to produce the same results if repeated on the same sample). Analytic validity depends on the molecular aspects of detecting a gene variant in a DNA sample rather than on the disease; hence, the considerations are the same for epilepsy as for other conditions.

Even when a test for a specific change within a gene is accurate, the test could still miss other important changes it is not designed to detect. Some tests examine only parts of a gene (exon sequencing), particular single nucleotide polymorphisms (SNPs), or the number of copies of the gene (copy number variations, or CNVs). No single test currently available examines all aspects of variation within a gene; therefore, a test result that reports "no change detected" does not exempt the gene from contributing to disease in any particular individual. On the other hand, a negative result when looking for a specific mutation that is present in other affected family members usually provides a definitive answer.

The source of the DNA sample provided is another important consideration. A DNA mutation present in all cells of the body is considered to be "germ line." In some cases, a mutation can occur during embryonic development, leading to uneven distribution of the mutation in different tissues, or "somatic mosaicism." With somatic mosaicism, a mutation can be detected in a sample of DNA from one source, for example, a hair follicle, but not in another, for example, blood lymphocytes. This implies that an individual who initially tests negative might later be found to carry a mutation only in specific cell lines after careful examination of different cell types using more sensitive methods of detection. This concept has been found to be important in the severe childhood encephalopathy Dravet syndrome, in which more than 70% of cases have mutations in *SCN1A*, the gene encoding the voltage-gated sodium channel alpha subunit $Na_V1.1$. In several families with two children with Dravet syndrome, initially no mutation was found in either parent by the usual techniques, but more detailed molecular studies showed parental gonadal and somatic mosaicism (Depienne et al., 2006; Gennaro et al., 2006; Marini et al., 2006; Morimoto et al., 2006). In other patients with Dravet syndrome who were initially found to be negative for *SCN1A* mutations on conventional sequence analysis, exon deletion or duplication, or submicroscopic chromosomal deletion involving *SCN1A* was later identified (Madia et al., 2006; Mulley et al., 2006; Suls et al., 2006; Wang et al., 2008; Marini et al., 2009). These findings suggest that to maximize the sensitivity of genetic testing, a wider array of molecular methods must be employed than previously appreciated. This detailed decision tree in the pursuit of the correct diagnosis is not fully explained in the process of obtaining a clinical genetic test result.

Clinical validity

Clinical validity refers to the ability of the test to determine whether or not a person is affected with the disorder of interest (or will become affected in the future). This depends in part on analytic validity—a test cannot accurately determine whether or not a person is affected if it does not have high analytic validity. Clinical validity is also influenced by several other important factors, including (1) clinical sensi-

Table 5. Examples of assessment of clinical validity and clinical utility for predictive testing in an unaffected relative of an affected individual who tests positive

	Gene(s)	How accurate is a positive mutation test for predicting occurrence of the syndrome?	Clinical utility: In an unaffected family member, how useful is knowledge of mutation status?
Syndromes beginning in first year of life			
Benign familial neonatal seizures	*KCNQ2* *KCNQ3*	Highly accurate because of high penetrance	*Not useful* Outcome usually benign Knowledge of mutation status before onset would usually not alter management decisions
Benign familial neonatal-infantile seizures	*SCN2A*	Not established	*Not useful* Outcome usually benign Knowledge of mutation status before onset would usually not alter management decisions
Ohtahara syndrome	*STXBP1* *ARX*	Not established	
Early onset spasms	*STK9/CDKL5*	Not established	
X-linked recessive infantile spasms (usually in boys)	*ARX*	Not established	
Syndromes with prominent febrile seizures			
Dravet syndrome (severe myoclonic epilepsy of infancy)	*SCN1A*	Highly accurate for truncation mutation identified in sibling of individual with the same mutation; missense less clear	*Very useful* Prenatal diagnosis may be considered Knowledge of high risk allows preparation for more aggressive treatment at onset
Genetic (formerly generalized) epilepsy with febrile seizures plus	*SCN1A* *SCN1B* *GABRG2*	Not accurate because of reduced penetrance and high phenotypic variability	*Not useful*
Epilepsy and mental retardation limited to females	*PCDH19*	Highly accurate because of high penetrance	*Very useful* Prenatal diagnosis may be considered Knowledge of high risk allows preparation for more aggressive treatment at onset
Idiopathic generalized epilepsy			
Early onset absence epilepsy	*SLC2A1*	Not established	
Focal epilepsies			
Autosomal dominant nocturnal frontal lobe epilepsy	*CHRNA4* *CHRNB2* *CHRNA2*	Not established; depends on penetrance	
Autosomal dominant partial epilepsy with auditory features	*LGI1*	Not very accurate: penetrance is approximately 67%, implying one-third of mutation carriers will remain unaffected	*Not useful* Outcome usually benign Knowledge of mutation status before onset would not alter management decisions
Epilepsies associated with other paroxysmal disorders			
Epilepsy with paroxysmal exercise-induced dyskinesia	*SLC2A1*	Not established	

tivity—the proportion of individuals who test positive, among those who have the disease; (2) clinical specificity—the proportion of individuals who test negative, among those who are unaffected; (3) positive predictive value (PPV)—the proportion of individuals who have the disease (or will develop it in the future), among those who test positive; and (4) negative predictive value—the proportion of individuals who do not have the disease (and will not develop it in the future), among those who test negative. PPV is strongly influenced by the prevalence of the disorder among tested individuals. For a given sensitivity and specificity, PPV is higher in a situation where many of those

Table 6. Genetic testing FAQs

1. What are the benefits of testing?
Test results can provide a sense of relief from uncertainty and help people make informed decisions about managing their health care. With diagnostic testing, a positive test result can confirm the diagnosis, save the patient and family from unnecessary diagnostic procedures, and may help in the selection of optimal therapy. With predictive testing, a negative result can provide relief, and a positive result can direct a person toward available monitoring and treatment options. Some test results can also help people make decisions about having children.

2. What are the risks or limitations of testing?
The primary risks of genetic testing relate to the emotional, social, or financial consequences of the test results. People may feel angry, depressed, anxious, or guilty about their results. Genetic testing may also affect family relationships because the results can reveal information about family members other than the person who is tested. The possibility of genetic discrimination in employment or insurance is also a concern.

3. What is the difference between clinical genetic testing and research genetic testing?
Clinical tests are performed for the purpose of diagnosis, prevention, or treatment in the care of individual patients, usually for a fee. The results are provided in writing to the provider or patient. In the United States, laboratories performing clinical tests must be CLIA approved. In contrast, research tests are performed for the purpose of increasing understanding of a disorder, or developing a clinical test. The cost of research testing is covered by the researcher, and test results are not generally given to patients or providers. Laboratories performing research testing are not subject to CLIA regulation.

4. How can I find out whether or not genetic testing is available for my patient and where it is performed?
Extensive information about the available clinical genetic tests for a wide array of syndromes may be found on the Gene Tests website (http://www.genetests.org), a publicly funded medical genetics information resource developed for physicians, other health care providers, and researchers. The site also contains authoritative reviews on the genetics of several epilepsy syndromes.

5. Should I offer a test to the patient?
For a diagnostic test, the first step is to arrive at an informed opinion about whether or not the patient is likely to have the disorder in question. This should involve a thorough clinical evaluation and careful family history. The next step is to evaluate the likely clinical utility of the test. Consider the following questions:
a. Is the test result likely to lead to a meaningful change in the procedures used for evaluation (e.g., repeated spinal tap or neuroimaging)?
b. Is the test result likely to lead to a change in the optimal treatment choice or prognosis?
c. Is the test result likely to have any other positive or negative social or psychological effects? For example, is the patient likely to be relieved or disturbed by the knowledge that he or she carries a mutation?
d. Is the test result likely to influence the patient's decisions about reproduction?

6. I believe the test could provide important information—what are the next steps?
The patient must make his or her own decision about whether or not to be tested. Because testing has both benefits and risks, the decision about whether to be tested is personal and complex. Before a person has a genetic test, he or she needs to make an informed choice, which involves understanding the testing procedure, the benefits and risks of the test, and the possible consequences of the test results. Pretest counseling by a trained genetic counselor is important for providing information about the pros and cons of the test and discussing the social and emotional aspects of testing. Testing must never be carried out without informed consent.
If the patient decides to proceed with genetic testing, a health care provider such as an epileptologist, clinical geneticist, or nurse practitioner may be able to order the test, depending on the country where the patient lives. Genetic tests are performed on a sample of blood, hair, skin, amniotic fluid (for prenatal diagnosis), or other tissue. The sample is sent to a laboratory where the molecular analyses appropriate for the suspected disorder or gene are performed. The laboratory reports the test results in writing to the provider who ordered the test.

7. Who should be tested in the family?
For diagnostic testing, usually one affected family member requests testing initially. If the test is positive, this has implications for other affected and unaffected family members. Unaffected family members should not be offered predictive testing unless an affected family member has obtained a specific molecular genetic diagnosis. Some unaffected family members in a family where affected family members have been found to carry a mutation may be "obligate carriers" and thus have known mutation status without being tested; for example, if an unaffected person has both a parent and a child who carry a specific rare mutation, he or she is almost certainly a carrier, regardless of epilepsy status.

8. If the test is negative, is my diagnosis incorrect?
Not necessarily. Epilepsy syndromes show extensive genetic heterogeneity, so that a negative test for a given gene does not mean the patient does not have the syndrome.

9. What is the best way to give the results to the patient?
The results should be explained to the patient in a posttest counseling session with a genetic counselor or clinical geneticist.

10. Is the cost of testing covered by insurance?
This depends on the country in which the patient lives. In the United States, some health insurance plans will cover the costs of diagnostic genetic testing, but health insurance providers have different policies about which tests are covered. Some people may choose not to use their insurance to pay for testing because the results of a genetic test might affect their health insurance coverage. The Genetic Information Nondiscrimination Act (GINA) is intended to protect against this but its effect is still unclear at the present time.

tested are actually clinically affected than in a situation where few of those tested are affected.

The clinical validity of a genetic test varies according to the type of genetic change identified. For example, a test that involves sequencing the gene (Table 2) can identify several types of sequence changes, including "synonymous" nucleotide substitutions that do not alter the amino acid sequence of the encoded protein, "nonsynonymous" or "missense" changes resulting in an amino acid substitution, and "nonsense" or "truncation" mutations that lead to a

fragment of the normal protein product. These different types of changes could have different implications for disease risk, and some changes could be normal variants found commonly in the population or could have uncertain clinical significance. A good example of this problem arises in *SCN1A*, where different types of mutations have been associated with different phenotypes. Among the mutations found in Dravet syndrome, truncation and missense each account for about 40% of mutations, and intragenic deletions and splice-site mutations occur much less frequently (Harkin et al., 2007; Depienne et al., 2009). In contrast, in families with GEFS+ all of the identified *SCN1A* mutations have been missense.

To maximize sensitivity and PPV, diagnostic testing should be offered in the context of an informed opinion that the affected individual is likely to have the disorder in question; otherwise testing would result in unnecessary expense with little potential benefit. In this evaluation, consistency of the patient's clinical epilepsy syndrome and family history with those previously described in individuals with mutations should be considered. The importance of taking a careful family history, with as much detail as possible about the clinical features in affected family members and laboratory exclusion of the most likely alternative diagnoses, cannot be overemphasized.

Almost all of the gene discoveries to date have been in monogenic epilepsies, which comprise only a tiny fraction of all epilepsies. Most people with epilepsy have no affected relatives, suggesting that in the great majority of cases, epilepsy is genetically complex (Ottman, 2005; Berkovic et al., 2006). The genetic mechanism underlying complex epilepsies could involve genetic variants that are common in the population, have only a small effect on disease risk, and act in concert with each other and with environmental factors, consistent with the "common disease, common variant" hypothesis. Alternatively (or perhaps in addition), the mechanism could involve multiple rare genetic variants acting in concert (Mulley et al., 2005a; Dibbens et al., 2007).

To date, success in identifying genes that raise risk for genetically complex epilepsies has been limited, but some genes are emerging such as the calcium channel subunit gene *CACNA1H* (Chen et al., 2003; Heron et al., 2004, 2007). Genetic association studies (Tan et al., 2004; Mullen et al., 2009) are also beginning to provide evidence for other genetic variants associated with increased risk (Cavalleri et al., 2007a,b; Helbig et al., 2009). One very interesting recent, confirmed finding is an association, found in approximately 1% of cases of idiopathic generalized epilepsies, of a microdeletion on chromosome 15q13.3 that was previously reported to occur less frequently in schizophrenia, mental retardation, and autism (Dibbens et al., 2009; Helbig et al., 2009).

With complex inheritance, each gene may have only a small effect on risk, so that using a genetic test to identify any one risk-raising variant is not likely to be very meaningful on its own. In addition, even in rare monogenic epilepsies, the relationship between mutation status and epilepsy phenotype is not straightforward. Several complexities in genotype–phenotype relationships influence the clinical validity of genetic tests.

Variable expressivity

One important aspect of this complexity is variable expressivity. The clinical epilepsy phenotype may vary widely, even among family members who carry the same mutation. For example, missense mutations in *SCN1A* are associated with genetic (formerly generalized) epilepsy with febrile seizures plus (GEFS+), a familial epilepsy syndrome with extremely variable expressivity. The effect of an *SCN1A* missense mutation may range from benign phenotypes such as typical age-dependent febrile seizures or febrile seizures plus (i.e., febrile seizures persisting beyond age 6 years or accompanied by afebrile generalized tonic–clonic seizures) to severe phenotypes such as Dravet syndrome (Mulley et al., 2005b; Lossin, 2009).

Modifier genes are likely to be an important cause of variable expressivity, although variation in as-yet-unidentified environmental exposures may also contribute in some cases. A recent study showed experimentally that two ion channel mutations, each capable of causing human epilepsy, can actually cancel out each other's effects when present in brain cells due to their opposing effects on neuronal excitability (Glasscock et al., 2007).

Variable expressivity reduces the PPV of a predictive genetic test because information about mutation status is a poor predictor of clinical outcome. In GEFS+, a positive test for an *SCN1A* mutation might strongly predict seizure occurrence in an individual from a family containing multiple affected individuals, but the clinical outcome could range from typical febrile seizures without any subsequent unprovoked seizures to severe epileptic encephalopathy with mental retardation. Moreover, as discussed below, since the penetrance of missense mutations in *SCN1A* in GEFS+ is only 60–70%, a significant proportion of mutation carriers will not develop seizures at all. In this case genetic testing for *SCN1A* mutations has much greater utility for diagnostic testing than for predictive testing, even if carried out in a family in which a mutation has been identified. In the future, prediction may improve when all of the genes that influence clinical outcome are identified—but this will involve complex protocols for genetic testing of multiple genes that have not been developed, as well as understanding how the multiple genes interact in their influence on risk.

Reduced penetrance

Another aspect of complexity in the relationship between genotype and phenotype is "penetrance": the likelihood of developing epilepsy for an individual who has a mutation in a disease-causing gene. Penetrance is particularly important

in considering the clinical validity of a predictive genetic test, offered to an unaffected individual in a family in which an affected person has been found to carry a mutation. For many of the previously identified genes, penetrance has been estimated as 67–80%. These previous penetrance estimates are likely to be inflated by ascertainment bias, since they are based on families selected for study because they contain multiple affected individuals (and thus high penetrance); therefore, the true penetrance may actually be lower for many syndromes. Reduced penetrance clearly reduces the PPV of a genetic test, because an individual who tests positive may never develop epilepsy. For example, a study of the penetrance of *LGI1* mutations in ADPEAF estimated penetrance at 67% (Rosanoff & Ottman, 2008), suggesting that about one-third of mutation carriers will not develop epilepsy. On the other hand, benign familial neonatal seizures (BFNS) has an unusually high penetrance of greater than 90%.

Genetic heterogeneity

Genetic heterogeneity is another important complexity in the relationship of genotype to phenotype in the epilepsies. In most monogenic epilepsy syndromes where genes have been identified, mutations have been discovered in different genes in different families with the same syndrome. Often the genes encode different subunits of the same ion channel. Examples include BFNS, in which the same phenotype is associated with mutations in two different genes encoding subunits of potassium channels (*KCNQ2* and *KCNQ3*) (Gardiner, 2006); autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) due to mutations in three different nicotinic acetylcholine receptor subunit genes, *CHRNA4, CHRNB2,* and *CHRNA2* (Marini & Guerrini, 2007); and GEFS+ due to mutations in *SCN1A*, *SCN1B*, and *GABRG2* (Scheffer et al., 2009).

In addition, many families with a given syndrome do not have mutations in any of the previously identified genes. For example, with ADNFLE only approximately 20% of individuals with a family history have mutations in the genes identified so far. Similarly, with autosomal dominant partial epilepsy with auditory features (ADPEAF), approximately 50% of families containing two or more individuals with ictal auditory symptoms have mutations in *LGI1* (Ottman et al., 2004). In GEFS+, only approximately 10% of families have mutations in *SCN1A*, and even fewer have mutations in the other previously identified genes (Scheffer et al., 2009).

Because of the potential for extensive genetic heterogeneity, even though a *positive* diagnostic genetic test result may be informative in these syndromes, a *negative* test for a given gene is generally uninformative, that is, the test has low negative predictive value. A test for a mutation in a specific gene does not mean the individual does not carry a disease-causing mutation in another gene not yet identified, or that the individual does not have the disorder in question, because the diagnosis is based on the clinical epilepsy syndrome rather than on the results of genetic testing.

For many genetic forms of epilepsy, patients with clinical features similar to those found in autosomal dominant families but who do not have any affected relatives (i.e., sporadic or isolated cases) are much less likely to have a mutation in previously identified genes than are familial cases; therefore, the sensitivity of a test will generally be much lower for isolated cases than for familial cases. In some of the genes identified so far, de novo mutations—that is, new mutations that occurred in a germ cell (egg or sperm) from one of the parents or in the fertilized egg itself, so that neither parent is a carrier—have been identified in isolated cases, but these are generally uncommon. For example, rare de novo mutations have been identified in *CHRNA4* and *CHRNB2* (genes associated with ADNFLE) in isolated patients with nocturnal frontal lobe epilepsy (Phillips et al., 2000; Bertrand et al., 2005), in *LGI1* (the gene associated with ADPEAF) in isolated patients with focal epilepsy with ictal auditory symptoms (Bisulli et al., 2004; Michelucci et al., 2007), and in *KCNQ2* in isolated patients with benign neonatal seizures (Claes et al., 2004; Ishii et al., 2009). For these disorders, the yield of a diagnostic test would be much lower in isolated cases than in familial cases; therefore, decisions about testing must be based on balancing the cost of testing with the clinical utility of the test. When a mutation is found in a sporadic case, it may have important genetic counseling implications but there is significant uncertainty in this situation.

However, the pattern is completely different in Dravet syndrome. In this syndrome current evidence suggests that more than 70% of patients have *SCN1A* mutations and more than 95% arise de novo (Mulley et al., 2005b; Harkin et al., 2007). Thus in a diagnostic genetic test for a mutation in *SCN1A* in Dravet syndrome, the clinical sensitivity is high regardless of family history.

Clinical utility

The clinical utility of a test refers to the benefits and harms involved in introducing a test into routine clinical practice, that is, the impact of a positive or negative test on patient care. One of the most important considerations is the availability of an effective intervention in individuals who test positive. In diagnostic testing, such an intervention might consist of a treatment choice that is especially effective or avoidance of treatments that are especially harmful, or avoidance of unpleasant or invasive diagnostic procedures (e.g., liver biopsy, repeated spinal tap or neuroimaging) in individuals who test positive. In predictive testing, interventions might someday include prophylactic medications (although none has been shown to have efficacy in any epileptic disorder so far). Other considerations include the costs associated with testing and the accessibility of tests and interventions to vulnerable populations.

The specific epilepsy features, associated illnesses and conditions, and family history are extremely important in

considering the clinical utility of a genetic test. For severe epilepsies associated with developmental delay (e.g., Dravet Syndrome), the issues to consider in offering testing are clearly different from those in epilepsies that respond well to treatment and do not have other associated features. Clinical utility may also differ according to the usual age at onset of the disorder—for epilepsies with onset in infancy and a severe course, parents may place a high value on predictive testing regardless of its uncertainties, whereas for epilepsies with adult onset and a mild course, the considerations will be quite different. The family context is also extremely important in this regard—if multiple family members are affected, some or all family members may already be aware that their risks are increased, so that genetic testing would not provide new information about the family's risk as a whole. However, predictive genetic testing in some family members could provide information about which specific individuals are more likely to develop epilepsy. Moreover, a positive test in one person might contain information relevant to others in the family, who may or may not wish to learn their genetic status (e.g., if an uncle and his niece are both carriers, one of the niece's parents also must be). Another family issue is related to biologic versus stated paternity, a distinction that may be discovered through genetic testing but is not usually divulged. This type of complexity should be explored fully in genetic counseling prior to testing.

Ethical, legal, and social implications

The fourth consideration in evaluating the utility of a genetic test is its ethical, legal, and social implications. This includes an understanding of the stigmatization and discrimination that may result from the test, as well as privacy and confidentiality issues, and personal, family, or social issues that could arise from testing. Some tests require that DNA samples be obtained from other family members in order to assess risk. Are these family members available and willing to be tested if the need should arise? Is the patient willing to approach them in order to gain their participation? Legal issues regarding consent and ownership of samples are also important to consider. Once the potential harms associated with testing are identified, the clinician should put safeguards in place to minimize them.

How to Test

Current information about genetic testing for many disorders, including several forms of epilepsy, is available from the Gene Tests website: http://www.ncbi.nlm.nih.gov/sites/GeneTests (Accessed September 28, 2009), a publicly funded medical genetics information resource. The Gene Tests site identifies both clinical laboratories and research laboratories that provide testing. It also contains educational materials about genetics and authoritative reviews on specific disorders, including ADNFLE, ADPEAF, progressive myoclonus epilepsy, and several other metabolic forms of epilepsy. For genetic tests judged to have clinical utility in a particular clinical context, this site provides information about whether or not a clinical genetic test is available, and if so, where to obtain it.

Before any test is ordered it is crucial to follow certain procedures. First, no molecular genetic test should ever be ordered without the patient's informed consent. Because genetics can be complicated, making sure the patient understands the ramifications of testing sufficiently to make an informed choice may not be straightforward. Second, no test should ever be done without pretest and posttest genetic counseling. Wherever possible, counseling should be carried out by a clinical genetics professional such as a medical geneticist, genetic counselor, or genetic nurse. A closer interaction between clinical genetics professionals and epileptologists would greatly improve counseling for patients with epilepsy.

The purpose of pretest genetic counseling is to ensure that the patient is informed and has time to weigh the advantages and disadvantages of being tested. It should include the collection of pedigree information, providing information about the disorder and its mode of inheritance, course, and treatment options; estimation of the risk of the disorder for the individual (or for a future offspring) if applicable; discussion of the medical, emotional, and social implications of a genetic test result for the individual and the family (including potential effects on health and life insurance); and details regarding the test itself and its limitations (e.g., the sample required, the information that will and will not be provided by the test). All of this information should be presented in a nonjudgmental and noncoercive manner, to assist the individual in making an informed decision.

Posttest genetic counseling is crucial to help the patient understand the test result and begin to digest it in the context of his or her life circumstances. The session should convey the test results in terms that the patient understands, discuss the implications for the patient and other family members, and provide referrals to other health professionals, educational materials, and community-based support groups as needed.

Application to Specific Epilepsy Syndromes and Genes

Although many genes have been identified in a range of epilepsy syndromes, few currently have high clinical utility for genetic testing. The importance of interpreting all molecular findings in their clinical context cannot be overemphasized. Relatively few of the molecular tests for the idiopathic epilepsies are useful in the clinical domain and those that deserve consideration are presented in Table 4 for diagnostic testing and Table 5 for predictive testing. Many

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of the remaining gene mutations have been identified only in single or a few reports, so molecular testing is still largely a research tool.

Although a genetic test may have a high PPV (i.e., a high probability of the diagnosis among individuals who test positive) in patients with the appropriate phenotype, discovery of a mutation may not influence clinical management (diagnostic procedures, treatment choices, or prognostic counseling). In some circumstances, it may have a bearing on genetic counseling but the question of whether the results would lead a family to alter their reproductive plans on the basis of the particular syndrome needs to be considered. For example, BFNS is usually benign (although severe cases have been reported) (Steinlein et al., 2007). Therefore, the finding of a potassium channel subunit mutation may be of interest, but the disorder would usually not be considered sufficiently severe for such a finding to affect reproductive choices. Moreover, the pattern of inheritance is usually clearly autosomal dominant with high penetrance, making the diagnosis straightforward without the need for molecular testing.

In some settings, the finding of a mutation does not provide information about phenotype and, therefore, cannot inform treatment or prognosis. As discussed earlier, the best example of this situation is a missense mutation of *SCN1A* in a family with GEFS+, which could be associated with phenotypes ranging from benign febrile seizures to severe epileptic encephalopathy. Interpretation of a mutation needs to be made in the context of the patient's electroclinical and developmental history. For example, a patient with febrile seizures would not require treatment and would have an excellent prognosis, whereas a patient with Dravet syndrome requires long-term management. In contrast, a de novo truncation mutation is very likely to be associated with Dravet syndrome. Therefore, diagnosis of an electroclinical syndrome such as Dravet syndrome, subsequently supported by mutational analysis (of *SCN1A* for example), could well lead to more aggressive treatment with a view to potentially improving developmental outcome.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

None of the authors has any conflict of interest to disclose.

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