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LETTER TO THE EDITOR

Early-onset genetic epilepsies reaching adult clinics

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Sir,

We read with great interest the article 'Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort' (Symonds *et al.*, 2019). We have extrapolated from these data to estimate the proportion of these epilepsies remaining active in adulthood: between one-third and three-quarters of the cohort will need the care of an adult neurologist.

Over recent years, studies of clinician-led (Helbig *et al.*, 2016; Berg *et al.*, 2017; Lindy *et al.*, 2018; Borlot *et al.*, 2019; Truty *et al.*, 2019) and standardized gene panel testing (Trump *et al.*, 2016; Butler *et al.*, 2017) have identified the most commonly implicated genes amongst those patients accessing the tests. However, ascertainment bias has obscured the true population-based frequency of these disorders. One previous study exploited a comprehensive healthcare system for population-based ascertainment but focused on early-onset severe epilepsies performing non-standardized genetic tests for 50 participants (Howell *et al.*, 2018). Symonds *et al.* (2019) must be commended on completing the first prospective study applying molecular testing systematically across a broad range of seizure disorders of unknown aetiology presenting before 3 years of age to calculate the frequency of these individually rare disorders in a population-based manner, neither biased by access to healthcare or research centres, nor limited to a narrow phenotypic group, and with their focus on genes, which already guide clinical management.

Whilst, the role of genetic testing is increasingly recognized in paediatrics where the health economic yield is greatest (Joshi *et al.*, 2016; Howell *et al.*, 2018; Oates *et al.*, 2018), less is known of the frequency at which adult neurologists should expect to encounter these monogenic epilepsies. Children grow into adults and with advances in paediatric care it is becoming increasingly common for children with even severe developmental and epileptic encephalopathies to reach transition. The majority of adults with early-onset epilepsies, however, will not have benefited from recent genetic diagnostic discoveries (Catarino *et al.*, 2011). With gradually increasing evidence to inform genetically stratified clinical management and increasing access to testing it is important that neurologists caring for adults with epilepsy recognize the frequency of these genetic disorders in their clinic population. Symonds *et al.* were able to recruit comprehensively from the limited number of centres likely to care for paediatric patients in Scotland; however, obtaining such comprehensive, unbiased population-based data in adulthood would be more challenging because of the greater number and range of care settings in which patients are cared for. Until our present analysis, the best estimates of population prevalence in adults are actually diagnostic yields of genetic tests in adults of various ages ascertained opportunistically from specialist settings (Borlot *et al.*, 2019; Truty *et al.*, 2019).

The International League Against Epilepsy emphasizes the use of molecular diagnostics as well as electroclinical

syndromes in clinical management (Scheffer *et al.*, 2017). Reviewing the natural histories and treatment responses reported for the electroclinical syndromes and genetically defined epilepsies identified by Symonds *et al.* we have estimated the number that will remain active, requiring treatment and neurology follow-up in adulthood. We have conservatively reported lower and higher estimates at the level of complete individuals because there is limited published data on the long-term prognosis of many of these syndromes and genetically defined epilepsies into adulthood.

Symonds *et al.* (2019) identified 76 individuals who had early childhood-onset epilepsy with a variant in one of 104 genes from a birth cohort of 169 470. Of these, we predict that 25–56 will continue to require neurological care in adulthood (Table 1 and Supplementary Table 1). Applying a 95% exact Poisson confidence interval of 16.2–72.7, this corresponds to a lifetime risk of 9.56–42.9/100 000. In 20–44 individuals (11.8–26.0/100 000; 95% confidence interval 7.21–34.9/100 000) the implicated gene may already guide treatment decisions.

In addition to the caveats discussed by Symonds *et al.* (2019) there are several limitations to the interpretation of these figures. First, to provide estimates that are easily generalized to other populations, we have forecasted the lifetime risk rather than cross-sectional prevalence at transition. Were Scotland's overall childhood mortality and migration rates to remain fixed at the 2018 figures of 272 deaths, 30 271 immigrants and 26 048 emigrants amongst 972 972 individuals under 17 years of age (National Records of Scotland, 2019), then overall childhood mortality would have little effect on the denominator. However, the effect of migration is harder to predict as little is known of the trends in migration of children with early-onset epilepsies. However, were the risk amongst the 55 826 17 year olds in Scotland in 2018 (National Records of Scotland, 2019) to be as predicted, one would expect 5–24 of them to have a history of seizures prior to 3 years of age and also to require neurological care in adulthood because of a variant detectable using the 104-gene panel.

Second, the estimates rely upon the very limited gene and syndrome specific data for long-term prognosis because most case series focused on childhood and those fewer studies of adults were biased to ascertain those with active epilepsy. Beyond Dravet syndrome (Cooper *et al.*, 2016) and *SCN8A*-related epilepsies (Johannesen *et al.*, 2018*b*) there is little knowledge of the total childhood mortality of specific genetic epilepsies. However, mortality is elevated in children with epilepsy (Jennum *et al.*, 2017), and this is likely to be greatest in those with developmental and epileptic encephalopathies (Berg *et al.*, 2004). Whilst a significant proportion of people with these early-onset epilepsies born over a decade ago will not have survived to transition, with advances in paediatric neurological and supportive care this may be pessimistic today. Similarly, most studies of long-term prognosis did not include surgical care, but long-term remission following surgery may occur in genetic epilepsies such as those caused by *DEPDC5* (Baulac *et al.*, 2015; Stevelink *et al.*, 2018). We speculate that in the future disease-modifying treatments may both ameliorate the phenotype and increase the proportion of children who need neurology care as adults because of their increased survival to transition and beyond.

Third, whilst in some genes the molecular consequences of variants may be associated with clinical features such as natural history and response to specific treatment (Wolff *et al.*, 2017), we have not been able to exploit genotype-phenotype associations at variant level because many variants are ultra-rare and the evidence of association between specific diagnostic variants and longitudinal phenotype is weak for many epilepsy genes.

Fourth, these figures probably underestimate the total lifetime risk of currently demonstrable genetic epilepsies in adulthood because Symonds *et al.* used a 104-gene panel rather than screening for all known genetic causes of epilepsy. Testing for further epilepsy genes (Borlot *et al.*, 2019), karyotype and copy number variants would yield additional diagnoses in adults with intellectual disability (Borlot *et al.*, 2017), which may explain the phenotype and inform prognostic counselling, despite currently having a lesser role in treatment stratification. In particular, as acknowledged by the authors, the panel did not include *TSC1* or *TSC2*, which may contribute up to 10 cases per 100 000 live births (Ebrahimi-Fakhari *et al.*, 2018) potentially benefiting from everolimus (French *et al.*, 2016). Four participants with diagnostic variants were not included in our calculations because they had not progressed to epilepsy during the study, but they remain at risk. Similarly, as noted by the authors, some children from this birth cohort may yet develop genetic epilepsies detectable by this panel but will not have met the threshold for testing by 36 months of age. We would add *CHD2* (Suls *et al.*, 2013; Thomas *et al.*, 2015; Trivisano *et al.*, 2015) to their list of genes with later onset chronic epilepsies.

Finally, we have assumed generalizability between the cohorts in the published studies of the various syndromic and genetically defined epilepsies and the cohort in this study. However, there may be biological differences, for example due to ancestral stratification. Despite the limitations of the additional analysis that we have performed, the figures we have extrapolated are the first population-based estimates of the lifetime risk of early-onset genetic epilepsies requiring neurological care in adulthood.

To understand the course of genetic epilepsies, we analysed longitudinal data from the Epilepsy Neurogenetics Initiative, which follows individuals with genetic epilepsies, including many individuals who are yet to reach adulthood (Fig. 1A–C). Given that the relative novelty of comprehensive gene panel testing implies that 'catch-up' testing is necessary for older children and adults, the few diagnoses in adolescence and adulthood suggest that many adults remain undiagnosed despite carrying detectable diagnostic variants (Fig. 1B). At least half of those individuals who have reached 18 years of age and attended clinics for any reason have active prescriptions for antiepileptic medications: a proxy measure for continuing neurological care (Fig. 1C and D).

Table 1 Estimates of the number of children with genetic epilepsy onset before 3 years of age who will require adult neurology care

Syndrome Gene	*n* in Symonds *et al.* (2019)			*n* estimated to require adult neurological care, range	Supporting evidence
	Total	Therapy-resistant seizures	Neurological development		
Self-limited infantile epilepsy *PRRT2*	15	0	2	0–3	Ebrahimi-Fakhari *et al.*, 2015
Dravet syndrome *SCN1A*	11	9	9	9–11	Jansen *et al.*, 2006; Akiyama *et al.*, 2010; Catarino *et al.*, 2011; Genton *et al.*, 2011; Cooper *et al.*, 2016
GLUT1-deficiency syndrome *SLC2A1*	7	2[a]	3	1–7	Leen *et al.*, 2014
Self-limited neonatal epilepsy *KCNQ2*	6	0	0	0–1	Miceli *et al.*, 2010; Grinton *et al.*, 2015
Early infantile-onset DEE *CDKL5*	4[b]	4	4	3–4	Bahi-Buisson *et al.*, 2008; Muller *et al.*, 2016; Liang *et al.*, 2019
Unclassified epilepsy *SLC6A1*	3	2	2	2–3	Carvill *et al.*, 2015c; Johannesen *et al.*, 2018*a*
PCDH19-related epilepsy *PCDH19*	3	3	2	1–3	van Harssel *et al.*, 2013; Trivisano *et al.*, 2018
Focal epilepsy *DEPDC5*	3	1	0	2–3	Baldassari *et al.*, 2019
Self-limited familial neonatal epilepsy *KCNQ3*	2	0	0	0–0	Miceli *et al.*, 2014
KCNQ2-related encephalopathy *KCNQ2*	2	1	2	0–2	Weckhuysen *et al.*, 2013
Self-limited infantile epilepsy *KCNQ2*	1	0	0	0–0	Miceli *et al.*, 2010; Grinton *et al.*, 2015
Genetic epilepsy with febrile seizures plus *SCN1A*	1	1	0	0–1	Zhang *et al.*, 2017; de Lange *et al.*, 2019
Absences with eyelid myoclonia *CHD2*	1	1	1	1–1	Caraballo *et al.*, 2009; Carvill *et al.*, 2015[a]
Early infantile-onset DEE *SCN8A*	1	1	1	1–1	Larsen *et al.*, 2015; Gardella *et al.*, 2018; Johannesen *et al.*, 2018*b*
Early infantile-onset DEE *STXBP1*	1	0	1	0–1	Stamberger *et al.*, 2016
Epilepsy of infancy with migrating focal seizures *GABRA1*	1	1	1	1–1	McTague *et al.*, 2013, 2016; Johannesen *et al.*, 2016
Epilepsy with myoclonic-atonic seizures *SLC6A1*	1	0	1	1–1	Carvill *et al.*, 2015c; Johannesen *et al.*, 2018*a*
Epilepsy with myoclonic-atonic seizures *STX1B*	1	1	0	0–1	Wolking *et al.*, 2019
Ohtahara syndrome *KCNT1*	1	1	1	1–1	Ohba *et al.*, 2015; Gertler *et al.*, 2018; McTague *et al.*, 2018
Progressive myoclonus epilepsy *POLG*	1	1	1	0–1	Wolf *et al.*, 2009; Lamperti and Zeviani, 2016
Rett syndrome *MECP2*	1	0	1	0–1	Steffenburg *et al.*, 2001; Glaze *et al.*, 2010
Unclassified epilepsy *COL4A1*	1	1	1	0–1	Zagaglia *et al.*, 2018
Unclassified epilepsy *PCDH19*	1	1	0	0–1	van Harssel *et al.*, 2013; Trivisano *et al.*, 2018
Unclassified epilepsy *PRRT2*	1	0	0	0–1	Ebrahimi-Fakhari *et al.*, 2015
Unclassified focal epilepsy *KCNA2*	1	0	0	0–1	Corbett *et al.*, 2016
Unclassified focal epilepsy *KCNQ2*	1	1	1	0–1	Weckhuysen *et al.*, 2013
Unclassified focal epilepsy *PRRT2*	1	0	1	0–1	Labate *et al.*, 2013; Ebrahimi-Fakhari *et al.*, 2015
Unclassified generalized epilepsy *CACNA1A*	1	0	1	0–1	Epi4K Consortium *et al.*, 2013; Damaj *et al.*, 2015; Epi4K Consortium, 2016
West syndrome *DEPDC5*	1	1	1	1–1	Carvill *et al.*, 2015*b*; Baldassari *et al.*, 2019
West syndrome *SCN2A*	1	1	1	1–1	Wolff *et al.*, 2017
Total	76	36	38	25–56 (33–74%)	

See Supplementary Table 1 for a version of this table citing evidence for estimates. DEE = developmental and epileptic encephalopathy.
[a]Missing data = 2.
[b]One male.

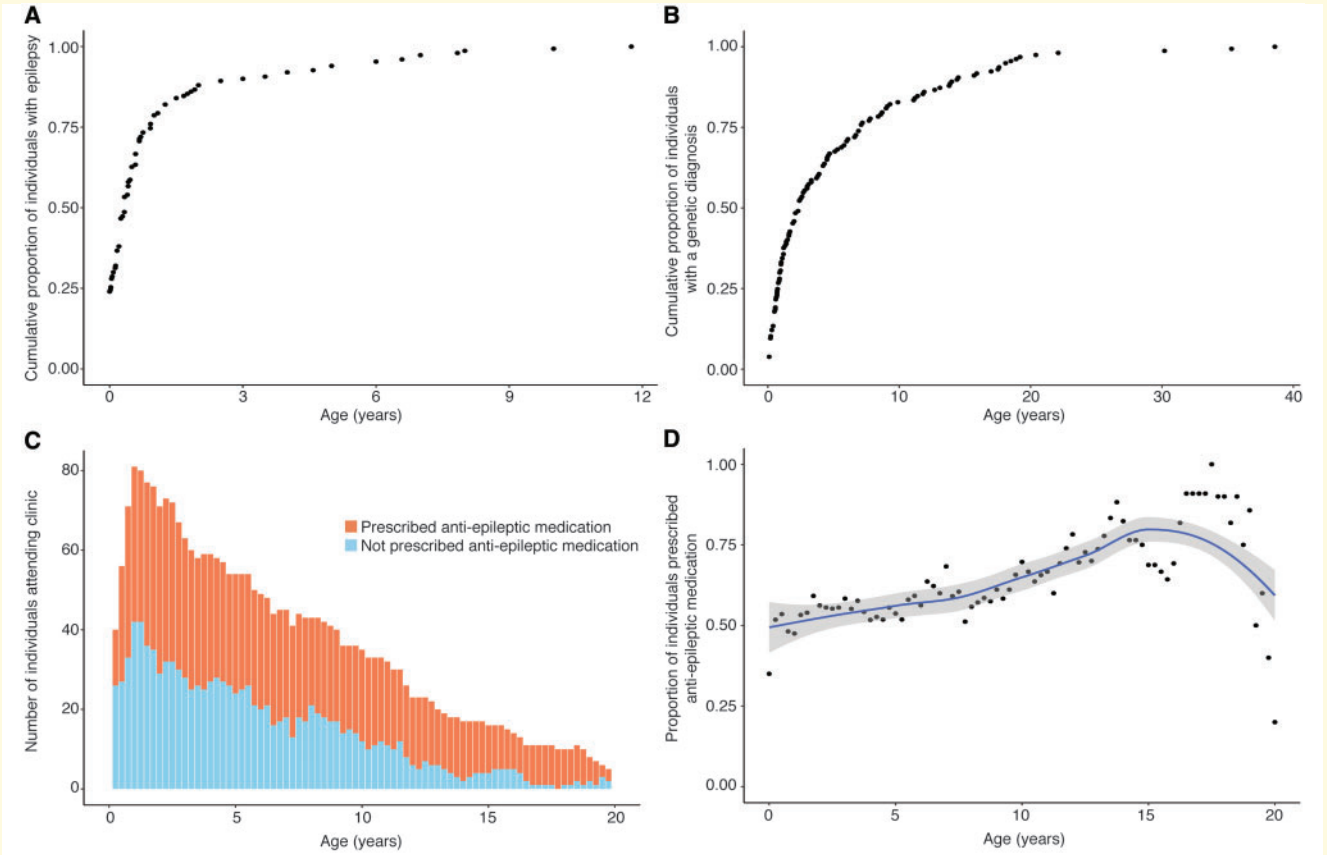

Figure 1 Longitudinal analysis of electronic medical record data from 158 individuals recruited within the Epilepsy Neurogenetics Initiative (ENGIN) at Children's Hospital of Philadelphia with epilepsies attributable to genes from the 104-gene panel in Symonds *et al.* (2019). (**A**) The cumulative distribution of seizure onset by age. (**B**) The cumulative distribution of genetic diagnoses by age, with points indicating the time of individual diagnoses. (**C**) The number of individuals with genetic epilepsies attending clinic by age in 3-month bins, with and without active prescriptions for 20 common antiepileptic medications. (**D**) The proportion of individuals with genetic epilepsies who are prescribed antiepileptic medication by time in 3-month bins, with 95% confidence intervals.

We conclude that at least 10–50/100 000 individuals will require the care of an adult neurologist because of a genetic disorder originally presenting as early-onset epilepsy. We hope that these extrapolated figures inform attitudes to genetic testing amongst adult neurologists who must consider the multitude of patients under their care who are too old to have benefited from modern genetic investigation under paediatric services, as well as researchers designing genetically stratified studies of the adult population.

Adult neurologists need to know that these conditions frequently reach the adult clinic manifesting as seizures or movement disorders, often but not always with associated intellectual disability or psychopathology, and that the yield of genetic testing in this group is 25%; in the majority of these a genetic diagnosis may inform treatment decisions (Borlot *et al.*, 2019; Symonds *et al.*, 2019). Testing with a panel of validated epilepsy genes, a copy number variant screen, and karyotyping should be strongly considered for adults (as well as children) who have unexplained epilepsy, intellectual disability or movement disorders originally presenting with seizures prior to 3 years of age.

Data availability

Data used for the prognostic estimates were found in the publications cited in the tables, in the main articles or their supplements. De-identified summaries of electronic medical record data used to generate Fig. 1 are available upon request.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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