

# A Recessive Ataxia Diagnosis Algorithm for the Next Generation Sequencing Era

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**Objective:** Differential diagnosis of autosomal recessive cerebellar ataxias can be challenging. A ranking algorithm named RADIAL that predicts the molecular diagnosis based on the clinical phenotype of a patient has been developed to guide genetic testing and to align genetic findings with the clinical context.

**Methods:** An algorithm that follows clinical practice, including patient history, clinical, magnetic resonance imaging, electromyography, and biomarker features, was developed following a review of the literature on 67 autosomal recessive cerebellar ataxias and personal clinical experience. Frequency and specificity of each feature were defined for each autosomal recessive cerebellar ataxia, and corresponding prediction scores were assigned. Clinical and paraclinical features of patients are entered into the algorithm, and a patient's total score for each autosomal recessive cerebellar ataxia is calculated, producing a ranking of possible diagnoses. Sensitivity and specificity of the algorithm were assessed by blinded analysis of a multinational cohort of 834 patients with molecularly confirmed autosomal recessive cerebellar ataxia. The performance of the algorithm was assessed versus a blinded panel of autosomal recessive cerebellar ataxia experts.

**Results:** The correct diagnosis was ranked within the top 3 highest-scoring diagnoses at a sensitivity and specificity of >90% for 84% and 91% of the evaluated genes, respectively. Mean sensitivity and specificity of the top 3 highest-scoring diagnoses were 92% and 95%, respectively. The algorithm outperformed the panel of ataxia experts ( $p = 0.001$ ).

**Interpretation:** Our algorithm is highly sensitive and specific, accurately predicting the underlying molecular diagnoses of autosomal recessive cerebellar ataxias, thereby guiding targeted sequencing or facilitating interpretation of next-generation sequencing data.

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Clinical heterogeneity and rarity of some neurological disorders may challenge the ability of clinicians to make timely diagnoses. This is true for autosomal recessive cerebellar ataxia (ARCA), a complex group of rare

disorders.<sup>1–4</sup> The revolution in molecular genetics, especially next generation sequencing (NGS),<sup>5</sup> has led to the identification of new ARCA-causing genes or novel phenotypes of known ARCA-causing genes, improving

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Members of the RADIAL Working Group are available as an online supplementary file (Supplementary Table 1).

Additional supporting information can be found in the online version of this article.

our understanding of these disorders and our ability to diagnose them.<sup>6,7</sup> However, NGS generates a huge number of data, including variants of unknown significance (VUSs) that may be difficult and time-consuming to correctly interpret and establish relationships between potential pathogenic variants and observed phenotypes.<sup>8</sup>

There is therefore an unmet need for a tool to assist physicians and geneticists in providing a comprehensive and balanced differential diagnosis (DD) of ARCAs. A DD tool that predicts the gene responsible for a phenotype by converting clinical and paraclinical data into a shortlist of likely molecular diagnoses could significantly increase the speed and yield of diagnosis for ARCAs, subsequently improving patient care, particularly in cases where treatments are available.

Our study aimed to create and validate a tool for the DD of patients with suspected ARCA.

## Materials and Methods

### The Recessive Ataxias ranking differential Diagnosis Algorithm (RADIAL)

A diagnostic algorithm for ARCA based on literature and expert opinion has been produced to guide neurologists who may encounter patients with ataxia in clinical practice (Fig 1). Recessive disorders (herein referred to as entities, each defined by mutations in specific gene[s]) with ataxia as a common but not necessarily an initial or prominent feature were identified from the literature according to previously published recommendations.<sup>1,2</sup>

Publications were identified by PubMed search for English language articles between January 1995 and January 2016, using the following terms: “recessive cerebellar ataxia”, “recessively inherited cerebellar ataxia”, or “inherited cerebellar ataxia”, and screened for reports of molecularly confirmed cases of recessively inherited disorders with cerebellar ataxia to include the majority of the most common ARCA cases; 281 articles were used to describe the entities included in the algorithm (Supplementary

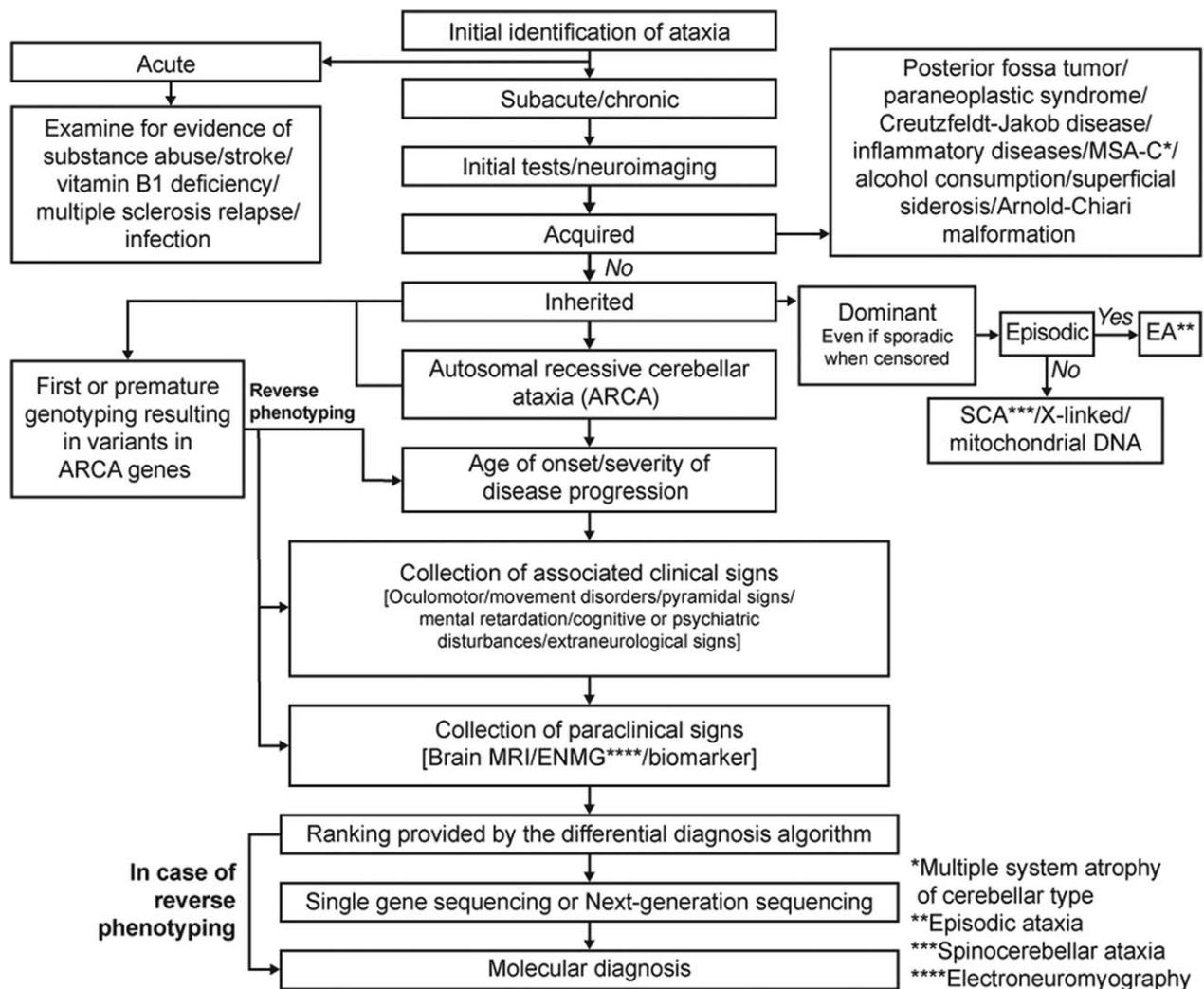


FIGURE 1: Algorithm outline. ARCA = autosomal recessive cerebellar ataxia; MRI = magnetic resonance imaging.

Table 2). To describe entities, 124 individual clinical and paraclinical findings including routine biomarkers (so-called features), were identified and refined by expert opinion.

The relationship between each feature and each entity was defined by frequency and/or specificity according to the literature and clinical experience of C.T. and M.A. as follows:

- High frequency (H): feature occurs in  $\geq 50\%$  of patients with the entity.
- Low frequency (L): feature occurs in  $< 50\%$  of patients with the entity. Where not clearly definable, low frequency is assumed.
- Specific (S): feature presents in  $< 10\%$  of entities.
- Not present (0): feature not considered to be associated with the entity.
- Not known (NK): feature not reported with the entity, but with insufficient evidence to exclude association.

These classifications were combined as necessary (eg, HS, high frequency and specific; LS, low frequency and specific).

For each entity, scores were assigned based on an assessment of the frequency and specificity of features, with more frequent and specific features scoring highest, and weighted based on the perceived importance for DD. Based on the opinion of M.A., NK, 0, L, H, LS, and HS were arbitrarily scored 0, -1, 1, 3, 7, and 9 points, respectively, for clinical features, neuroimaging, and electromyography, whereas scores were doubled for age of onset, severity of disease progression, and biomarkers (Table). For example, if a patient with suspected ARCA has a *cataract*, they would score +3 points for cerebrotendinous xanthomatosis, in which *cataract* is high frequency (H), but would score -1 points for Friedreich ataxia, in which *cataract* is not reported (0). A second patient who does not present with *cataract* would score 0 points for both cerebrotendinous xanthomatosis and Friedreich ataxia.

The outcome of this process was RADIAL (Recessive Ataxias Ranking Differential Diagnosis Algorithm), comprising a knowledge base that defines the association of each clinical

and paraclinical feature with each entity, with a corresponding score assigned to each feature–entity association (Supplementary File 1).

### ARCA Patient Clinical Features Data Collection

The diagnostic performance of RADIAL was assessed by applying it blindly to a population of patients with molecularly confirmed ARCA, for whom a description of clinical and paraclinical features at the time of molecular diagnosis was available.

The clinical and paraclinical features recorded at the time of molecular diagnosis of a worldwide patient cohort were collected by retrospective chart review between February and May 2016. The persons responsible for data collection from collaborating centers were blinded to the scoring and weighting of features within the algorithm.

All patient data were blinded by the contributor so that names, addresses, and other identifying information were not available to any other party involved in the analysis or review of the data. All investigators adhered to local privacy laws and regulations to ensure patient confidentiality. Patients gave written consent, and ethical approval for the study was provided by the local ethics committee of the Strasbourg University Hospital, France.

### Statistical Analysis

**PERFORMANCE ASSESSMENT OF RADIAL.** Features of each patient were assessed against the knowledge base according to the aforementioned calculation method. For each patient, the sum of scores for each feature was calculated for each entity. The total score for each entity defined its position on a ranked list of most likely (highest score) to least likely (lowest score) molecular diagnoses. Algorithm performance was a measurement of sensitivity and specificity. Correct patient classification was defined as a ranking of the correct diagnosis within the first, third, and fifth highest scores. The primary outcome of the performance assessment was the ability of RADIAL to correctly predict entities within the top 3 highest scores. Other

**TABLE. Convention for Notation and Scoring for Frequency and/or Specificity for Each Category of Signs and Symptoms Included in the Algorithm**

Category	Clinical Features	Neuroimaging	Electromyography	Age of Onset	Rapid Disease Progression	Biomarkers
NK	0	0	0	0	0	0
0	-1	-1	-1	-2	-2	-2
L	1	1	1	2	2	2
H	3	3	3	6	6	6
LS	7	7	7	14	14	14
HS	9	9	9	18	18	18

0 = no association; H = high frequency ( $\geq 50\%$  of patients); HS = high frequency ( $\geq 50\%$  of patients) and specific ( $< 10\%$  of entities); L = low frequency ( $< 50\%$  of patients); LS = low frequency ( $< 50\%$  of patients) and specific ( $< 10\%$  of entities); NK = extent of association not known.

outcomes were: correctly predicting entities within the top 1 and top 5 highest scores, average sensitivity and specificity for all patients, the ability of RADIAL to correctly identify an entity compared to that of a panel of ARCA experts, and correlation between performance and the total number and/or number of specific clinical features per entity.

**BLIND EVALUATION AGAINST AN ARCA EXPERT PANEL.**

The ability of RADIAL to correctly identify an entity within the top 3 highest scores was compared against a blind evaluation by a panel of 5 ARCA experts (F.M., M.P., M.S., C.T., and B.v.d.W.) in a sample of 100 patients for each expert, randomly selected from the patient cohort. The experts were given the same list of features provided by the investigators for the algorithm assessment, and produced a ranked shortlist of the 3 most likely diagnoses for each patient. The experts were able to consult the literature (eg. PubMed) and were allowed as much time as required to complete the task. The 3 most likely diagnoses were compared against the top 3 diagnoses provided by RADIAL for the same 100 patients. For mutations in the *FXN* gene, the diagnosis was considered correct when Friedreich ataxia, late-onset Friedreich ataxia (LOFA), and very-late-onset Friedreich ataxia (vLOFA) were proposed. Statistical differences were assessed by McNemar exact test.

Correlation was tested using Pearson correlation coefficient. All statistical analyses were performed using the statistical package SAS v9.3.

**Results**

**RADIAL**

The algorithm knowledge base contains 67 individual ARCAs (Supplementary Table 3), and was populated using the clinical findings of a total of 2,906 patients from the 281 articles (see Supplementary Table 2) and clinical experience. The well-described variants LOFA and vLOFA were considered a single entity distinct from Friedreich ataxia within the knowledge base and these analyses.<sup>9,10</sup> The RADIAL knowledge base contains

8,308 individual correlations between 67 entities and 124 features (see Supplementary File 1).

**Details of the Patient Cohort**

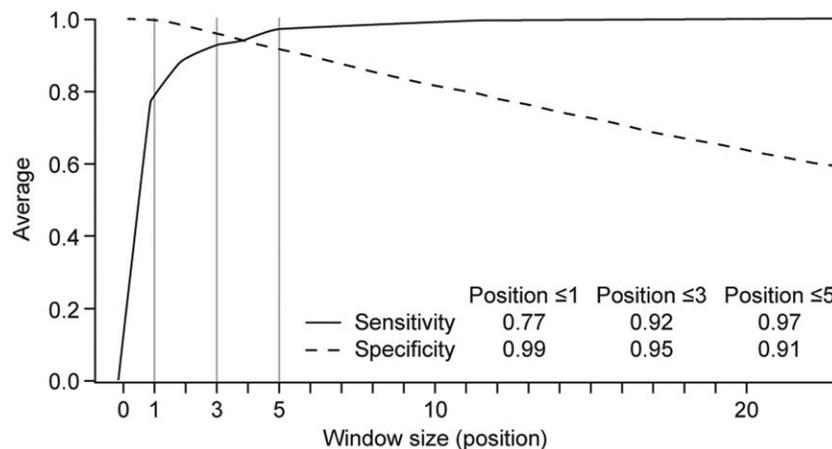
Data for 834 patients from 18 different countries and representing 45 distinct entities were collected (Supplementary Table 4). Among these 834 patients, 618 (74%) were reported in the literature used to create the knowledge base, corresponding to 21% of the 2,906 patients used to create the knowledge base.

A broad symptomatology was reported in the patient cohort; a summary of the symptomatology observed in the entire cohort and in the 8 entities with  $\geq 30$  patients is presented in Supplementary Table 5.

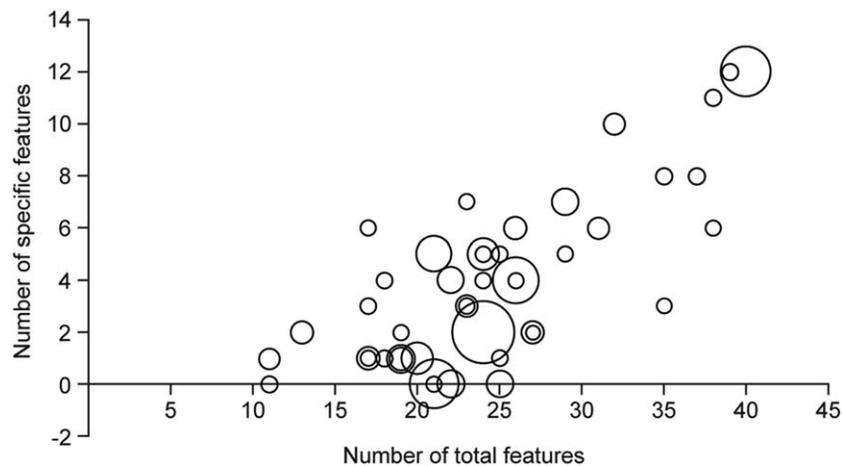
**Algorithm Performance**

Of the 45 entities tested, 91% (41/45) were ranked within the top 3 highest-scoring diagnoses at a specificity of  $>90\%$  and 84% (38/45) at a sensitivity of  $>90\%$  (Supplementary Table 6). Among these entities, the correct diagnosis was the highest scoring in 23 entities (51%), and was always found within the top 16 highest-scoring entities. The top 3 highest-scoring diagnoses had an average sensitivity and specificity of 92.2% and 95.4%, respectively (Supplementary Table 7 and Fig 2). The highest-scoring diagnosis had an average sensitivity and specificity of 77.1% and 99.3%, respectively. The top 5 highest-scoring diagnoses had an average sensitivity and specificity of 96.8% and 91.1%. Average sensitivity and specificity plots including all tested disorders are shown in Figure 2. *ADCK3*,<sup>11</sup> *OPAI*,<sup>12</sup> *PNPLA6*,<sup>13</sup> *STUB1*,<sup>14</sup> and *SYNE1*<sup>15</sup> and LOFA/vLOFA<sup>9,10</sup> were not identified within the top 3 scores with a sensitivity  $>90\%$ .

Assessment of the correlation between the number of specific features associated with each entity and



**FIGURE 2:** Average sensitivity and specificity for all patients related to the window size, defined as the position of the entity in the ranking list.



**FIGURE 3:** Relationship between the total number of features (x-axis), the number of specific features (y-axis), and the required window size, defined as the position of the entity in the ranking list, to reach 90% sensitivity (diameter of bubble increases as performance decreases). The figure shows the lack of association between performance of the algorithm and the number of features. Pearson correlation coefficient for total number of features versus window size:  $r = 0.052$ ,  $p = 0.730$ ; specific number of features versus window size:  $r = -0.033$ ,  $p = 0.830$ .

RADIAL performance, and between the total number of features associated with each entity and RADIAL performance, showed that neither the number of total signs ( $r = 0.052$ ,  $p = 0.730$ ) nor specific signs ( $r = -0.033$ ,  $p = 0.830$ ) influence discriminatory ability (Fig 3).

#### **RADIAL versus Expert Panel Challenge**

RADIAL performed well compared with a panel of 5 ARCA experts. In 5 series of 100 patients randomly selected from the patient cohort, RADIAL placed the correct diagnosis in the top 3 highest-scoring entities in 95.2% of patients versus 77.8% identified by the experts ( $p < 0.001$ ; McNemar exact test) and as the highest-scoring entity in 80.6% of patients versus 67.6% identified by the experts ( $p < 0.001$ ; McNemar exact test). The experts required an average of 7.2 hours (range = 6–10) to complete their 100 cases.

#### **Discussion**

This study describes RADIAL, an algorithm that aims to improve the DD approach toward ARCA by using patients' features to predict the underlying responsible gene. Sensitivity and specificity of the algorithm in correctly identifying the diagnosis within the top 3 highest-scoring entities was excellent, even outperforming a panel of ARCA experts.

In clinical practice, use of RADIAL should be considered in all patients suspected of ARCA. The diagnostic workup outlined in Figure 1 takes a stepwise approach to the patient with ataxia,<sup>1,2,16,17</sup> also indicating how the point of suspecting ARCA is reached.

Performance of RADIAL depends on accurate identification of the patient's features, and could be impaired

in the absence of sufficiently detailed information. In such cases, the algorithm could be used to guide clinical investigations based on the features of the highest-scoring entities from the knowledge base. The knowledge base could also clarify the clinical phenotype in a “genotype-first”<sup>18,19</sup> (ie, genotyping before phenotyping) or “reverse phenotyping” (ie, phenotyping following genotyping according to genetic results) method.<sup>20</sup> However, due to the risk of missing a correct diagnosis, we would not recommend a genotype-first approach, and reverse phenotyping should be considered with caution. Regardless of where in the diagnostic workup it occurs, a sufficiently detailed phenotypic evaluation is always mandatory. RADIAL could also be used to identify one high likelihood entity that can be confirmed by single gene sequencing. Thus, in this phenotype-first approach, the algorithm could also guide molecular analyses. Whether the phenotype-first or genotype-first approach is followed, the entity ranking provided by RADIAL supports identification of the gene responsible for the phenotype. RADIAL should be considered as an interface between phenotype and genotype, enabling each to complement the other.

Beyond its efficacy to predict the underlying molecular defect based on clinical data, RADIAL will provide guidance on best practice for the diagnostic workup of patients with suspected ARCA, including medical history, clinical examination, and paraclinical signs, serving as a reminder to assess many features that may otherwise be overlooked.

Given the performance of RADIAL, it could facilitate the interpretation of large volumes of data provided by NGS (panel gene sequencing, whole exome or whole

genome sequencing), and pathogenicity of VUSs could be more easily determined.<sup>21</sup> For instance, the probability of a VUS being pathogenic when the affected gene is not within the top 16 entities should be very low, whereas a VUS in a high-ranking gene, especially one within the top 3, is much more likely, facilitating interpretation of NGS data and guiding searches for a second mutation in the same gene. The good sensitivity of RADIAL is important to avoid a missed diagnosis. Conversely, the good specificity provides confidence in the identified top-scoring genes, especially when use of RADIAL follows molecular analyses. In such cases, RADIAL could be helpful to identify which VUSs are pathogenic mutations responsible for the phenotype and which VUSs are polymorphisms.

RADIAL also represents an up-to-date knowledge base comprising clinical descriptions of 67 individual ARCA based on the integration of numerous references and expert clinical experience. The 67 entities described in the knowledge base include the majority of the most common ARCA, but are not an exhaustive list, because there are several other recessively inherited diseases that may include cerebellar ataxia. Some of these diseases have not been included in the current knowledge base as they lack sufficiently detailed information on their clinical features (eg, *KIAA0226*).<sup>22,23</sup> Several other entities included in the knowledge base could be viewed as controversial, as cerebellar ataxia is not the initial or most prominent feature of the disease. However, the entities were included in the knowledge base because cerebellar ataxia was sufficiently well described as a clinical feature. Following this initial study, periodic updates of the knowledge base as the literature grows could add or redefine associations between features and entities, further improving performance of RADIAL, particularly for entities that are currently poorly characterized, and allowing addition of new entities. One may hypothesize that increasing the number of entities covered by the algorithm may increase its superiority to the experts.

RADIAL performance is limited by the quality and completeness of data published in the literature. The knowledge base should be helpful to any physician facing ataxia, or interested in becoming more specialized within this field. The extensive list of features allows a very precise description of each entity (124 features equate to  $> 2.1 \times 10^{37}$  pairwise combinations), leading to good differentiation between entities, even those with similar but nonidentical phenotypes. The performance and flexibility of RADIAL means that an exhaustive assessment of all the signs in patients suspected with ARCA is not required for good performance, and that accurate diagnoses for many patients are possible with few clinical

features. A second class of entities, including *ADCK3*,<sup>11</sup> *OPAI*,<sup>12</sup> *PNPLA6*,<sup>13</sup> *STUB1*,<sup>14</sup> and *SYNE1*,<sup>15</sup> are still poorly recognized by RADIAL. These entities are unlikely to appear near the top of the ranked lists, but should be considered as DD when genetic analyses are inconclusive and the clinical phenotype does not clearly match the highest-scoring entities. The poorer performance of RADIAL in recognizing these entities might be attributable to an intrinsic difficulty in their identification due to pleiotropic, overlapping clinical phenotypes (eg, pure cerebellar ataxia in *ADCK3* and *SYNE1*),<sup>11,15</sup> the lack of helpful biomarkers, or limitations in our classification of their specific clinical features due to their novelty (eg, *PNPLA6* and *STUB1*).<sup>24,25</sup> RADIAL was not able to recognize vLOFA and LOFA as effectively as Friedreich ataxia. However, given that the former are variants of Friedreich ataxia, the performance of RADIAL is successful at identifying *FXN* gene mutations. Moreover, Friedreich ataxia, including LOFA and vLOFA, is not diagnosed by NGS; therefore, validating a VUS on the basis of such diagnoses is not pertinent.

The use of real-life clinical data to test the accuracy of RADIAL addresses many of the limitations discussed above, as the excellent diagnostic performance suggests that the knowledge base provides a good representation of the clinical characteristics of each entity. This is reinforced by the algorithm outperforming an ARCA expert panel in correctly identifying diagnoses in both the top 1 and top 3 positions, a method commonly used to validate the performance of diagnostic algorithms, despite recent evidence showing that the superiority of the physician is maintained over several algorithms.<sup>26</sup> In the same way, the potential interest of computer-based evaluation of photographs to diagnose facial dysmorphism has recently been studied.<sup>27</sup>

The true incidence of ARCA observed in clinical practice is not reflected in the patient cohort. We were particularly interested in testing the algorithm with a broad sample of entities, especially those that are not well known and/or difficult to diagnose, which is not the case for Friedreich ataxia, the most frequent ARCA.<sup>1</sup> Because the ranking calculation does not take into account the prevalence/incidence of a disease, we do not believe that this negatively impacted the validation. To obtain a sufficient quantity of data to robustly validate RADIAL performance, it was necessary to obtain previously reported patient data with clear-cut molecular diagnoses by retrospective chart review. Unfortunately, the main limitation of this approach is that many patients who were used to assess the final algorithm were also used to construct the knowledge base; this is more problematic with the rarer entities, for which the published cases may represent the majority of the global

patient population. Regardless, many more patients whose data were used in construction of the knowledge base were not assessed in the study. It is also of worth considering that the data reported in the literature are generally less precise and detailed than the clinical data provided by the collaborators. Thus, even if we used the same patients, their data used to create the tool and to evaluate the tool were not identical. Moreover, the strength of RADIAL is not only to identify a specific disorder, but rather to identify a specific disorder among 67 other entities, which is much more difficult. Finally, that the expert panel was able to correctly identify the diagnosis in the majority of cases also supports the accuracy of the phenotypic definitions of each entity that were used to construct the knowledge base. Taken together, these arguments support the genuinely very good diagnostic performance of RADIAL.

Another consideration is the difficulty in accurately determining the frequency and specificity of clinical features, especially in rare entities where reported patient numbers are low. Future large-scale prospective real-world validation of RADIAL should be undertaken to address these concerns, and further validate and if necessary refine RADIAL. A prospective study would also allow the opportunity to assess the utility of RADIAL for interpretation of NGS-derived data, and assess whether RADIAL can predict the pathogenicity of novel VUSs. For this purpose, RADIAL is available to all health care professionals as a free-to-use electronic application. RADIAL can be accessed online at <http://radial-ataxia-algorithm.com/> or as an offline version in Supplementary File 2.

This algorithmic approach may be of further interest for many other diseases with inherent diagnostic difficulties, including neurological (eg, autosomal dominant cerebellar ataxias, hereditary spastic paraplegias, neuropathy, myopathy, complex dystonia, and early dementia) and non-neurological disorders.

In summary, we have developed a tool that facilitates the differential diagnosis of ARCA. RADIAL uses patients' features to produce a list of potential diagnoses ranked by likelihood, which may be used to inform further confirmatory clinical or genetic testing, and assist the interpretation of NGS data.

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Actelion Pharmaceuticals markets a treatment for Niemann–Pick disease type C, a rare form of autosomal recessive cerebellar ataxia, and has provided funds for the development of the RADIAL algorithm. The RADIAL algorithm was created by M.A. and will remain the property of Actelion Pharmaceuticals. RADIAL will be available to users free of charge and is anticipated to assist the assessment of patients with ARCA, including those with Niemann–Pick disease type C.

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## Author Contributions

M.A., C.T., M.R., M.K., and J.V.T.M. contributed to conception and design of the study; all authors contributed to the acquisition and analysis of the data; all authors contributed to drafting the text, preparing figures, and approving the final manuscript.

Members of the RADIAL Working Group (see Supplementary Table 1) who were not authors contributed patient data but did not have substantial involvement in drafting the manuscript.

## Potential Conflicts of Interest

M.A. reports travel grants and personal fees from Actelion Pharmaceuticals. S.A.K. is an employee of Actelion Pharmaceuticals. M.P. reports the patent "Direct Molecular Diagnosis of Friedreich's Ataxia," with royalties paid; this molecular diagnosis is included in RADIAL. J.V.T.M. of Syntax for Science performed statistical analyses paid for by Actelion Pharmaceuticals. M.K., F.M., M.R., M.Sy, C.T., and B.v.d.W. do not have anything to report.

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