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Conventional clinical characteristics do not predict the result of genetic testing in adults with epilepsy☆

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ABSTRACT

Background and objectives: Genetic testing in epilepsy has become increasingly available, and recommendations for its use have been set forth by professional society guidelines. The development of a user-friendly risk prediction model may aid providers in selecting adult patients with a high likelihood of receiving a positive genetic test result.

Methods: Adults who underwent multigene panel testing for epilepsy from March 2016 to June 2024 were divided into a training ($n = 1449$) and a testing set ($n = 1450$). We developed prediction models based on clinical characteristics using logistic regression and FasterRisk scores for positive genetic tests and evaluated their performance.

Results: The prediction models had poor discriminative power and failed to predict positive results, suggesting that conventional clinical characteristics (sex, intellectual disability, developmental delay, autism, medically refractory epilepsy, family history of epilepsy, and age at seizure onset) are insufficient for selecting patients for genetic testing.

Discussion: Our findings suggest that routine genetic testing may be broadly warranted for adults with unexplained epilepsy, as clinical characteristics alone appear unable to reliably identify which patients are likely to have positive results on multigene panels. Future models may benefit from incorporating physical exam findings, neuroimaging, and electroencephalogram data, as well as larger training sets.

1. Introduction

Genetic testing in epilepsy has significantly increased in recent years. The primary reasons for pursuing genetic testing in patients with epilepsy are to clarify the diagnosis, to provide insight into the prognosis, and to potentially guide treatment. The National Society of Genetic Counselors' practice guidelines – which have been endorsed by the American Epilepsy Society (AES) – recommend that individuals with unexplained epilepsies should undergo genetic testing without any age limitation [1] Similarly, the International League Against Epilepsy (ILAE) Genetics Commission and the Task Force on Clinical Genetic Testing in the Epilepsies recommend genetic testing in the following conditions, provided there is no other identifiable cause: severe childhood-onset epilepsies, particularly developmental and/or epileptic encephalopathies; epilepsy with intellectual disability, autism, and/or other comorbidities; progressive myoclonus epilepsies and progressive phenotypes generally; and non-acquired focal epilepsies in specific familial syndromes [2]

In the adult population, genetic testing of patients with epilepsy has not yet become standard practice. This lag is due to multiple factors, including insurance coverage and unfamiliarity of adult providers with the indications for and process of ordering tests, as well as interpreting the results and providing counseling [3] Therefore, the development of a user-friendly risk prediction model may help clinicians identify adults

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Table 1
Logistic regression and FasterRisk models
ID: intellectual disability. DD: developmental delay. MRE: medically-refractory epilepsy. FH: family history of epilepsy. SoA: seizure onset in adulthood. In FasterRisk models, individual points are assigned to specific variables, and a final score is calculated by the summation of the points obtained in each variable. The probability is the predicted probability of a positive genetic test of a certain score.

Logistic regression model, without age of seizure onset Accuracy=89.0 %, Recall=0 %								
Variables	Male	ID	DD	Autism	MRE	FH	Intercept	
Effect estimate	−0.20	**0.51**	0.40	0.15	0.19	−0.17	−2.05	
P-value	0.23	**0.01**	0.16	0.59	0.28	0.35	$<2 \times 10^{-16}$	
FasterRisk model, without age of seizure onset Accuracy=89.0 %, Recall=0 %								
Variables (points)	Male (−1)	ID (2)	DD (2)	Autism (0)	MRE (1)	FH (−1)		
Score (probability)	−2 (8.2 %)	−1 (10.1 %)	0 (12.2 %)	1 (14.8 %)	2 (17.7 %)	3 (21.2 %)	4 (25.1 %)	5 (29.4 %)
Logistic regression model, with age of seizure onset Accuracy=89.1 %, Recall=0 %								
Variables	Male	ID	DD	Autism	MRE	FH	SoA	Intercept
Effect estimate	−0.39	0.41	0.40	0.13	0.24	−0.25	**−0.68**	−1.70
P-value	0.10	0.15	0.30	0.72	0.34	0.33	**0.05**	6×10^{-16}
FasterRisk model, with age of seizure onset Accuracy=89.1 %, Recall=0 %								
Variables (points)	Male (−2)	ID (2)	DD (2)	Autism (0)	MRE (0)	FH (−1)	SoA (−3)	
Score (probability)	−6 (4.9 %)	−5 (6.1 %)	−4 (7.5 %)	−3 (9.3 %)	−2 (11.4 %)	−1 (13.9 %)	0 (16.8 %)	1 (20.3 %)
	2 (24.2 %)	3 (28.7 %)	4 (33.5 %)					

with unexplained epilepsy who are most likely to have a positive result and, consequently, benefit from genetic testing. This study aims to develop and test a model based on the clinical characteristics of a large pool of adults who underwent genetic testing for epilepsy using multigene panels.

2. Material and methods

2.1. Study population

We included individuals aged 18 years and older who underwent diagnostic genetic testing for epilepsy at Invitae (now Labcorp Genetics) between March 2016 and June 2024 using comprehensive, next-generation sequencing-based, targeted gene panels. The referring clinician of each individual completed a test requisition form and provided patient demographics along with brief clinical information, which was the source of the features used in the predictive models. In this study, review and analysis of deidentified data were approved by the WCG Institutional Review Board (study number 1167406).

2.2. Genetic testing and result interpretation

Patients received an epilepsy multigene panel that contained 89–302 genes, depending on the time of testing during this study period. Additional panels or genes could also be ordered (median: 291 genes, interquartile range: 168–305, Supplementary material, Figure S1). Genes were sequenced using DNA extracted from blood, saliva, or buccal swab samples. Variants identified by the bioinformatics pipeline were analyzed and categorized as pathogenic, likely pathogenic, variant of uncertain significance, benign, and likely benign using a validated, score-based refinement of the guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology [3,4] A positive genetic test was defined as a heterozygote of a pathogenic variant for a dominant disease, a hemizygote of a pathogenic variant for an X-linked recessive (male predominant) disease, or two pathogenic variants (either a homozygote of a pathogenic variant or a compound heterozygote of two distinct pathogenic variants) for a recessive disease in an epilepsy-related gene.

3. Data analysis

The individuals were randomly divided into the training set or the testing set, in a 1:1 ratio. In univariate analyses, odds ratios (ORs) and *p*-values from χ^2 tests for independence between clinical characteristics and positive genetic test were calculated. In multivariate analyses, logistic regression models were developed and evaluated in the training and testing sets, with and without the age of seizure onset information,

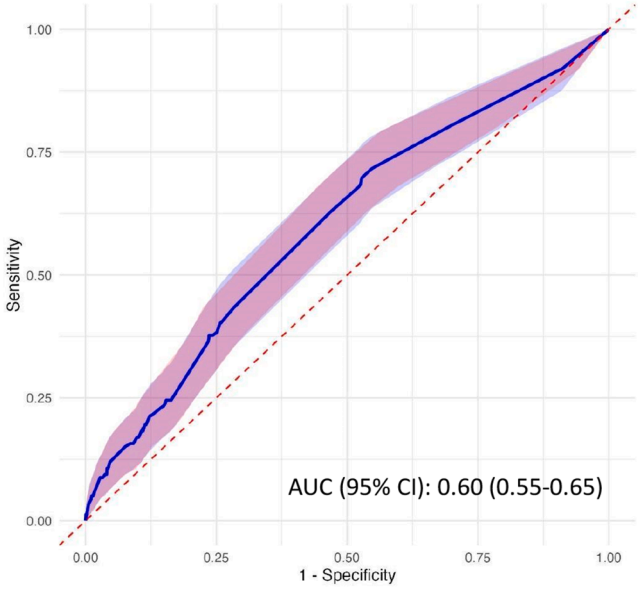

Fig. 1. The testing ROC curve of the logistic regression model, without age of seizure onset
Blue shade: the 95 % confidence interval (CI) for sensitivity. Red shade: the 95 % CI for 1 – specificity. Red dashed line: the null classifier.

which was only available in a subset of individuals. Variances explained by the logistic regression models were calculated in the testing set. To construct a scoring mechanism for assessing the probability of a positive genetic test, FasterRisk [5] models were developed, which provide a pool of prediction models by incorporating various features. The best model was selected by the smallest logistic loss. In both the logistic regression models and the FasterRisk models, the probability of a positive genetic test was calculated for each of the individuals in the testing set, with a probability of >50 % signaling a predicted positive genetic test. The model performance was then quantified by accuracy, recall, the Receiver Operating Characteristic (ROC) curve, and the area under the ROC curve (AUC). The number needed to test to obtain one positive result was also calculated. Data analyses were conducted in R 4.3.3 and Python 3.11.7. The data that support the findings of this study are available from the corresponding author upon request.

4. Results

Among the 2899 unique individuals included in the analysis, 1449

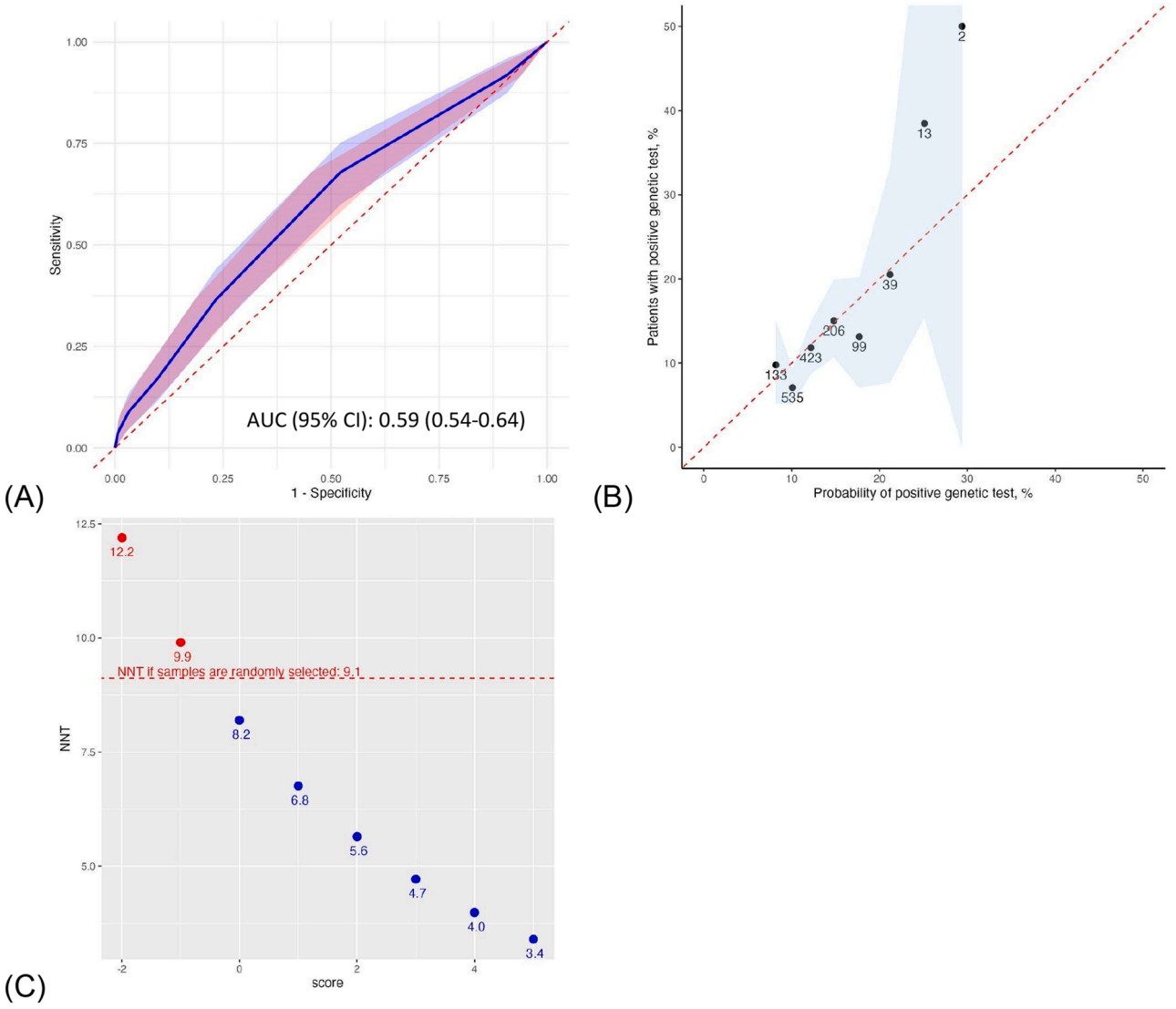

Fig. 2. The testing ROC curve (A), testing performance (B) of the FasterRisk model, without age of seizure onset, and (C) the number needed to test (NNT) to obtain one positive result

Blue shade: the 95 % confidence interval (CI) for sensitivity. Red shade: the 95 % CI for 1 – specificity. Red dashed line: the null classifier. (B) Each dot represents a score value from −2 to 5. The x-axis is the probability of positive genetic test estimated by the FasterRisk model. The y-axis is the actual observed percentage of patients with positive genetic test. The red dashed line has a slope of 1 and intercept at the origin. Proximity to this line indicates goodness of fit and is used as a marker to look for bias. The number associated with each dot is the number of patients in the testing set with the associated number of scores. The shaded blue area is the 95 % confidence interval provided by the bootstrapping from the testing set. (C) Red dashed line: number needed to test to obtain one positive result.

were randomly selected for the training set and 1450 for the testing set. There were 172 and 159 positive genetic tests in the training and testing sets, respectively. In the univariate analyses (Supplementary material, Table S1), seizure onset in adulthood, biological sex, intellectual disability, developmental delay, and medically refractory epilepsy were statistically significantly associated with a positive genetic test, but not autism or family history of epilepsy. In addition, seizure onset in adulthood (OR=0.38) was associated with a decreased probability of a positive genetic test.

In the multivariate analyses (Table 1), with all possible clinical features included, only seizure onset in adulthood (effect estimate=−0.68, p-value = 0.05) and intellectual disability (effect estimate = 0.51, p-value = 0.01) reached statistical significance, in the analyses with and without the age at seizure onset included, respectively. Seizure onset in adulthood continued to be associated with a decreased probability of a positive genetic test, consistent with the univariate analyses. The logistic regression classifiers failed to predict any positive genetic tests in the testing set, without (accuracy = 89.0 %, recall = 0 %, AUC = 0.60, Fig. 1) or with (accuracy = 89.1 %, recall = 0 %, AUC = 0.60, Supplementary material, Figure S2) the information of age at seizure onset. The variances in the testing set explained by the logistic regressions were 1.0 % and 1.5 % without or with age at seizure onset, respectively.

The best FasterRisk models are presented in Table 1, as well as their testing performance and the probabilities of a positive genetic test in corresponding summary score categories (Fig. 2A, B, Supplementary material, and Figure S3). The number needed to test to obtain one positive result is 12 and 3 in the lowest and highest score categories, respectively, as shown in Fig. 2C, using the FasterRisk scores without the information on the age at seizure onset.

5. Discussion

We developed prediction models based on select clinical characteristics using logistic regression and FasterRisk scores for receiving a positive genetic test in adults with epilepsy, and tested their performance in one of the largest cohorts of genetically tested adults with

epilepsy to date. Clinical characteristics included sex, intellectual disability, developmental delay, autism, medically refractory epilepsy, family history of epilepsy, and age at seizure onset. Our analyses showed that the prediction models had poor discriminative power and failed to predict positive results. These findings suggest that using only conventional clinical features may be insufficient for identifying which patients will benefit from genetic testing. Importantly, these results support the recommendations of the National Society of Genetic Counselors that individuals with unexplained epilepsies should undergo genetic testing without age limitation, as we cannot reliably predict in advance which adults with epilepsy will receive a positive result.

Our study has limitations. First, our analysis relied on clinician-reported patient information, which was inconsistently provided and, therefore, may have impacted model performance. Second, the poor predictive performance of the models may have originated from the high correlation of the clinical features used (Supplementary material, Table S2). The features appear to cluster into two groups, with positive correlations within each group, and negative correlations between the groups: (a) intellectual disability, developmental delay, autism, and medically refractory epilepsy in one group, and (b) family history of epilepsy and seizure onset in adulthood in the other group. These features were limited to hallmark clinical characteristics, and excluded parameters related to the physical exam and other diagnostic modalities such as neuroimaging and electroencephalogram. Third, the individuals studied exclusively underwent testing using targeted epilepsy multigene panels, and not more comprehensive tests such as exome sequencing (ES) or genome sequencing (GS). The diagnostic yield of these testing modalities varies, with a yield up to 25 % in multigene panels, 45 % in ES, and 48 % in GS [6] While we cannot assess how the models would have performed using ES or GS data, we speculate that the performance may not have improved substantially, given the limited variance explained by the current models based on multigene panel data.

6. Conclusions

Our findings suggest that routine genetic testing may be warranted for adults with unexplained epilepsy, as conventional clinical characteristics alone appear insufficient to predict which patients will have positive results. This aligns with and provides empirical support for current guidelines from the National Society of Genetic Counselors recommending genetic testing for individuals with unexplained epilepsies regardless of age. While our effort to develop a predictive model was unsuccessful, the results have important clinical implications in supporting a more inclusive approach to genetic testing in adult epilepsy populations. Future research may benefit from incorporating larger training datasets and a broader, consistently reported range of features – including physical exam findings, neuroimaging, and EEG data – along with more comprehensive genetic testing. Such an approach may help determine if any combination of clinical and paraclinical data could improve the prediction of genetic testing results.

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Declaration of competing interest

Yi-Lee Ting and Daniel E. Pineda Alvarez are employees of Labcorp. Sarah R. Poll is a former employee of Labcorp and current employee of GeneDx. Dr. Westover is a co-founder, scientific advisor, consultant to, and has personal equity interest in Beacon Biosignals.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2025.10.015.

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