

BRIEF REPORT

Scoring Algorithm-Based Genomic Testing in Dystonia: A Prospective Validation Study

Michael Zech, MD,^{1,2*} Robert Jech, MD, PhD,³ 
 Sylvia Boesch, MD,⁴ Matej Škorvánek, MD, PhD,^{5,6}
 Ján Necpál, MD,⁷  Jana Švantnerová, MD,⁸
 Matias Wagner, MD,^{1,2}  Ariane Sadr-Nabavi, PhD,^{9,10,11}
 Felix Distelmaier, MD,¹² Martin Krenn, MD, PhD,^{2,13}
 Tereza Serranová, MD, PhD,³ 
 Irena Rektorová, MD, PhD,¹⁴ Petra Havránková, MD, PhD,³
 Alexandra Mosejová, MD,^{5,6} Iva Příkladová, MD, PhD,³
 Jana Šarláková, MD,¹⁵ Kristína Kulcsarová, MD,^{5,6}
 Olga Ulmanová, MD, PhD,³ Karel Bechyně, MD,¹⁶
 Miriam Ostrozovičová, MD,^{5,6} Vladimír Haň, MD, PhD,^{5,6}
 Joaquim Ribeiro Ventosa, MD,^{5,6} Theresa Brunet, MD,²
 Riccardo Berutti, PhD,² Mohammad Shariati, MD,^{10,11}
 Ali Shoeibi, MD,¹⁰ Susanne A. Schneider, MD,¹⁷
 Alice Kuster, MD,¹⁸ Matthias Baumann, MD,¹⁹
 David Weise, MD,²⁰ Friederike Wilbert, MD,²¹
 Wibke G. Janzarik, MD,²¹ Matthias Eckenweiler, MD,²¹
 Volker Mall, MD,^{22,23} Bernhard Haslinger, MD,²⁴
 Steffen Berweck, MD,^{25,26} Juliane Winkelmann, MD,^{1,2,27,28#}
 and Konrad Oexle, MD^{1,2#}

¹Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany ²Institute of Human Genetics, Technical University of Munich, Munich, Germany ³Department of Neurology, Charles University, 1st Faculty of Medicine and General University Hospital in Prague, Prague, Czech Republic ⁴Department of Neurology, Medical University Innsbruck, Innsbruck, Austria ⁵Department of Neurology, P.J. Safarik University, Kosice, Slovak Republic ⁶Department of Neurology, University Hospital of L. Pasteur, Kosice, Slovak Republic ⁷Department of Neurology, Zvolen Hospital, Zvolen, Slovakia ⁸Second Department of Neurology, Faculty of Medicine, Comenius University, University Hospital Bratislava, Bratislava, Slovakia ⁹Department of Medical Genetics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran ¹⁰Department of Neurology, Faculty of Medicine, Mashhad University of Medical Sciences, Qaem Medical Center, Mashhad, Iran ¹¹Academic Center for Education, Culture and Research (ACECR)-Khorasan Razavi, Mashhad, Iran ¹²Department

of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany ¹³Department of Neurology, Medical University of Vienna, Vienna, Austria ¹⁴First Department of Neurology, Faculty of Medicine, St. Anne's University Hospital and CEITEC, Masaryk University, Brno, Czech Republic ¹⁵Department of Neurology, University Hospital, Hradec Kralove, Czech Republic ¹⁶Hospital Pisek, Pisek, Czech Republic ¹⁷Department of Neurology, Ludwig-Maximilians-University, Munich, Germany ¹⁸Inborn Errors of Metabolism, Pediatric Intensive Care Unit, University Hospital of Nantes, Nantes, France ¹⁹Department of Pediatrics, Medical University Innsbruck, Innsbruck, Austria ²⁰Klinik für Neurologie, Asklepios Fachklinikum Stadtroda, Stadtroda, Germany ²¹Department of Neuropediatrics and Muscle Disorders, University Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany ²²Lehrstuhl für Sozialpädiatrie, Technische Universität München, Munich, Germany ²³kbo-Kinderzentrum München, Munich, Germany ²⁴Klinik und Poliklinik für Neurologie, Klinikum rechts der Isar, Technische Universität München, Munich, Germany ²⁵Ludwig Maximilian University of Munich, Munich, Germany ²⁶Hospital for Neuropediatrics and Neurological Rehabilitation, Centre of Epilepsy for Children and Adolescents, Schoen Klinik Vogtareuth, Vogtareuth, Germany ²⁷Lehrstuhl für Neurogenetik, Technische Universität München, Munich, Germany ²⁸Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

ABSTRACT: Background: Despite the established value of genomic testing strategies, practice guidelines for their use do not exist in many indications.

Objectives: We sought to validate a recently introduced scoring algorithm for dystonia, predicting the diagnostic utility of whole-exome sequencing (WES) based on individual phenotypic aspects (age-at-onset, body distribution, presenting comorbidity).

Methods: We prospectively enrolled a set of 209 dystonia-affected families and obtained summary scores (0–5 points) according to the algorithm. Singleton (N = 146), duo (N = 11), and trio (N = 52) WES data were generated to identify genetic diagnoses.

Results: Diagnostic yield was highest (51%) among individuals with a summary score of 5, corresponding to a manifestation of early-onset segmental or generalized dystonia with coexisting non-movement

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

***Correspondence to:** Dr. Michael Zech, Institute of Neurogenomics, Helmholtz Zentrum München. Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), Ingolstädter Landstraße 1, 85764 Neuherberg, Germany; E-mail: michael.zech@mri.tum.de

#These authors contributed equally to this work.

Disclosures concerning the present manuscript: Nothing to report.

Funding: This study was funded by in-house institutional funding from Technische Universität München, Munich, Germany; Helmholtz Zentrum

München, Munich, Germany; Medizinische Universität Innsbruck, Innsbruck, Austria; and Charles University, Prague, Czech Republic (PROGRES Q27). This study was also funded by the Czech Ministry of Education under grant AZV: NV19-04-00233 and under the frame of EJP RD, the European Joint Programme on Rare Diseases (EJP RD COFUND-EJP N° 825575), as well as the Slovak Grant and Development Agency under contract APVV-18-0547 and the Operational Programme Integrated Infrastructure, funded by the ERDF under No. ITMS2014+: 313011V455.

Received: 6 November 2020; **Revised:** 22 February 2021; **Accepted:** 26 March 2021

Published online in Wiley Online Library
 (wileyonlinelibrary.com). DOI: 10.1002/mds.28614

disorder-related neurological symptoms. Sensitivity and specificity at the previously suggested threshold for implementation of WES (3 points) was 96% and 52%, with area under the curve of 0.81.

Conclusions: The algorithm is a useful predictive tool and could be integrated into dystonia routine diagnostic protocols. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson Movement Disorder Society

Key Words: exome sequencing; diagnostic yield; dystonia; prediction; scoring algorithm; rare disease

Introduction

Genomic (whole-exome and whole-genome) sequencing assays have gained broad use in the clinical setting, enabling accurate etiologic diagnosis, disorder-specific counselling, prognostication, and personalization of management.^{1,2} However, molecular diagnostic rates with genomic sequencing vary across testing indications,³ and may also differ substantially between patients with the same disease entity depending on individual phenotypic factors.⁴⁻⁷ There is a clinically and economically grounded need to identify patients who are more likely to carry pathogenic DNA variation detectable by genomic sequencing, and therefore would be more likely to benefit from such testing.^{8,9} Recently, we took advantage of a very large collection of whole-exome sequencing (WES) data from patients with dystonia to isolate clinical variables significantly associated with diagnostic outcome; these included (i) an onset of dystonia before the age of 21 years, (ii) a manifestation of segmental or generalized dystonia, and (iii) a combination of dystonia with non-dystonic neurological features (other movement disorders and/or non-movement disorder-related symptoms).¹⁰ On the basis of the predictor variables, we developed a weighted seven-component, five-point-maximum score that allows quantification of the likelihood of arriving at a molecular diagnosis through the application of WES.¹⁰ The scoring algorithm could serve as a tool to guide patient selection for WES-based diagnostics in dystonia. In this study, we applied WES to 209 prospectively recruited patients with various types of dystonia as well as 115 first-degree relatives of these patients to validate the predictive ability of the algorithm.

Methods

Validation Cohort

Eligible index patients with dystonia (N = 209) were enrolled from tertiary care institutions (centers

specializing in movement disorders and/or pediatric neurology) in Austria, Czech Republic, France, Germany, and Slovakia between August 2019 and October 2020. Affected and unaffected family members were recruited whenever possible to complete WES analyses in duo (N = 11) and trio (N = 52) formats. Patients with known genetic or non-genetic causes of their conditions were excluded from the study. Written informed consent was obtained from all participating subjects or their legal guardians under protocols approved by local ethics review boards. The cohort of index patients comprised 117 males (56%), and 55% of patients (N = 114) had dystonia onset before the age of 21 years; segmental dystonia was documented in 62 patients (30%) and generalized dystonia in 82 (39%). Dystonia manifestations were classified as “isolated dystonia” in 44% (N = 92), “combined dystonia” in 19% (N = 40), and “dystonia (isolated or combined) with coexisting non-movement disorder-related neurological symptoms” in 37% (N = 77) of patients.^{11,12} The spectrum of presenting comorbidities is summarized in Fig. S1A; a complete description of demographic and clinical characteristics for the cohort can be found in Table S1.

Application of the Scoring Algorithm

Detailed phenotype information was collected for the cohort (Fig. S1A; Table S1) and a recently described regression coefficient-based algorithm¹⁰ was employed to assign scoring points to each index patient. Clinical characteristics in the following categories were considered by the algorithm (Fig. 1): age at dystonia onset (< 21 years – 2 points; ≥ 21 years – 0 points); anatomic distribution of dystonia (segmental or generalized dystonia – 1 point; focal dystonia – 0 points); and coexistence of non-dystonic neurological features (isolated or combined dystonia with coexisting non-movement disorder-related neurological symptoms – 2 points; combined dystonia without additional symptoms – 1 point; isolated dystonia without additional symptoms – 0 points). The points for each characteristic were used to produce individualized summary scores (0 to 5 points, Fig. 1).¹⁰

WES and Genetic Diagnoses

We performed WES and established genetic diagnoses at the Helmholtz Center Munich and the Technical University of Munich, Munich, Germany as detailed earlier.^{10,13} The SureSelect Human All Exon 60 Mb kit (Agilent Technologies, Santa Clara, CA) was used for capture of exonic and flanking splicing regions and a HiSeq4000 (Illumina, San Diego, CA) for sequence determination. Variant annotation and filtering were carried out with a clinically

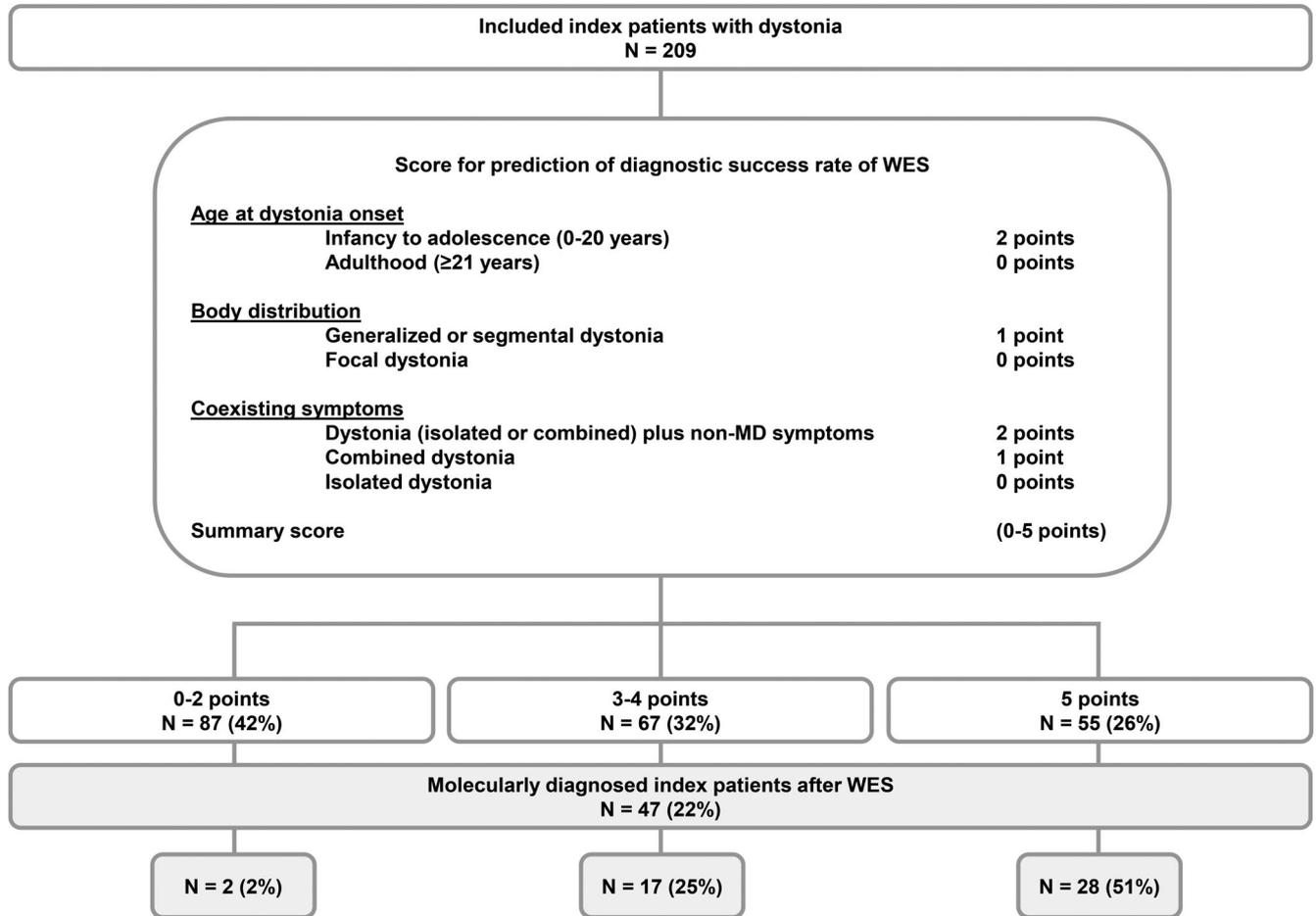


FIG. 1. Study flowchart. Abbreviations: non-MD symptoms, non-movement disorder-related neurological symptoms; WES, whole-exome sequencing.

oriented in-house bioinformatics pipeline, integrating custom-developed software packages (Burrows-Wheeler Aligner, SAMtools, PINDEL, Genome-Analysis-Toolkit, ExomeDepth) and information from diverse genomic databases (ClinVar,¹⁴ the Human Gene Mutation Database,¹⁵ dbSNP, Genome Aggregation Database). The analysis was focused on predetermined sets of described disease-related genes, identified via searches in the Online Mendelian Inheritance in Man database¹⁶ and the literature. Assignment of disease causality for prioritized variants was based on ClinVar¹⁴ and/or literature report, recommendations of the American College of Medical Genetics and Genomics (ACMG),¹⁷ and multidisciplinary expert review. Visual verification of variants was done with the Integrative Genomics Viewer. The full variant prioritization and interpretation protocol has been published previously.¹⁰

Assessment of the Algorithm’s Performance

The performance of the algorithm was examined using the statistics program R version 3.2.3, as described.¹⁰ We constructed a receiver operating characteristic

(ROC) curve and calculated the area under the curve by applying the package “pROC” version 1.16.2.

Results

The distribution of the algorithm-derived summary scores for the validation cohort is presented in Fig. 1. WES and evidence-based variant prioritization established the diagnoses for a total of 47 index patients, leading to an overall diagnostic yield of 22%; the diagnostic yields for different subtypes of dystonia are shown in Fig. S1B. Of the diagnosed patients, 22 (47%) had known pathogenic variants, and 26 (55%) had novel variants that were considered to be pathogenic or likely pathogenic in the context of the ACMG standards for the interpretation of sequence alterations¹⁷ (Table S2). Twenty-nine of 38 identified distinct diagnoses (76%) were due to autosomal-dominant variants and nine were due to homozygous or compound heterozygous autosomal-recessive variants (Table S2). Of these diagnoses, 14 (37%) have also been found in the original score-derivation cohort¹⁰

TABLE 1 Diagnostic rates per summary score value and breakdown of genes in which pathogenic or likely pathogenic variants were identified

Summary score	Diagnostic rate among patients with this score ^a	Involved disease genes
0	0/44 (0%)	–
1	0/22 (0%)	–
2	2/21 (9.5%)	<i>ADCK3*</i> , <i>LRRK2</i>
3	10/41 (24.4%)	<i>BRPF1*</i> , <i>CUL3*</i> , <i>ERCC4</i> , <i>GNAL</i> , <i>PSEN1</i> , <i>THAP1</i> , <i>TOR1A</i> ^{patient 72 & patient 129} , <i>VPS16</i> ^{patient 87 & patient 128}
4	7/26 (26.9%)	<i>ATP5G3</i> , <i>FGF14</i> , <i>GCH1</i> ^{patient 110 & patient 126} , <i>SGCE</i> ^{patient 51 & patient 69 & patient 193}
5	28/55 (50.9%)	<i>ARSA*</i> , <i>ATP1A3*</i> , <i>ATP8A2*</i> , <i>BRAF*</i> , <i>CACNA1A*</i> ^b , <i>CAMTA1*</i> , <i>CHD4*</i> , <i>DNAJC6</i> , <i>DNM1L*</i> , <i>DNMT1</i> , <i>FBXO31*</i> , <i>FOXC1*</i> ^{patient 92 & patient 130} , <i>GABBR2*</i> , <i>GNAO1*</i> , <i>GNB1*</i> , <i>IRF2BPL*</i> ^b , <i>KMT2B*</i> ^{patient 46 & patient 88} , <i>MAG*</i> , <i>PANK2*</i> , <i>PNPLA6</i> , <i>SGCE</i> , <i>SON*</i> , <i>SPAST*</i> , <i>VPS16</i> , <i>WARS2*</i> ^{patient 29 & patient 196} , <i>YY1*</i>

Genes known to be associated with neurodevelopmental disorders are marked with asterisks (*). Genes highlighted in bold are those for which the associated dystonia manifestations were interpreted as expansions of the previously recognized phenotypes related to these genes.

^aNumber of patients with a molecular diagnosis after whole-exome sequencing/total number of patients (percent).

^bIdentified in the same individual (patient 203).

(Fig. S2A). One patient had a dual molecular diagnosis (patient 203 – *CACNA1A*- and *IRF2BPL*-related disorder; Table 1; Table S2). Twenty-four of the 38 distinct diagnoses (63%) were attributable to variants in genes which have been previously associated with neurodevelopmental disorders; for six of these diagnoses (*BRPF1*-, *CAMTA1*-, *CHD4*-, *FBXO31*-, *MAG*-, and *SON*-related disorders) the observed dystonia manifestations were interpreted as phenotypic expansions (Table 1). We also observed unusual dystonia-predominant manifestations associated with variants in *LRRK2* and *PSEN1*, phenomena described previously.^{18,19} Diagnostic rates per summary scores 0 to 5 in the validation cohort were as follows (Fig. 1; Table 1): 0 to 2 points – 2% (2/87); 3 to 4 points – 25% (17/67); and 5 points – 51% (28/55). In the evaluation of the predictive power of the algorithm, we obtained an area under the ROC curve (AUROC) of 0.81 (95% CI, 0.76–0.87) (Fig. S2B). Application of the previously proposed score cutoff for optimized utilization of WES-based testing (3 points)¹⁰ provided a sensitivity of 96% and a specificity of 52%. Thus, the algorithm identified the patients most suitable for diagnostic evaluation with WES with high accuracy (negative predictive value of 98% and positive predictive value of 37% at the cutoff value of 3 points).

Discussion

Although WES has the potential to revolutionize diagnostic assessment of dystonia, it is still unclear to

most medical professionals when to best apply it. Clinical scores are helpful tools to support decision-making in routine practice, but require validation in separate patient cohorts prior to widespread implementation.²⁰ We have previously shown that the clinical variables age-at-onset, body distribution, and presenting comorbidity, all associated with diagnostic outcome of WES in a multiple logistic regression analysis, could feasibly be deployed to form a scoring algorithm for dystonia.¹⁰ We hypothesized that the score, which is easy to calculate and incorporates parameters readily available during the clinical evaluation process, could become a routine instrument to prioritize patients for whom WES is beneficial. We herein assessed the predictive accuracy of the scoring algorithm in a prospective cohort of 209 dystonia-affected families displaying phenotype characteristics similar to those of the original score-derivation cohort¹⁰ (Table S1). The diagnostic yields per summary scores were comparable between the validation and derivation cohorts (0 to 2 points – 2% vs. 1%; 3 to 4 points – 25% vs. 26%; 5 points – 51% vs. 50% in the validation and derivation cohorts, respectively). Our model proved robust, with similar performances in the validation and derivation cohorts (AUROC of 0.81 in the validation cohort vs. 0.85 in the derivation cohort), demonstrating that the algorithm's summary scores lent sufficient validity to the prediction of WES-based diagnostic outcome in dystonia. We were also able to confirm the score's high discriminative ability at the proposed decision threshold (cutoff score of 3 points; associated negative predictive value of 98%). We suggest to implement WES as a

standard primary diagnostic test in dystonia for patients with a summary score of 3 points or higher, although we stress that this should not be considered a rigorous cutoff. On a case-specific basis, WES may also be beneficial for patients with summary scores of 0 to 2 points¹⁰ (diagnostic yield of 2% in the present study). We note that atypical late-onset presentations of DYT-TOR1A and DYT-THAP1 as well as adult-onset monogenic dystonias such as DYT-GNAL could escape genetic diagnosis if diagnostic decisions are not made on a case-by-case basis. Other certain clues, which were either not considered during the construction of the score (eg, parental consanguinity, increased paternal age, and known parental genetic defects) or not significantly associated with diagnostic outcome in the score-derivation cohort (eg, positive family history), should also be taken into account when guiding genomic testing in dystonia. Moreover, careful examination by movement-disorder neurologists as well as regular re-evaluation of a given patient is warranted to ensure accurate application of the scoring criteria.

Our results support the idea¹⁰ that the diagnostic success of WES in dystonia is largely driven by the clinical variables (i) “early symptom onset” (< 21 years of age), (ii) “more widespread anatomical involvement” (segmental or generalized distribution of dystonic symptoms), and (iii) “coexistence of non-dystonic neurological features” (other movement disorders and/or non-movement disorder-related symptoms). The finding of a high proportion (55%, 26/47) of diagnosed patients with (likely) pathogenic variants in neurodevelopmental disorder-associated genes further highlights a convergence in the genetics of dystonia and neurodevelopmental disorders.^{10,21} In addition, we found that 63% (24/38) of the specific diagnoses in the validation cohort did not overlap with those established in the original score-derivation cohort,¹⁰ indicating a marked degree of genetic heterogeneity and providing justification for the use of unbiased, genome-scale screening methods in the etiologic evaluation of dystonia.²²

Our analysis needs to be interpreted in the context of its potential limitations. First, validation was done in a relatively small cohort recruited from clinical sites also involved in the development of the scoring algorithm. “True” external validation in an independent clinical setting would be desirable to ensure reproducibility of the algorithm. Second, although potentially contributing to improved predictions, certain variables such as rate and type of targeted genetic testing prior to WES, the temporal pattern of an observed dystonia manifestation, and the sequencing mode (eg, trio WES analysis vs. proband-only WES) were not considered.¹⁰ Third, discoveries of novel dystonia-causing genes could increase the diagnostic yield in the future, necessitating refinement of the scoring items.

To conclude, we proposed and validated a decision support tool for incorporation of WES in the diagnostic

workup of dystonia. Additional studies are warranted to corroborate the clinical meaningfulness of the scoring algorithm, which could be adapted to improve diagnostic accuracy and guide appropriate management in the field of dystonia. We encourage multicenter collaboration to develop consensus guidelines for the application of genomic testing in dystonia. ■

Acknowledgments: We thank the families who participated in this study.

REFERENCES

- Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. *NPJ Genom Med* 2018;3:16.
- Rexach J, Lee H, Martinez-Agosto JA, Nemeth AH, Fogel BL. Clinical application of next-generation sequencing to the practice of neurology. *Lancet Neurol* 2019;18(5):492–503.
- Trujillano D, Bertoli-Avella AM, Kumar Kandaswamy K, et al. Clinical exome sequencing: results from 2819 samples reflecting 1000 families. *Eur J Hum Genet* 2017;25(2):176–182.
- Sun M, Johnson AK, Nelakuditi V, et al. Targeted exome analysis identifies the genetic basis of disease in over 50% of patients with a wide range of ataxia-related phenotypes. *Genet Med* 2019;21(1):195–206.
- Trinh J, Lohmann K, Baumann H, et al. Utility and implications of exome sequencing in early-onset Parkinson’s disease. *Mov Disord* 2019;34(1):133–137.
- Krenn M, Wagner M, Hotzy C, et al. Diagnostic exome sequencing in non-acquired focal epilepsies highlights a major role of GATOR1 complex genes. *J Med Genet* 2020;57(9):624–633.
- Topf A, Johnson K, Bates A, et al. Sequential targeted exome sequencing of 1001 patients affected by unexplained limb-girdle weakness. *Genet Med* 2020;22(9):1478–1488.
- Shashi V, McConkie-Rosell A, Rosell B, et al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. *Genet Med* 2014;16(2):176–182.
- Vrijenhoek T, Middelburg EM, Monroe GR, et al. Whole-exome sequencing in intellectual disability; cost before and after a diagnosis. *Eur J Hum Genet* 2018;26(11):1566–1571.
- Zech M, Jech R, Boesch S, et al. Monogenic variants in dystonia: an exome-wide sequencing study. *Lancet Neurol* 2020;19(11):908–918.
- Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013;28(7):863–873.
- Albanese A, Bhatia K, DeLong MR, et al. “Complex” dystonia is not a category in the new 2013 consensus classification. *Mov Disord* 2016;31(11):1758–1759.
- Zech M, Boesch S, Jochim A, et al. Clinical exome sequencing in early-onset generalized dystonia and large-scale resequencing follow-up. *Mov Disord* 2017;32(4):549–559.
- Landrum MJ, Lee JM, Benson M, et al. ClinVar: public archive of interpretations of clinically relevant variants. *Nucleic Acids Res* 2016;44(D1):D862–D868.
- Stenson PD, Mort M, Ball EV, et al. The human gene mutation database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. *Hum Genet* 2017;136(6):665–677.
- Hamosh A, Scott AF, Amberger JS, Bocchini CA, McKusick VA. Online Mendelian inheritance in man (OMIM), a knowledgebase of human genes and genetic disorders. *Nucleic Acids Res* 2005; 33(Database issue):D514–D517.

17. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17(5):405–424.
18. Bouhouche A, Tibar H, Ben El Haj R, et al. LRRK2 G2019S mutation: prevalence and clinical features in Moroccans with Parkinson's disease. *Parkinsons Dis* 2017;2017:2412486.
19. Appel-Cresswell S, Guella I, Lehman A, Foti D, Farrer MJ. PSEN1 p.Met233Val in a complex neurodegenerative movement and neuropsychiatric disorder. *J Mov Disord* 2018;11(1):45–48.
20. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;21(1):128–138.
21. Wirth T, Tranchant C, Drouot N, et al. Increased diagnostic yield in complex dystonia through exome sequencing. *Parkinsonism Relat Disord* 2020;74:50–56.
22. Olgiami S, Quadri M, Bonifati V. Genetics of movement disorders in the next-generation sequencing era. *Mov Disord* 2016;31(4): 458–470.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

SGML and CITI Use Only
DO NOT PRINT

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution, D. Data acquisition; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique; (4) Other: A. Co-developed score; B. Study supervision.

M.Z.: 1A, 1D, 2A, 2B, 3A, 4A

R.J., S.B., M. Škorvánek, J.N., J.S., M.W., A.S.-N., F.D., M.K., T.S., I.R., P.H., A.M., I.P., J.Š., K.K., O.U., K.B., M.O., V.H., J.R.V., T.B., R.B., M. Shariati, A.S., S.A.S., A.K., M.B., D.W., F.W., W.G.J., M.E., V.M., B.H., S.B.: 1D, 3B

J.W.: 1D, 3B, 4B

K.O.: 1A, 2A, 2B, 3B, 4A, 4B

Financial Disclosures (for the preceding 12 months)

M.Z. was supported by an internal research program at Helmholtz Zentrum München, Munich, Germany (“Physician Scientists for Groundbreaking Projects”). R.J. received honoraria and consultancies from Medtronic, Cardion, Ipsen, and NeuroPa centrum. J.Š. reports personal fees from Medtronic. V.H. received speaker honoraria from AbbVie and UCB. S.B. received honoraria from Pharm Allergan, Ipsen, and Merz Pharmaceuticals. The other authors report no disclosures.