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Utilization of Genetic Testing Prior to Subspecialist Referral for Cerebellar Ataxia

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Objective: To evaluate the utilization of laboratory testing in the diagnosis of cerebellar ataxia, including the completeness of initial standard testing for acquired causes, the early use of genetic testing, and associated clinical and nonclinical factors, among a cohort referred for subspecialty consultation. *Methods:* Data were abstracted from records of 95 consecutive ataxia patients referred to one neurogenetics subspecialist from 2006–2010 and linked to publicly available data on characteristics of referral clinicians. Multivariable logistic and linear regression models were used to analyze unique associations of clinical and nonclinical factors with laboratory investigation of acquired causes and with early genetic testing prior to referral. *Results:* At referral, 27 of 95 patients lacked evidence of any of 14 laboratory studies suggested for initial work-up of an acquired cause for ataxia (average number of tests = 4.5). In contrast, 92% of patients had undergone brain magnetic resonance imaging prior to referral. Overall, 41.1% ($n = 39$) had genetic testing prior to referral; there was no association between family history of ataxia and obtaining genetic testing prior to referral ($p = 0.39$). The level of early genetic testing was 31.6%, primarily due to genetic testing despite an incomplete laboratory evaluation for acquired causes and no family history. A positive family history was consistently associated with less extensive laboratory testing ($p = 0.004$), and referral by a neurologist was associated with higher levels of early genetic testing. *Conclusions:* Among consecutive referrals to a single center, a substantial proportion of sporadic cases had genetic testing without evidence of a work-up for acquired causes. Better strategies to guide decision making and subspecialty referrals in rare neurologic disorders are needed, given the cost and consequences of genetic testing.

Introduction

The role of genetic testing in neurology is rapidly expanding with the advent of new technologies for the identification of causative genes and the rapid sequencing of DNA (Fogel and Geschwind, 2012). As these tests become increasingly more commonplace, an important consideration becomes understanding how they are clinically utilized by neurologists and other clinicians caring for these patients in community settings, where the majority of this patient care takes place.

Today, genetic testing is often utilized in the evaluation of patients with chronic cerebellar ataxia, a symptom that can arise from a diverse array of causes, both acquired and hereditary (Finsterer, 2009; Manto and Marmolino, 2009; Klockgether, 2010), often posing a diagnostic dilemma for the clinician. Sporadic cerebellar ataxia of late onset, occurring after 50 years of age, can be particularly challenging to diagnose due to its myriad causes and the typical diversity of the differential diagnosis (Fogel and Perlman, 2006; Klockgether, 2010). Among this group, perhaps the most challenging subset of patients includes those with a suspected neurodegenerative cause, which can be further divided into hereditary or sporadic classes (Klockgether, 2010).

Of the hereditary disorders, a large number of genes have been identified whose mutation can cause cerebellar ataxia; all modes of genetic inheritance are represented (Fogel and Perlman, 2007; Manto and Marmolino, 2009; Durr, 2010). While the literature abounds with examples of schemes to utilize in the approach to the diagnosis of these patients (Schols *et al.*, 2004; Fogel and Perlman, 2006; Brusse *et al.*, 2007; Fogel and Perlman, 2007; Manto and Marmolino, 2009; Durr, 2010; Klockgether, 2010; Fogel and Perlman, 2011; Fogel, 2012), there are no established guidelines from professional specialty or subspecialty organizations for such evaluations with respect to the use of genetic testing.

At the same time, there are special constraints and considerations involved when ordering genetic tests to diagnose

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cerebellar ataxias. While tests can be individually ordered from various laboratories by clinicians, given the number of genes involved and the phenotypic heterogeneity among certain ataxic disorders, large commercial genetic testing facilities have endorsed a policy of grouping and marketing multiple genetic tests into large panels, generally based on suspected mode of inheritance rather than phenotypic characteristics. In contrast, in the general practice of neurogenetics, the typical diagnostic strategy for hereditary disease involves the tailored selection of genetic tests based on phenotype and other key characteristics of the patient in addition to mode of inheritance (Fogel and Geschwind, 2012). Therefore the use of genetic testing panels, while more comprehensive, has a high potential to test for genes with a low probability of mutation in a specific individual and thus increase cost without corresponding benefit.

Further complicating decision making is that expansion of available genetic tests is occurring rapidly, which represents a challenge for general neurologists who see such patients relatively infrequently and may not have ready access or time to assess the medical literature for updates on the appropriate indications for new tests. In fact, growth in the development and marketing of genetic tests for a widening range of conditions, including neurological ones, has exponentially advanced in recent years. In 1997 there were ~300 labs and biotech companies engaged in the development or clinical use of fewer than 500 genetic tests, whereas by 2012 there were 626 labs testing for 2806 different genetic diseases (www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests). Further advances in gene discovery techniques (e.g., genome-wide association studies and whole exome/genome sequencing) will undoubtedly continue this trend (www.genome.gov/10002390) (Coppola and Geschwind, 2012).

Although genetic causes represent an important subgroup of cerebellar ataxia cases, it is important that clinicians also be mindful of acquired causes as well, given that many may be modifiable and, in some cases, treatable (Fogel and Perlman, 2006; Klockgether, 2010; Fogel and Perlman, 2011). Worldwide, genetic ataxias are rare, with both dominant and recessive disorders showing an equal prevalence of ~4 cases per 100,000 individuals, with specific disorders varying dramatically by geography and ethnicity (Schols *et al.*, 2004; Fogel and Perlman, 2006; Fogel and Perlman, 2007; Manto and Marmolino, 2009; Durr, 2010; Fogel and Perlman, 2011; Fogel *et al.*, 2012). This is in contrast to the prevalence of many common disorders—across all populations—that can lead to ataxia, including diabetes, cancer, autoimmune disease, and alcoholism, among many others (Fogel and Perlman, 2006; Klockgether, 2010; Fogel and Perlman, 2011). Even in cases of suspected but unconfirmed genetic ataxia, testing for basic common acquired etiologies must be considered initially because of their high occurrence relative to genetic causes, and the markedly different approach to management that their diagnosis would entail. (Fogel and Perlman, 2006; Fogel and Perlman, 2011; Fogel and Geschwind, 2012).

An alternative to attempting to increase individual clinicians' knowledge about the appropriate use of genetic testing for patients with neurodegenerative conditions would be referral to a subspecialist. (Cheng *et al.*, 2007; Fogel and Geschwind, 2012). However, the extent to which clinicians, including general neurologists, use each strategy is unknown (Birbeck *et al.*, 2004; Swarztrauber and Vickrey, 2004). Therefore, to explore how genetic testing is being clinically utilized by a geographically broad group of community physicians referring to a single major tertiary center in southern California, we examined the diagnostic evaluations of a consecutive series of patients referred to a tertiary care neurogenetics center for evaluation of cerebellar ataxia. We specifically analyzed the extent to which an initial standard laboratory and imaging work-up for acquired causes of ataxia occurred, and patient- and physician-factors associated with this (Aim 1), and the extent of early use of genetic testing prior to the referral to the subspecialist, and patient and physician factors associated with this (Aim 2).

Methods

Sample

UCLA is a tertiary care referral center for ataxic disorders, with a referral base primarily from southern California and southern Nevada. This sample was drawn from a consecutive series of 102 initial consultations–primarily adult–to a single subspecialist neurologist (B.L.F.) in the institution's ataxia and neurogenetics program between 2006 and 2010. We excluded from analyses seven patients in whom the subspecialist did not confirm ataxia, for a final analytic sample of 95 (Table 1).

Sources of data and data collection

Data sources for patient-level variables were the subspecialist's initial consultation medical record note, and all referring physicians' notes, letters, and test results that had been sent or brought in by the patient for that initial consultation, occasionally including prior outside records that came in within a week following the patient visit. Characteristics of referring physicians (clinical specialty, year of medical school graduation, location of practice, and board certification status) were obtained from publicly available sources including the Medical Board of California "Physician License Lookup" web site (www.mbc.ca.gov/lookup.html) and the American Board of Medical Specialties.

After assigning each patient a numerical code and abstracting their age, gender, and insurance status, patient records were de-identified then abstracted by a research assistant (J.W.W.) using a standardized form developed by the study team, with a 25% subset abstracted by a second person (C.H.B.). After obtaining information from public sources about each referring physician, these data were also assigned a numerical code unique to each physician, maintaining numerical links to the patient-level referral data, then de-identified for subsequent analyses.

Dependent variables

The dependent variable for our first aim is the extent of a laboratory and imaging work-up for acquired causes of ataxia that were obtained prior to the consultation with the subspecialist. We abstracted whether each of the 14 laboratory tests (Table 3) had been done. As there are no consensus guidelines from professional specialty or subspecialty organizations available, this list was based on one set of expert's recommendations. (Fogel and Perlman, 2006; Fogel and Perlman, 2011). No patient had had all 14 of these laboratory tests prior to the subspecialist consultation. We measured extent of preconsultation laboratory testing in two ways: (1) a

dichotomous variable for none versus one or more of the laboratory tests, and (2) a continuous variable of the count of number of these laboratory tests that had been obtained prior to the consultation.

The dependent variable for our second aim is whether or not there was early ordering of genetic testing prior to the subspecialist consultation. Early genetic testing in this study was defined as, prior to the referral; genetic testing had been obtained in the absence of a definite or possible family history of ataxia and without evidence of a comprehensive laboratory work-up for acquired causes of ataxia. We also defined early use of genetic testing in a second way, by additionally including those patients in which genetic testing had been obtained and who did have a definite or possible family history of an unknown ataxia (not yet genetically-defined), but no laboratory tests had been obtained for acquired causes. Because currently there are no official practice guidelines, we defined early genetic testing in these ways because they are relatively lenient, allowing a broad range of clinical circumstances for obtaining genetic testing that could be considered standard care.

Independent variables

For our first aim, factors that we explored as potentially associated with ordering laboratory testing to work up an acquired cause of ataxia included *patient demographic characteristics* (gender, age); *family history* (four dichotomous variables for: ataxia, developmental disorders, early deaths, other neurologic disorders); *other relevant aspects of the presenting history* (four dichotomous variables for: whether the referring physician indicated ataxia as the primary reason for referral, having fallen within the prior 6 months, whether symptom onset had been gradual/slow, whether symptoms were episodic); and *characteristics of the referring physician* (three dichotomous variables for whether the referring physician is located in southern California, a neurologist, and board certified, and a continuous variable for number of years since medical school graduation).

Our second aim defined a process measure of care (test ordering) in a way that took into account the clinical context. Thus, the potential explanatory factors we explored were factors that should be unrelated to clinical context. For this particular care process, these included *patient demographic characteristics* (gender and age); *patient insurance status* (Medicare/MediCal versus other state or private insurance plans including self-pay); and *characteristics of the referring physician* (three dichotomous variables for whether the referring physician is located in southern California, a neurologist, and board certified, and a continuous variable for number of years since medical school graduation).

Analysis

Bivariate comparisons of dependent variables for aims 1 and 2 with each independent variable were made using appropriate statistical tests (chi-square, Pearson's correlations for dichotomous and ordered variables, and analysis of variance). We also examined associations of independent variables for significant collinearity; all covariates had correlations of $r \leq |0.50|$ with each other. Multivariable linear and logistic regression–both with full models and using stepwise regression ($p < 0.30$ to enter the model and $p < 0.15$ to remain in the model) were used to analyze the relative associations of the independent variables with each dependent variable. All analyses were performed using Stata (11.0), setting an a priori p-value of $p \leq 0.05$ for significance. We conducted sensitivity analyses for Aim 2 that expanded the definition of a negative family history as also excluding family history of developmental disorder or early death.

Standard protocol approvals, registrations, and patient consents

All study methods were approved by the Institutional Review Board of the University of California, Los Angeles. Direct patient consent was waived for the purpose of retrospective review of the de-identified medical records.

Results

Sociodemographic and clinical characteristics of the referral cohort ($n = 95$) are shown in Table 1; only 16 patients had a definite family history of ataxia, with another 18 patients judged by the consulting subspecialist as having a possible family history of ataxia. Characteristics of the 89 referring physicians are in Table 2; about one third of referring physicians were not neurologists. Imaging, laboratory testing for acquired causes, and genetic testing that was documented in the referring physician's notes or in other documents brought to the consultation visit are shown in Table 3.

Regarding Aim 1, 27 of the 95 patients (28%) were referred without evidence of any of the 14 laboratory studies suggested for initial work-up of an acquired cause (Table 3). Overall, the average number of laboratory studies obtained out of these 14 was 4.5 (SD = 4.1). In contrast, nearly all

Table 1. Patient Characteristics ($n = 95$)

Female, *N* (%)	46 (48.4%)
Mean age at referral, years (SD)	54.2 (18.2)
Insurance, *N* (%)	
Medicare/Medi-Cal	30 (31.6%)
Private/other insurance	62 (65.3%)
Self-pay	3 (3.2%)
Referring physician's primary reason for referral, N (%)	
Ataxia	65 (68.4%)
Trouble walking	13 (13.7%)
Episodic symptoms	5 (5.3%)
Adrenoleukodystrophy	2 (2.1%)
Genetic	5 (5.3%)
Abnormal MRI	4 (4.2%)
Other	16 (16.8%)
Presenting history at initial consultation with subspecialist, *N* (%)	
Symptom onset gradual/slow	65 (68.4%)
Fallen within last 6 months	37 (38.9%)
Worsening of symptoms	59 (62.1%)
Episodic symptoms	10 (10.5%)
Family history, *N* (%)	
Ataxia–definitely	16 (16.8%)
Ataxia–possibly	18 (18.9%)
Developmental disorders	8 (8.4%)
Early deaths	6 (6.3%)
Other neurological disorders	39 (41.1%)

MRI, magnetic resonance imaging.

Table 2. Characteristics of Referring Physicians ($n=89$)

Number of patients referred, *N* (%)	
1	83 (93.3%)
2	5 (5.6%)
3	1 (1.1%)
Geographic location, *N* (%)	
Southern California	69 (77.5%)
Other California	1 (1.1%)
Nevada	5 (5.6%)
Other	14 (15.7%)
Clinical specialty, *N* (%)	
Neurology	59 (66.3%)
Internal medicine	4 (4.5%)
Family medicine	7 (7.9%)
Other	12 (13.5%)
Unknown	7 (7.9%)
Board certified, *N* (%)	70 (78.7%)
Mean number of years since medical school graduation (SD)	27.5 (9.4) Range = 7 to 48 Median = 27.5

Table 3. Imaging and Testing Documented as Obtained Prior to Referral to Subspecialist

Laboratory studies, *N* (%)	
Complete blood count	45 (47.4%)
Vitamin B12	45 (47.4%)
Serum electrolytes	41 (43.2%)
Renal function	40 (42.1%)
Thyroid stimulating hormone	39 (41.1%)
Liver function	36 (37.9%)
Anti-nuclear antibodies	34 (35.8%)
Erythrocyte sedimentation rate	34 (35.8%)
Vitamin E	28 (29.5%)
Rapid plasma reagin/fluorescent treponemal antibody	24 (25.3%)
Folate	23 (24.2%)
Hemoglobin A1C	15 (15.8%)
Homocysteine	13 (13.7%)
Methylmalonic acid	13 (13.7%)
All of these laboratory studies	0 (0%)
None of these laboratory studies	27 (28.4%)
Imaging studies, *N* (%)	
Brain MRI	87 (91.6%)
Spine MRI	49 (51.6%)
CT scan of chest/abdomen/pelvis	12 (12.6%)
All of these imaging studies	8 (8.4%)
None of these imaging studies	0 (0%)
Genetic testing, *N* (%)	
Any prior genetic testing	39 (41.1%)
Mixed dominant and recessive multi-gene testing	17 (17.9%)
Dominant multi-gene testing	9 (9.5%)
Individual gene testing	13 (13.7%)
Early use of genetic testing prior to referral, *N* (%)	
No definite or possible family history of ataxia, a full laboratory workup for acquired causes was not obtained, and genetic testing had been obtained	27 (28.4%)
Definite or possible family history of an unknown ataxia, none of the 14 laboratory tests had been obtained, and genetic testing had been obtained	3 (3.2%)

patients (91.6%) had undergone brain magnetic resonance imaging (MRI) prior to referral. In multivariate analysis of factors associated with whether any of the 14 laboratory tests for acquired causes were obtained prior to consultation (Aim 1; Table 4), worsening of symptoms was associated with being more likely to obtain at least one of these tests ($p=0.05$), whereas a family history of ataxia ($p=0.002$) and a family history of other neurologic disorders ($p=0.04$) were each uniquely associated with being less likely to obtain any laboratory tests for an acquired cause; results were the same with a stepwise model. Regarding factors associated with the number of laboratory tests for acquired causes obtained prior to consultation, a family history of ataxia was associated with having fewer laboratory tests for acquired causes ($p=0.004$).

Overall, 41.1% ($n=39$) of the referral cohort had evidence of genetic testing prior to referral for subspecialist consultation. With respect to Aim 2, the level of early genetic testing, according to the two ways we operationalized this construct, was 28.4% ($n=27$; Table 3) when defined as no possible or definite family history of ataxia and an incomplete laboratory evaluation for acquired causes, and it was 31.6% ($n=30$), for the expanded definition that also included three patients with a family history but in whom no laboratory testing for acquired testing was evident. Regarding factors associated with early genetic testing (Aim 2; Table 5), the only factors that we studied that were associated with early use were neurologist referral ($p=0.04$ or $p=0.06$, depending on whether a full or a stepwise model), and patient age, where lower patient age ($p=0.01$) was associated with early genetic test ordering but only in the second, expanded definition of that construct (Table 5B). Sensitivity analyses that further expanded the definition of a negative family history beyond ataxia to exclude family history of developmental disorders or of early deaths yielded similar results. A *post hoc* analysis revealed no association overall in our sample between a definite or

Table 4.

A. Logistic regression model of factors associated with obtaining at least one laboratory test for acquired causes of ataxia prior to referral to subspecialist

At least one lab test completed	*Odds ratio (95% CI)*	p-*Value*
Full model:		
Worsening of symptoms	2.76 (0.99 to 7.66)	0.051
Family history of ataxia	0.15 (0.05 to 0.51)	0.002
Family history of other neurological disorders	0.34 (0.12 to 0.94)	0.04
Stepwise model:		
SAME AS FULL MODEL		

B. Linear regression model of factors associated with number of laboratory tests for acquired causes of ataxia obtained prior to referral to subspecialist

Number of laboratory tests for acquired causes	*Coef. (95% CI)*	p-*Value*
Full model:		
Referred for ataxia	−1.45 (−3.04 to 0.12)	0.07
Family history of ataxia	−3.68 (−5.64 to −1.71)	0.004
Stepwise model:		
SAME AS FULL MODEL		

Table 5.

A. Variable: Model A version 1 (logistic regression)		
Model A: Dependent variable: family history is not positive AND genetic testing is ordered; n = 27	*Odds ratio (95% CI)*	p-*Value*
Full model:		
Neurologist	2.89 (0.97–8.64)	0.06
Stepwise model:		
Neurologist	3.08 (1.04–9.11)	0.04
B. Variable: Model B version 1 (logistic regression)		
Model B: Dependent variable: (1) family history is not positive AND genetic testing is ordered OR (2) family history is positive and genetic testing is ordered and no initial workup; n = *30*	*Odds Ratio (95% CI)*	p-*Value*
Full model:		
Patient age	0.97 (0.94–0.99)	0.01
Neurologist	2.74 (0.95–7.89)	0.06
Stepwise model:		
Patient age	0.96 (0.94–0.99)	0.006
Neurologist	3.12 (1.06–9.20)	0.04

possible family history of ataxia and having had genetic testing prior to referral (chi-square *p*-value = 0.39).

Sixteen patients from the cohort ultimately received a final genetic diagnosis; of these 16, 10 were not genetically tested prior to referral. Of the six who did have genetic testing prior to referral, one received mixed dominant and recessive multi-gene testing (negative result), one received dominant multi-gene testing (positive result), and four received phenotype-directed individual gene testing (three positive results) (Table 3). The diagnostic yield of genetic testing by referring physicians was 4/39 (10%) overall; the breakdown of yield by type of testing was 0/17 (0%) for mixed dominant and recessive multi-gene testing, 1/9 (11%) for dominant multi-gene testing, and 3/13 (23%) for individual gene testing. Upon consultation with the subspecialist, 43 patients (45%) were recommended for additional genetic testing, most commonly phenotype-directed individual gene testing. Twelve cases were diagnosed based on genetic testing, as recommended by the subspecialist, for an overall subspecialist diagnostic yield of 12/43 (28%).

Discussion

We observed that among a consecutive series of 95 sporadic ataxia cases, nearly 30% received genetic testing prior to referral in the absence of a clinical evaluation for acquired causes (Table 3). Even more striking was the observation that genetic testing was unrelated to the presence of a family history of disease. Given that these were cases of sporadic ataxia, acquired causes would be predicted to be more common etiologies in this population (Fogel and Perlman, 2006; Klockgether, 2010; Fogel and Perlman, 2011).

That neurologists were more likely to have ordered genetic testing prior to referral (Table 5) as compared with other physicians may reflect more knowledge of potential genetic etiologies that cause ataxia. While it is certainly possible that recessive or *de novo* genetic mutations could potentially explain a small subset of cases,(Fogel and Geschwind, 2012; Fogel *et al.*, 2012) and such thinking could potentially be supported by a trend toward increased genetic testing in patients of younger age (Table 5), the majority of multi-gene testing performed was focused on dominant hereditary ataxias (Table 3), which would only very rarely be expected to present sporadically.(Durr, 2010; Fogel *et al.*, 2012) Further, in a sporadic ataxia population, testing for individual rare genetic ataxias (found in <1% of patients worldwide) may inherently have only a very limited benefit but incur substantial cost.(Fogel *et al.*, 2012) In the future, it is likely that the clinical utilization of next-generation sequencing strategies may alleviate some of these challenges by greatly increasing the number of testable genes while reducing the overall cost (Coppola and Geschwind, 2012); however, comprehensive data do not yet exist regarding the contribution of genetic etiologies to sporadic ataxia cases as compared to acquired or idiopathic causes. The unanticipated finding that family history was not associated with genetic testing prior to referral coupled with the overall use of early genetic testing underlie a more fundamental concern regarding the high utilization of genetic testing in potentially low-yield cases for currently nontreatable conditions, in lieu of consideration for potentially modifiable acquired causes in patients presenting with a sporadic ataxia.

Importantly, the majority of patients received an MRI of the brain prior to referral, a critical initial step in the evaluation of cerebellar ataxia, which can exclude a variety of common acquired etiologies (Fogel and Perlman, 2006; Fogel *et al.*, 2009; Fogel and Perlman, 2011). However, patients did not receive a majority of basic blood testing suggested as initial for evaluation of acquired causes of cerebellar ataxia (Fogel and Perlman, 2006; Fogel and Perlman, 2011) with most patients receiving, on average, only 4.5 out of 14 tests, and 28% receiving no laboratory testing at all prior to subspecialty referral. We acknowledge that because no consensus guidelines from professional specialty or subspecialty organizations are available, clinicians in our study may hold varying opinions on the necessity of all the tests we consider to represent an initial evaluation for acquired causes of ataxia. Additionally, because we were limited to reviewing only the materials provided on referral, it is possible that, in some cases, some of this testing may have been obtained and records were not brought in or sent. However, in all cases, attempts were made to obtain all prior records before the initial consultation. Further, given the variability associated with referral practices and our limitation that all cases were obtained from a single referral physician, it is possible that a larger and more diverse sampling would produce a different pattern of findings.

We also found that less laboratory testing was consistently associated with the presence of a definite or possible family history, suggesting that physicians may have been assuming that such a work-up would be less valuable if a genetic etiology were suspected. Although a positive family history certainly strongly supports an underlying genetic disorder, in the absence of a confirmatory genetic test, one cannot conclude identical etiologies among family members, particularly in older patients more at risk for underlying acquired ataxia causes (Fogel and Perlman, 2006; Fogel and Perlman, 2011;

Fogel and Geschwind, 2012). Further, having a genetic etiology does not preclude an individual from having a common comorbid acquired cause as well (e.g., diabetes, alcohol-related cerebellar ataxia, vitamin B12 deficiency, etc.), which could potentially be more damaging in the setting of an ongoing neurodegenerative process.

Moving forward, from a cost-benefit perspective, it would be important to emphasize that initial testing for acquired causes prior to genetic testing in patients with sporadic ataxia would be less expensive and more likely to identify a modifiable etiology. The establishment of guidelines for this and for the appropriate use of genetic testing and/or strategies to maximize cost benefit in patient populations with either a high incidence (or perceived high incidence) of genetic etiologies would be valuable to guide future education and decision support strategies to improve the current situation, although such documents must include considerations for the rapidly emerging use of next-generation sequencing strategies (Coppola and Geschwind, 2012).

As the role of genetic testing in neurological disease increases, it is likely that more physician education will be needed (Mindemark and Larsson, 2009) in both genetics and in the integrative evaluation of disorders with both acquired and genetic causes, such as cerebellar ataxia. In addition, incorporating decision guidance in support of appropriate clinical testing into health information technology systems has been advocated for improving quality and efficiency of care and should be developed for genetic testing in neurology (Wright *et al.*, 2009; Vickrey *et al.*, 2010).

Statistical analysis

Data analysis plan was formulated by BL Fogel, BG Vickrey, and CH Browner. Statistical programming was completed by SD Vassar.

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B.G. Vickrey serves on scientific advisory boards for the Sports Concussion Institute, American Heart Association, and the NIH; serves on the editorial boards of *Neurorehabilitation and Neural Repair* and *Circulation: Cardiovascular Quality and Outcomes*, and he is a section editor for *Stroke*; receives research support from the NIH (NIA, NINDS), the US Veterans Administration Health Services Research and Development Service, and the American Heart Association; and is a consultant to EMD Serono Canada and to Imperial Clinical Research Services, Inc.

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