Quality improvement in neurology
Headache Quality Measurement Set

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Headache is the most frequent reason for a person to seek care from a neurologist and is the most common subspecialty practice focus identified by neurologists.[1] Although headache is most commonly encountered in primary care,[2,3] it is also the fourth leading cause of emergency department visits,[4] with 1.2 million encounters annually in US emergency departments for migraine alone.[5]

Primary headache disorders are extraordinarily common and for many people contribute to significant disability. Although most of the population experiences a primary headache disorder in their lifetime with tension-type headache as the most common disorder,[6] migraine alone affects 12% of the population in any given year and is accompanied by substantial comorbidities.[7] The most severe form of migraine, chronic migraine, features a 1% population prevalence, disproportionate disability, and high individual and societal cost.[8] Recent estimates demonstrate a total annual societal cost on average for a person with chronic migraine exceeding $8,000 and for episodic migraine approximating $3,000.[9]

Migraine has its most severe disability during young and middle age, when people are most economically productive in society, adding to the disproportionate burden. According to the 2016 Global Burden of Disease study by the World Health Organization, migraine ranks second among all causes of years lost to disability (YLD)[10] and is the *top* cause of YLD worldwide among persons aged 15–49 years.[11] Although less common, cluster headache, the most common trigeminal autonomic cephalalgia, features a lifetime prevalence of 1 in 1,000 persons[12] and is particularly intractable and burdensome.[13] Cluster headache features extraordinarily severe attacks of pain accompanied by autonomic symptoms. Cluster headache is incredibly disabling; recent studies demonstrate people with cluster headache are twice as likely to miss work[14] and 3 times as likely to have depression.[15]

Headache disorders are chronic neurologic diseases characterized by episodic attacks. Therefore, treatment typically consists of a combination of acute strategies meant to reduce attack symptoms and preventive strategies meant to reduce attack frequency. Recent and emerging advances in the treatment of migraine, cluster headache, and other headache disorders have great potential to influence clinical practice across a variety of age groups. These advances include acute and preventive pharmacological therapies, procedures, and nonpharmacological treatments such as neuromodulation devices and behavioral therapies.

In 2015, the American Academy of Neurology (AAN) published the first set of quality measures for headache, with the goal of providing a standard to measure and improve care for patients with headache disorders.[16] Because of such advances in our understanding of these disorders,

and in their diagnosis and treatment, we provide an update for quality measurement in headache.

Opportunities for improvement

Treatment advances

Management of headache disorders has rapidly evolved in the recent years, featuring advances in pharmacological, neuro-modulation, and behavioral therapies. Since the previous headache measure set publication in 2015, the Food and Drug Administration has approved 8 new migraine-specific preventive and acute medications and cleared 4 neuromodulation devices, including 2 treatments for cluster headache (external vagus nerve stimulation, galcanezumab) and one treatment with a label extending to adolescents (single pulse transcranial magnetic stimulation). Divergent pharmacological treatment patterns across adult and pediatric populations[17,18] reinforce the need to conceptualize preventive treatment more broadly, as a concept not just restricted to medications.

Opioid use

The prevalent and excessive use of opioids is a public health concern and adversely affects people with headache disorders in a variety of care settings.[5,19] Excessive opioid use is a risk factor for migraine progression to chronic migraine.[20] The AAN and other organizations already feature quality measures directly addressing appropriate opioid use and misuse (table 1), and these measures address opioids in the context of acute therapy recommendations and migraine progression risk factor assessment.

Adherence to treatments

Therapy adherence is a critical issue in the care for patients with headache disorders. Underutilization of prescribed acute migraine-specific therapies may be a risk factor for migraine to progress to chronic migraine.[21] Acute therapies often require a complex decision-making procedure, taking into account the trade-offs between early treatment to improve efficacy and limiting the use to reduce the risk of medication overuse.[22,23] Unfortunately, adherence to preventive therapies is particularly challenging[24,25] for chronic disorders when episodic symptoms are not active every day. Furthermore, many preventive therapies are intolerable for some patients but often have a latency period requiring consistent use before efficacy manifests to permit patients to make an informed decision about the trade-off between side effects and efficacy. More recent treatments such as monoclonal antibodies, self-administered monthly or quarterly, and onabotulinumtoxinA, administered in the office every 12 weeks, make treatment adherence a less practical factor to assess. Therefore, this measure concept was not developed further. A quality measure on therapy adherence should be considered in the future, not only for medications but also for neuromodulation devices and behavioral therapies as well.

Tension-type headache and neuroimaging

Although tension-type headache is the most prevalent headache disorder in the population and chronic tension-type headache can be disabling, the evidence for preventive treatment is not robust. Therefore, quality measures for the treatment of tension-type headache should be revisited after the emergence of a higher quality of level of evidence. Finally, to exclude secondary causes of headache, clinicians may turn to neuroimaging. An existing AAN quality measure addresses imaging overuse,[26] the American College of Radiology has developed appropriateness criteria,[27] and the American Headache Society (AHS) has both a Choosing Wisely statement[28] and a more specific guideline.[29] The quality of more specific neuroimaging hospital protocols for thunderclap headache presentations specifically, including communication between the managing clinician and the radiologist, may be a topic for future consideration.

Methods

The AAN and the AHS formed a work group of key stakeholders from care team members that care for patients with headache. Details of the full measure development process are available online.[30] The construction of the work group began

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Table 1 Additional relevant measures

ICSI guideline on the diagnosis and treatment of headache
icsi.org/wp-content/uploads/2019/01/Headache.pdf
**Quality measures start on page 49

Use of opioids at high dosage in persons without cancer
pqaalliance.org/opioid-core-measure-set

Documentation of signed opioid treatment agreement
aan.com/policy-and-guidelines/quality/quality-measures2/quality-measures/other/documentation-of-signed-opioid-treatment-agreement/

Evaluation or interview for risk of opioid misuse
aan.com/policy-and-guidelines/quality/quality-measures2/quality-measures/other/evaluation-of-interview-for-risk-of-opioid-misuse/

Opioid therapy follow-up evaluation
aan.com/policy-and-guidelines/quality/quality-measures2/quality-measures/other/opioid-therapy-follow-up-evaluation/

Overuse of imaging for the evaluation of primary headache
aan.com/siteassets/home-page/policy-and-guidelines/quality/quality-measures/other-neurologic-conditions/2018universalneurologymeasurementset.pdf

with a nomination process from the AAN, which led to the formation of the 12-member work group.

All work group members were required to disclose potential conflicts of interest and completed applications summarizing experiences and interests. The facilitators and chair independently selected members from the pool of qualified specialists and expert nominees. The selection was based on the nominee's experience in performance measures, quality improvement, and clinical activities.

The measure development process included the following: (1) evidence-based literature search, (2) establishing a multidisciplinary work group adhering to the AAN conflict of interest policy, (3) drafting candidate measures and technical specifications, (4) convening the work group virtually to review candidate measures, (5) refining and discussion of the candidate measures, (6) soliciting public comments on approved measures during a 21-day period, (7) refining the final measures according to the input received during the public comment period and corresponding technical specifications, and (8) obtaining approvals from the work group, AAN Quality Measures Subcommittee, AAN Quality Committee, American Academy of Neurology Institute Board of Directors, and AHS Board of Directors.

The work group sought to develop evidence-based measures to support the delivery of high-quality care and to improve patient outcomes. The work group, guided by a medical librarian, conducted a comprehensive literature search, identifying 6,676 abstracts relevant to the potential measures. Data available from AAN.com (Appendix e-2, aan.com/siteassets/home-page/policy-and-guidelines/quality/quality-measures/headache/appendix-2-headache-lit-search.pdf). AAN staff conducted a preliminary review of the literature results to deduplicate articles and eliminate articles that were not pertinent to the topic. The remaining citations were given to the expert work group to review and identify relevant guidelines, systematic reviews, meta-analyses, and quality improvement articles. This yielded 22 guidelines, systematic reviews, and meta-analyses to represent a core feature of the evidence base for the measures developed. After the development of draft measure concepts during the virtual meeting, a public comment period resulted in comments from 17 individuals. This feedback drove concept refinement, which resulted in 6 measures that were approved (table 2). The work group approved measures most applicable to outpatient settings.

The AAN plans to provide resources to review these measures every 6 months. Thus, this measure set aims to provide a working framework for measurement, rather than a long-term mandate.

Results

Our work group developed 6 approved measures. The first 4 topics receiving priority included migraine frequency documentation, counseling, and management using acute and preventive therapies. The final measures focus on the acute and preventive treatment of cluster headache.

Documentation of migraine frequency

Proper assessment of migraine attack frequency is a core metric foundational for diagnosis, assessing migraine impact, determining appropriate treatment plans, and assessing the impact of treatment. A diagnosis of migraine without aura and migraine with aura requires a cumulative number of attacks in the International Classification of Headache Disorders.[31] Migraine attack frequency is the major feature that enables the diagnosis of chronic migraine, defined in someone with migraine by having the presence of headache on more than 15 days per month for at least 3 months, of which at least 8 headache days per month fulfill migraine criteria or respond to a migraine-specific medication. 2.5% of people with episodic migraine (<15 days per month of headache) progress to chronic migraine annually, rendering it an important public health problem.[20]

The decision to initiate preventive therapy for migraine is grounded in an assessment of migraine attack frequency.[7] Documenting the reduction of migraine frequency is a desired outcome for preventive treatment and requires asking the patient and documenting frequency in a standard format in the medical record.[32] A retrospective recall is sufficient for documenting headache and migraine attack frequency. However, migraine attack frequency may be captured more accurately using headache diaries including electronic-based recording tools such as apps on a mobile phone because synchronous monitoring reduces biases associated with retrospective recall.[33]

Modifiable lifestyle and chronification factors counseling for migraine

Lifestyle factors influence migraine severity and attack frequency. These include high and variable stress, poor quality sleep, skipping meals, alcohol, and irregular caffeine intake[34,35] from other dietary sources or medication sources, or both. Assessment and counseling to manage lifestyle factors associated with attack frequency and migraine severity is a fundamental part of education for patients with migraine and requires an individualized approach. This treatment aspect may be particularly important for the pediatric population, especially in the absence of strong evidence for medical preventive therapy.

Lifestyle factors are also potentially modifiable risk factors for migraine to progress to chronic migraine.[34] It is particularly important to assess and counsel patients regarding acute medication overuse. Defined as regular use of acute medications more than 10 or 15 days per month depending on medication class,[31] acute medication overuse is highly disabling,[10] prevalent, and prominently associated with a risk of migraine progressing to chronic

Table 2 2019 AAN headache measurement set

Title	Numerator	Denominator	Exclusions
Documentation of migraine frequency	Patients who had their migraine frequency documented in one of the following formats at each visit: • "Patient has [#] migraine attacks each [wk/mo/y]" • "Patient has [#] migraine days each [wk/mo/y]" • "Patient has [#] bad/severe headache days each [wk/mo/y]" • "Patient has daily migraine symptoms"	Patients ≥6 years of age diagnosed with migraine	• Patient and/or caregiver decline to answer • Patient has cognitive impairment, and no caregiver is available
Modifiable lifestyle and chronification factors counseling for migraine	Documentation that the patient was counseled on at least 1 modifiable lifestyle or chronification factor once during the measurement period	Patients ≥6 years of age diagnosed with migraine	• Patient and/or caregiver decline counseling
Treatment prescribed for acute migraine attacks	Patients who were prescribed a guideline recommended or FDA approved/cleared treatment for acute migraine attacks once during the measurement period	Patients ≥6 years of age diagnosed with migraine	• Treatments are medically contraindicated or ineffective for the patient. • Patient is already on an effective acute migraine medication. • Patient has history of acute migraine medication overuse. • Patient has minimal or no pain with migraine. • Patient and/or caregiver decline.
Migraine preventive therapy management	Patients whose migraine frequency is ≥6 days per month/4 attacks per month who were managed with an evidence-based preventive migraine therapy, including therapies prescribed by another clinician once during the measurement period	Patients ≥6 years of age diagnosed with migraine	• Patient migraine frequency <6 days per month or <4 attacks per month • Patient and/or caregiver decline therapies
Acute treatment prescribed for cluster headache	Patients who were prescribed an acute treatment, including treatments prescribed by a different clinician once during the measurement period	Patients ≥18 years of age with a diagnosis of cluster headache	• Guideline recommended treatment is medically contraindicated or ineffective for the patient. • Patient reports no CH attacks within the past 12 months. • CH are sufficiently controlled with over the counter [OTC] medications. • Patient and/or caregiver decline. • Lack of insurance or insurance coverage for treatment prescribed.
Preventive treatment prescribed for cluster headache	Patients who were prescribed short-term and/or long-term preventive treatment, including treatments prescribed by a different clinician once during the measurement period	Patients ≥18 years of age with a diagnosis of cluster headache	• Provider determined attack frequency does not warrant preventive treatment • Same 5 exclusions as Acute Treatment Prescribed for Cluster Headache measure

migraine, particularly with the regular use of barbiturates and opioids.[20]

Treatment prescribed for acute migraine attack

Recommending treatment for acute migraine attacks is a critical therapeutic component for all patients with migraine in any care setting. Migraine attacks are acutely debilitating because of symptoms through the attack phases: premonitory symptoms, aura, headache, and postdrome. Undertreatment of acute attacks is common and associated with migraine progression to chronic migraine,[21] rendering it an important modifiable risk factor. Optimal acute treatment strategies are required for all patients, and there are templates available that can help to communicate these treatment recommendations consistently.[36,37] Acute treatment approaches for migraine usually feature over-the-counter or prescription medications but may also include neuromodulation devices.

Acute medication overuse is a complicating factor in patients with frequent migraine attacks[38] and may also be a risk factor for migraine progression to chronic migraine.[20] Therefore, an allowable exclusion for not offering a prescription may be the presence of acute medication overuse to avoid potential escalation of this more nuanced clinical situation where a complex set of decisions need to be made, making the "Modifiable Lifestyle and Chronification Factors Counseling for Migraine" a more useful measure to apply.

Migraine preventive therapy management

Preventive therapy is a cornerstone of migraine management. The goal of preventive therapy is to reduce the frequency and severity of individual attacks, improve responsiveness to acute therapies, reduce the ictal and interictal burden and disability, and potentially to induce a remission of migraine as a disease, including those with chronic migraine. Preventive treatments should be offered when people with migraine have ≥6

Table 3 Proposed concepts considered but not developed

Topic	Description
Opioids	Percentage of patients with primary headache who were assessed for addiction risk had a documented reason for needing opioid or barbiturate therapy and received less than 8 days of an opioid medication or less than 5 days of barbiturate medication
	Percentage of patients with a primary headache disorder who were treated initially with an opioid (inverse measure)
Treatment adherence	Percentage of patients with a diagnosis of primary headache who were assessed for adherence to therapy protocol
Thunderclap headache	Percentage of hospitals that have a protocol for transmitting suspected diagnosis information for patient presenting with lone acute headache in the radiology request for CT procedure
Chronic tension-type headache	Percentage of patients who were prescribed a preventive therapy for chronic tension-type headache

monthly headache days, ≥4 monthly headache days with some impairment, or ≥3 monthly headache days with severe impairment or bed rest. Preventive therapy can be considered with ≥4 monthly migraine days with normal functioning, ≥3 monthly migraine days with some impairment, or ≥2 monthly migraine days with severe impairment.[7] These criteria were recently reiterated by an AHS position article.[32] In the general population, the American Migraine Prevalence and Prevention study suggests approximately 38% of people with migraine need preventive therapy, but only 13% currently use preventive therapy,[7] showing a huge unmet need. Reduction of migraine attack frequency is likely a treatment that can prevent the onset of chronic migraine in people with episodic migraine.

Acute and preventive treatment prescribed for cluster headache

Patients with cluster headache either have episodic cluster headache where periods of attack freedom exceed 3 months annually, or chronic cluster headache, where remission periods last less than 3 months annually. Nonetheless, all patients with cluster headache can feature attack periods of weeks to month in duration that are extremely disabling. Therefore, the default approach for patients with cluster headache is to require a treatment strategy to manage individual attacks and reduce attack frequency and severity. The quality measure for cluster headache includes both of these treatment approaches in a paired measure.

Proposed concepts and retired measures

The process to update the 2015 Headache Quality Measurement Set involved reviewing the existing measures and proposing new measure concepts. Work group members proposed 5 measure concepts that were not approved because they lacked the evidence or were not feasible to implement in clinical practice at this time (table 3). These

Table 4 Retired headache quality measures

Title	Retirement rationale
Assessment of headache medication overuse in the treatment of primary headache disorders	Retired in favor of other existing measures on appropriate medication prescribing for primary headache.
Plan of care or referral for possible medication overuse headache	Feasibility concerns noted. Difficult to extract information without a chart review.
Overuse of neuroimaging for patients with primary headache and a normal neurologic examination	Retired in favor of a new measure created as part of the AAN Universal Neurology Quality Measurement Set.
Migraine or cervicogenic headache-related disability functional status	Feasibility concerns noted. Difficult to extract information without a chart review.
Plan of care for migraine or cervicogenic headache developed or reviewed	Feasibility concerns noted. Difficult to extract information without a chart review.
Overuse of opioid containing medications for primary headache disorders	Retired in favor of other existing opioid measures.
Overuse of barbiturate containing medications for primary headache disorders	Retired in favor of other existing measures on appropriate medication prescribing for primary headache.
Preventive migraine medication prescribed	Retired standalone measure in favor of incorporating this concept into 3 separate concepts which are part of the new measurement set.
Quality of life assessment for patients with primary headache disorders	Feasibility concerns noted. Difficult to recommend only one tool for use in practice. Quality of life scores are not uniformly documented in the medical record.

Abbreviation: AAN = American Academy of Neurology.

concepts will be revisited over time to see if they are ready for development.

The work group retired a number of measures from the 2015 headache quality measurement set[16] (table 4). Many of these measures remain of critical importance and have since been incorporated into other endorsed measure sets by the AAN and other organizations already in use (table 3). Others have been reorganized into more consolidated or paired measures in this update. We felt the disproportionate emphasis on acute medication overuse in the previous headache measures could inadvertently lead to perverse incentives, whereby neurologists and other clinicians who serve challenging patients with higher disease severity would be penalized, potentially giving providers another reason to avoid treating this high-priority patient group. Acute medication overuse is a controversial topic,[39] and its persistence may be related to the underutilization of pharmacological and nonpharmacological preventive therapies, which we address. Many preventive therapies of different classes have evidence for effectiveness when acute medication overuse is present,[40,41] although limited studies exist with primary analyses.[42] We also did not include measures for cervicogenic headache in the current quality measures because their optimal approach for study, assessment, and treatment does not have a clear consensus.[43]

Finally, we removed uses of the term "migraines" in our measures to use the proper, defined term of either "migraine," "migraine attacks," or "chronic migraine." The term "migraines" is felt to be inaccurate[31] and potentially stigmatizing to patients.[44] Migraine is a singular neurologic disorder defined by a plurality of attacks,[31] features disabling symptoms including but not limited to headache, and has a substantial ictal and interictal burden.

Conclusions

These quality measures provide assessment tools for the appropriate care of patients with headache disorders, including migraine and cluster headache. As treatment advances in the field of headache medicine continue to develop rapidly, these measures will require revision in future years. We aimed to create measures that provided feasibility for the practicing clinician while also being patient-centered in our approach. Aside from including an assessment of migraine attack frequency, we did not include other specific outcome measures, such as standardized disability assessments, which do not currently have a uniform, feasible approach for standardized implementation in clinical practice. However, our measures provide the flexibility to measure contemporary headache clinical practice, including the use of all evidence-based treatments such as novel pharmaceuticals, neuromodulation, and behavioral therapies. Ongoing and future studies including the selection of specific acute and preventive therapies in both adult and pediatric populations and the appropriate

management strategy for acute medication overuse in people with migraine will influence future revision of these measures.

Appendix Authors

Name	Location	Contribution
Matthew S. Robbins, MD	Weill Cornell Medicine, New York NY	Study concept and design, acquisition of data, analysis and/or interpretation of data, drafting/revising the manuscript, critical revisions of the manuscript for important intellectual content, and study supervision including responsibility for conduct of research and final approval.

Appendix *(continued)*

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Appendix *(continued)*

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Quality improvement in neurology: Headache Quality Measurement Set

Matthew S. Robbins, M. Cristina Victorio, Mark Bailey, et al.

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Disputes & Debates: Editors' Choice

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Editors' Note: In Vivo Distribution of α-Synuclein in Multiple Tissues and Biofluids in Parkinson Disease

In the Systemic Synuclein Sampling Study (S4)—a cross-sectional observational study of 59 participants with early, moderate, or advanced Parkinson disease (PD) and 21 healthy controls (HCs)—Dr. Chahine et al. found lower total α-synuclein levels in the CSF of patients with PD compared with HCs with a reasonable sensitivity of 87%, but this finding had low specificity. On the other hand, α-synuclein immunoreactivity in skin and submandibular gland was specific for PD but not sensitive. In response, Dr. Gibbons et al. cite previous studies that reported much higher sensitivities (80%–95% vs 24.1%) for the detection of α-synuclein in the skin in patients with PD. They argue that this discrepancy cannot be explained by inclusion of late-stage PD in such studies, citing high-detection rates of phosphorylated α-synuclein in patients with early-stage PD and REM sleep behavioral disorder (RBD), and low-false positivity. They propose that the discrepant results in the S4 study may be explained by the study's methodology of formalin fixation of the skin biopsies, which they claim has not gained acceptance in the study of peripheral nerve tissue because of the diminished integrity of peripheral antigen retrieval; paraffin embedding of the tissue, which they argue provides only a fraction of the volume obtained with larger frozen tissue sections; and automated immunohistochemical staining. They suggest that future studies in this area should use more accepted standardized methods for processing skin biopsy tissue for phosphorylated α-synuclein. Responding to these comments, the authors suggest that previous conflicting results have primarily been due to relatively low levels of study rigor in assessing the accuracy of the various immunohistochemistry methods, which, in the S4 study group, included multiple independent slide-reading judges, third-party blinding of such judges, and validation against gold standard neuropathologic diagnosis. They agree that reports of high sensitivity of peripheral α-synuclein detection in patients with idiopathic RBD are encouraging for the early detection of α-synucleinopathies but argue that not all patients with PD have preceding RBD and that those who do tend to have more widespread and severe brain synucleinopathy. They counter that technical differences in paraformaldehyde and formalin fixation are minimal and cite previous methods from S4 authors supporting the use of formalin-fixed, paraffin-embedded (FFPE) tissue. They also argue that the multiple S4 tissue sections that they assessed for each tissue site and subject resulted in sufficient tissue volumes to overcome any limitations of individual paraffin-embedded samples. They note that thick sections and immunofluorescent signal development methods require rare technical expertise, whereas FFPE methods and autostainers are more widely available, with autostaining methods also providing greater replicability and potentially better long-term storage than free-floating immunohistochemical methods. This exchange highlights enduring methodological uncertainties, tradeoffs, and debates regarding the detection of antigens such as synuclein in tissue samples, which need to be more definitively resolved before such detection is adopted into clinical practice.

Reader Response: In Vivo Distribution of α-Synuclein in Multiple Tissues and Biofluids in Parkinson Disease

Christopher Gibbons (Boston), Vincenzo Donadio (Bologna, Italy), Claudia Sommer (Würzburg, Germany), Rocco Liguori (Bologna, Italy), Giuseppe Lauria Pinter (Milan, Italy), Raffaella Lombardi (Milan, Italy), Kathrin Doppler (Würzburg, Germany), and Roy Freeman (Boston)

We read with interest the publication entitled "In vivo distribution of α-synuclein in multiple tissues and biofluids in Parkinson disease."[1] In the article, Chahine et al.[1] discuss the results of the Systemic Synuclein Sampling Study (S4 study). This was an important step toward the in vivo diagnosis of synucleinopathy. Unfortunately, although the detection of phosphorylated alpha-synuclein was highly specific, sensitivity was quite poor, particularly for skin (with a sensitivity of 24.1%). The authors note that there were several explanations for such findings, including the earlier diagnosis of PD in the S4 study compared with the relatively small studies performed at other centers.

At present, there are many studies that include the use of skin for the detection of alpha-synuclein, many with numbers of similar or even larger size than the results of the present study with sensitivities of testing in the 80%–95%+ range.[2-4] Chahine et al. suggest that the high-positive rates in the previous publications are because of the inclusion of late-stage disease PD. This notion has largely been disproven by the high-detection rates of phosphorylated alpha-synuclein in patients with REM sleep behavioral disorder and in studies only including Hoehn and Yahr stages 1 and 2, which confirm that early detection is not only possible but can be performed with sensitivities much higher than reported in the S4 study.[1,5-7] The notion of higher rates of false-positive cases in previous studies—as also suggested by Chahine et al.—is opposed to the 100% specificity that has been reported before.[8,9]

To understand the major discrepancies between the S4 study and the synuclein literature published by several different groups, one must closely compare the methods between the groups. Based on our long experience in skin biopsy processing, the lack of sensitivity in the S4 study can be explained by the following: the methodology used in the S4 study included formalin fixation of the skin biopsies, paraffin embedding of the tissue, and automated immunohistochemical staining.[10]

The use of formalin-fixed paraffin-embedded tissue has never gained acceptance in the study of peripheral nerve tissue, where decades of peripheral nerve research have resulted in well-defined, standardized methods for standard skin biopsy processing using only thick, freshly fixed frozen tissue sections.[11,12] These international standards have been established because formalin fixation reduces the integrity of peripheral antigen retrieval, and therefore, only paraformaldehyde-based fixatives are used.[3,11,13,14] In addition, there is a need to obtain thicker tissue sections for adequate cutaneous nerve fiber and tissue sampling. As the authors of the S4 study note, the deposition of alpha-synuclein is "patchy." A standard 4-mm-thick paraffin-embedded tissue section provides only a fraction of the tissue volume obtained with a 20–50-mm frozen tissue section.[3,13,15] Thus, a significant sampling error is introduced by using paraffin-embedded sections unless much greater numbers of samples are processed. In addition, thin tissue sections disrupt a nerve fiber structure and reduce the ability to visualize intraneural synuclein deposition.

The association between the use of thicker cryosections and the higher sensitivity of phospho-alpha-synuclein detection is reflected in the literature: phosphorylated alpha-synuclein was first reported in premortem skin biopsies of patients with Parkinson disease with low sensitivity by using formalin-fixed paraffin-embedded tissue.[16] In 2013, 3 independent research groups—all

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Author disclosures are available upon request (journal@neurology.org).

from the field of peripheral nerve research with long experience in the study of cutaneous autonomic and somatosensory small fibers—simultaneously reported the detection of phospho-alpha-synuclein or an increase of total alpha-synuclein in dermal nerve fibers in patients with the Parkinson disease with a much higher sensitivity.[8,9,17] In the meantime, several studies have been published confirming these data.[18-20]

The results of the current study simply confirm that formalin-fixed paraffin-embedded tissue sections should not be used in the study of the skin biopsy analysis of peripheral nerve and do not inform about the utility of skin biopsy in the detection of phosphorylated alpha-synuclein. Future studies of this nature should be performed using the accepted standardized methods for processing of skin biopsy tissue for phosphorylated alpha-synuclein.

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Author Response: In Vivo Distribution of α-Synuclein in Multiple Tissues and Biofluids in Parkinson Disease

Thomas Beach (Sun City, AZ), Lana M. Chahine (Pittsburgh), Charles H. Adler (Scottsdale, AZ), and Brit Mollenhauer (Göttingen, Germany)

We appreciate the opportunity to reply to the letter by Gibbons et al. on our article.[1] Over recent years, there have been many, often widely conflicting reports on the diagnostic accuracy for the Parkinson disease (PD) of immunohistochemical (IHC) staining of pathologic α-synuclein (aSyn) in peripheral tissue biopsies.[2] We suggest that these conflicts have primarily

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been because of the relatively low levels of study rigor in assessing the accuracy of the various IHC methods. Unlike for the S4 study, other published diagnostic IHC methods for aSyn in skin or any other peripheral tissues subjected to rigorous assessments are rare—such as those performed in a series of studies conducted under the sponsorship of the Michael J. Fox Foundation—including the S4 study,[1] which is the subject of the current communications. These rigorous studies have included multiple independent slide-reading judges, third-party blinding of such judges, and validation against gold standard neuropathologic diagnosis.[3-5] We answer specific points mentioned by Gibbons et al. below:

1. Regarding the sensitivity of IHC aSyn methods in participants with idiopathic REM sleep behavioral disorder (RBD), we agree that these are encouraging for the early detection of α-synucleinopathies but point out that not all participants with PD or dementia with Lew bodies (DLB) have RBD and those who do tend to have more widespread and severe aSyn brain histopathology as compared with those without RBD.[6] This may also be true for prodromal participants with and without RBD.

2. Regarding the difference between paraformaldehyde and formalin fixation, we believe that this is minimal or nonexistent provided the concentration, in solution, of formaldehyde is equivalent. Most laboratories use commercially obtained 10% formalin in aqueous buffer, which has a formaldehyde concentration of approximately 4%. Many other laboratories, as indicated by Gibbons et al., prepare fixative solutions from solid paraformaldehyde, but this converts on dissolution into formaldehyde, and most laboratories aim for a final formaldehyde concentration of 4%. Because of this, formalin-fixed and paraformaldehyde-fixed tissues cause equivalent antigen (epitope) masking as long as they have equivalent formaldehyde concentrations. Much published work is available that indicates that excellent sensitivity may be obtained in formalin-fixed, paraffin-embedded (FFPE) tissue when optimal antigen exposure methods are used, including published work by some of the S4 authors on aSyn IHC methods.[7]

3. Greater section thicknesses such as those obtained with sliding-freezing microtomes or vibratomes do give additional tissue volume as compared to thinner paraffin sections, and this may give increased sensitivity, but, as Drs. Gibbons, Freeman and co-workers pointed out themselves in their very recent publication,[8] this is easily made equivalent by staining more paraffin sections to give equivalent tissue volumes. We believe that the multiple S4 tissue sections that we assessed for each tissue site and participant will have given the study sufficient tissue volumes so as to exclude this as a limiting factor for achieving optimal sensitivity. The S4 group has, in fact, conducted follow-up studies that confirmed that additional stained sections did not further improve sensitivity.

4. Although thick sections and immunofluorescent signal development—such as those used by Gibbons et al.—have been used by some (but not all) laboratories for the investigation of peripheral nerve pathology, these methods have distinct and limiting drawbacks. They require technical expertise that a very few laboratories possess, whereas FFPE methods and autostainers are used by virtually every diagnostic hospital pathology unit in the developed world. The use of autostainers and associated standardized reagents provides replicable interlaboratory slide staining that is difficult to obtain with free-floating section methods that are idiosyncratic to each laboratory. The fluorescent slides obtained with the free-floating section methods are not well preserved in long-term storage and would be difficult to exchange between centers.

We therefore disagree with Gibbons et al. in their conclusion that FFPE sections should not be used for skin biopsy analysis, whether for the study of aSyn or other features. We look forward to more rigorous assessments of the free-floating aSyn IHC methods used by the authors, including the usage of third-party blinding, multiple independent judges, and gold standard autopsy diagnosed cases. Such a rigor is especially critical before aSyn detection methods are offered in the clinical setting.

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Editors' Note: Longitudinal Changes of Brain Microstructure and Function in Nonconcussed Female Rugby Players

Dr. Manning et al. found cross-sectional and longitudinal changes in the white matter diffusion measures and resting-state functional MRI network connectivity in 73 concussion-free female rugby players compared with 31 age-matched female swimmers and rowers. They concluded that longitudinal changes occur in the microstructure and function of the brain in otherwise healthy, asymptomatic athletes participating in contact sport and that further research is needed to understand the long-term brain health and biological implications of these changes. In response, Drs. Shahim and Diaz-Arrastia note that repetitive head impacts over decades have been associated with late-life dementia in previous studies of professional contact-sport athletes, but that it is less clear whether participation in such sports at the amateur level poses similar risks. They note that the finding of white matter microstructural disruption seen in the study by Dr. Manning et al. is also seen as a consequence of more severe traumatic brain injuries. While commending the longitudinal data provided by the study, they caution that imaging techniques such as diffusion tensor imaging and rsfMRI may detect small degrees of disruption that are not functionally limiting and also have limited availability and cumbersome processing needs that preclude their use for routine assessment of athletes. They call for further studies of more inexpensive blood-based biomarkers and their correlation with imaging markers of axonal disruption after concussive and subconcussive head impacts. Responding to these comments, the authors agree that cognitive reserve in the individuals studies may be sufficiently high that they are functionally unaffected by the identified MRI markers of tissue and network disruption but argue that they may eventually affect the brain's response to other insults later in life. They agree that these MRI approaches are presently intended for research purposes. Noting that they have undertaken further work on blood-based markers on this cohort, they comment that metabolomic signatures may be more relevant than classical markers of injury while acknowledging the need for better correlation with imaging results and cognitive testing. This exchange underscores our evolving, but incomplete, understanding of the clinical significance of imaging and blood-based markers of axonal injury in otherwise healthy athletes engaged in contact sports.

Aravind Ganesh, MD, DPhil, FRCPC, and Steven Galetta, MD

Reader Response: Longitudinal Changes of Brain Microstructure and Function in Nonconcussed Female Rugby Players

Pashtun Shahim (Bethesda, MD) and Ramon Diaz-Arrastia (Philadelphia)

We read the article by Manning et al.[1] with interest. Studies of professional contact-sports athletes have made clear that exposures to repetitive head impacts over decades are associated with late-life neurodegenerative dementia.[2,3] It is less clear whether participation in contact sports at the amateur level results in comparable risks. The study by Manning et al. found white matter (WM) microstructural disruption—especially in the corpus callosum and impaired functional connectivity in the default mode network over time in concussion-free and asymptomatic female rugby players—using diffusion tensor (DTI) and resting-state connectivity MRI (rsMRI), respectively.[1] These WM tracts are known to be disrupted as a consequence of more severe traumatic brain injuries.[4] In contrast to the existing studies,[5] Manning et al. assessed WM and functional changes in female athletes and noncontact sport athletes longitudinally, which is a novel and strong study design. Although the results of the Manning et al. study are compelling, they should be interpreted with caution. Although DTI and rsMRI are sensitive for identifying WM disruption, it is likely that there is substantial cognitive reserve built into brain and that these elegant imaging techniques may detect small degrees of disruption that are unlikely to result in functional limitations. Future studies with larger sample sizes and longer follow-up will be required to answer this important question. Finally, the DTI and rsMRI methods have several limitations, including limited availability and cumbersome image processing, which limits their usefulness for routine assessment of athletes. Future studies should include blood-based biomarkers, such as neurofilament light and glial fibrillary acidic protein, which are inexpensive and straightforward to interpret, as markers of axonal disruption. How well blood biomarkers correlate with the imaging biomarkers of axonal injury after concussive and subconcussive head impacts is a critical issue which remains to be resolved.

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Author Response: Longitudinal Changes of Brain Microstructure and Function in Nonconcussed Female Rugby Players

Kathryn Y. Manning (Calgary, AB) and Ravi S. Menon (London, ON)

We are in agreement with the caveats put forward by Drs. Shahim and Diaz-Arrastia regarding our article.[1] It is entirely possible that the MRI methods put forward in this paper are so sensitive that they detect changes that are of no functional consequence now. It is also possible that cognitive reserve in these individuals is sufficiently high that these changes have no consequence in the future. However, one could imagine that every life event that chips away at the brain's capacity for recovery and plasticity can ultimately affect the brain's response to a later-in-life insult, such as stroke or plaque formation. It is simply unknown whether this is a linear process or one in which a threshold needs to be surmounted, and hence, whether these

are important or trivial changes. We would not advocate that these MRI approaches be used in a diagnostic manner. As noted in the comment, these are sophisticated and expensive approaches and are designed to study populations and inform directions for further research (and perhaps policy). One such direction is the use of blood biomarkers. We do have additional publications with data on this cohort in preparation but can note in passing that GFAP showed no changes at the sensitivity threshold of our techniques. In mild TBI or asymptomatic participants, metabolomic signatures may be more relevant than the classical markers such as GFAP or NFL, as we have previously noted.[2] These would be more appropriate as accessible screening tools once we understand their relationship to the imaging results and perhaps more incisive cognitive testing.

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Long-term Employment Outcomes After Epilepsy Surgery in Childhood

In the article "Long-term Employment Outcomes After Epilepsy Surgery in Childhood" by Reinholdson et al.,[1] there is an error in figure 1. The blue box (sixth from the bottom) directly below the green and yellow boxes titled "15-year" should read: "Included: 105 Lost: 16." The authors regret the error.

Reference

1. Reinholdson J, Olsson I, Tranberg AE, Malmgren K. Long-term employment outcomes after epilepsy surgery in childhood. Neurology 2020;94:e205–e216.

Quality Improvement in Neurology

Headache Quality Measurement Set

In the AAN Special Article "Quality Improvement in Neurology: Headache Quality Measurement Set" by Robbins et al.,[1] author Nathaniel M. Schuster was listed incorrectly in the author list. The publisher regrets the error.

Reference

1. Robbins MS, Victorio MC, Bailey M, et al. Quality improvement in neurology: Headache Quality Measurement Set. Neurology 2020;95:866–873.