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RESEARCH SUBMISSION

The headache research priorities: Research goals from the American Headache Society and an international multistakeholder expert group

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Abstract

Objective: To identify and disseminate research priorities for the headache field that should be areas of research focus during the next 10 years.

Background: Establishing research priorities helps focus and synergize the work of headache investigators, allowing them to reach the most important research goals more efficiently and completely.

Methods: The Headache Research Priorities organizing and executive committees and working group chairs led a multistakeholder and international group of experts to develop headache research priorities. The research priorities were developed and reviewed by clinicians, scientists, people with headache, representatives from headache organizations, health-care industry representatives, and the public. Priorities were revised and finalized after receiving feedback from members of the research priorities working groups and after a public comment period.

Results: Twenty-five research priorities across eight categories were identified: human models, animal models, pathophysiology, diagnosis and management, treatment, inequities and disparities, research workforce development, and quality of life. The priorities address research models and methods, development and optimization of outcome measures and endpoints, pain and non-pain symptoms of primary and secondary headaches, investigations into mechanisms underlying headache attacks and chronification of headache disorders, treatment optimization, research workforce

Abbreviations: AHS, American Headache Society; MRI, magnetic resonance imaging; NIH, National Institutes of Health; NINDS, National Institutes of Neurological Disorders and Stroke; QOL, quality of life; SMART, sequential multiple assignment randomized trial.

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*See Acknowledgements section for working group rosters.

For affiliations refer to page 926.

recruitment, development, expansion, and support, and inequities and disparities in the headache field. The priorities are focused enough that they help to guide headache research and broad enough that they are widely applicable to multiple headache types and various research methods.

Conclusions: These research priorities serve as guidance for headache investigators when planning their research studies and as benchmarks by which the headache field can measure its progress over time. These priorities will need updating as research goals are met and new priorities arise.

Plain Language Summary

The American Headache Society led a large, international, multistakeholder process to identify headache research topics that should be prioritized during the next 10 years. With input from headache clinicians, scientists, people with headache, representatives from headache organizations, health-care industry representatives, and the public, 25 research priorities within 8 categories were identified. These research priorities can help guide headache researchers when planning their studies and as benchmarks by which the headache field can measure its progress over time.

KEYWORDS
diagnosis, disparities, migraine, pathophysiology, quality of life, treatment

INTRODUCTION

Identifying and disseminating research priorities can unify and strengthen a field toward reaching its most important goals. By establishing clear milestones that address these priorities, the path toward achieving them becomes more transparent, streamlined, and efficient. Furthermore, the process of identifying research priorities and setting milestones can be an important learning process for those involved, including the opportunity to understand better and discuss priorities among multiple stakeholders such as scientists, clinicians, those with the diseases of interest, health-care industry representatives, medical and patient society leaders, advocates, granting organizations, and the general public.

In line with this approach, the American Headache Society (AHS) and the National Institutes of Health's (NIH) National Institutes of Neurological Disorders and Stroke (NINDS), in collaboration with members of the board of the International Headache Society, led a process to develop headache research priorities. The objective of this effort was to involve an international group of expert representatives from multiple stakeholder groups to develop and disseminate headache research priorities that should be addressed within the next 10 years.

METHODS

The development of these headache research priorities, which began in December 2021, was led by an organizing committee (authors TJS, AAP, MLO, MFB, HR, NL), executive committee (authors PJG and CT, presidents of the American Headache Society and International Headache Society at the time of launching the development of these research priorities), and working group chairs (authors AC, MA, RB, AAG, DWD, PPR, RBL, JA, CLS, LC, KBD, AFR, DCB, SWP). Eight research priority working groups were established: human models, animal models, pathophysiology, diagnosis and management, treatment, inequities and disparities, research workforce development, and quality of life. Working group chairs attended a project meeting during which objectives and methods were discussed with the organizing and executive committee members. Working group chairs then proposed eight to ten individuals to serve on their working group committees, making sure to include people from multiple stakeholder groups, including health-care professional clinicians, scientists, methodologists, persons with headache, health-care industry representatives, and advocates. After the proposed working group rosters were reviewed by the organizing and executive committees to ensure diversity, the working groups were populated with members (see working group rosters in the Acknowledgments section). Working groups were tasked with developing priorities in headache research for the next 10 years, with research milestones that must be achieved to accomplish the goals for each priority. After their initial development, the research priorities were shared with the other working groups during multiple online virtual meetings and through e-mail communications. Post-meeting feedback was used to revise the research priorities and milestones further. The research priorities were then made available for public review and comments using an online platform, IdeaScale (ninds.ideascalegov.com), from April 2023

through November 2023. The opportunity for public comment was widely publicized by sending e-mail invitations to 100 professional and patient organizations, through AHS e-mail communications, and via in-person presentations at the AHS Annual Scientific Meeting, the AHS Scottsdale Headache Symposium, and the International Headache Society International Headache Congress. All public comments were shared with working group chairs, and a final round of revisions was undertaken. Included herein are the research priorities, the rationale for choosing each priority, and milestones that need to be reached to achieve the goals defined by each research priority.

RESULTS

Human models

Research Priority #1: Identify and understand molecular signaling pathways that contribute to and are associated with the development of headache disorders, initiation of headache episodes, and evolution of headache disorders.

A key feature of headache disorders is that a range of factors can initiate an episode of headache or cause exacerbation of headache. This phenomenon provides a unique opportunity to investigate the underlying pathophysiological mechanisms of headache disorders by experimentally inducing headache, which allows for systematic monitoring of patients before, during, and after episodes of headache.[1]

Five-Year Milestones:

- Identify the site of action and molecular targets of existing and emerging pharmacological provocation agents used in experimental human models of headache.
- Integrate existing and emerging pharmacological treatment options into experimental human models of headache.
- Develop and refine an experimental human model of migraine aura.
- Develop and refine experimental human models of headache that can be integrated into and inform drug discovery, development, and clinical trials of potential therapeutic approaches.

Ten-Year Milestones:

- Identify and differentiate between molecular signaling pathways at peripheral and central sites of action responsible for initiating episodes of headache.
- Understand the role of specific molecular targets (receptors, ion channels) in pain transmission during migraine attacks.
- Identify molecular signaling pathways responsible for initiating episodes of tension-type headache.

Research Priority #2: Identify and understand alterations in biochemistry that contribute to and are associated with the development of headache disorders, initiation of headache episodes, and evolution of headache disorders.

Biochemistry biomarkers may contribute to understanding underlying molecular mechanisms of headache disorders.[2] Furthermore, establishing accessible biochemistry biomarkers may allow for prediction of and monitoring of treatment response in individuals with headache disorders.[3]

Five-Year Milestones:

- Identify alterations in biological fluid biochemistry, either single-sample or panel of multiple samples, which can be used as a biomarker of migraine.
- Identify alterations in biological fluid biochemistry, either single-sample or panel of multiple samples, which can be used to predict and monitor treatment response in migraine.

Ten-Year Milestones:

- Identify alterations in biological fluid biochemistry, either single-sample or panel of multiple samples, which can be used as a biomarker of chronification of headache disorders.
- Identify alterations in biological fluid biochemistry, either single-sample or panel of multiple samples, which can be used as a biomarker of rarer headache disorders, such as the trigeminal autonomic cephalalgias.
- Identify alterations in biological fluid biochemistry, either single-sample or panel of multiple samples, which can be used as a biomarker of tension-type headache.

Research Priority #3: Identify and understand alterations in brain structure and function that are associated with the development of headache disorders, initiation of headache episodes, and evolution of headache disorders.

Advances in multimodal magnetic resonance imaging (MRI) demonstrate alterations of brain structure and function in individuals with headache disorders suggesting that MRI-based and other research imaging techniques provide a useful tool to dissect the mechanistic complexities underlying headache disorders.[2]

Five-Year Milestones:

- Identify structural and functional imaging findings that can be used to differentiate between individuals with migraine without aura and individuals with migraine with aura.
- Identify structural and functional imaging findings that can be used to differentiate between individuals with migraine and individuals with post-traumatic headache.
- Establish uniformity of imaging paradigms for reproducibility of results and comparison between studies.

Ten-Year Milestones:

- Identify structural and functional imaging findings that can be used to predict and monitor treatment response in migraine.

- Identify structural and functional imaging findings that can be used to differentiate between individuals with migraine and individuals with cluster headache.
- Identify structural and functional imaging findings that can be used to differentiate between individuals with different trigeminal autonomic cephalalgias.
- Identify structural and functional imaging findings that can be used to differentiate between individuals with migraine and individuals with tension-type headache.
- Identify structural and functional imaging findings that can be used to differentiate between individuals with episodic migraine and individuals with chronic migraine.
- Establish multicenter collaborations to build and validate imaging models.

Research Priority #4: Improve translation and integration between experimental human models of headache with spontaneous episodes of headache.

As episodes of headache are transient and onset is unpredictable, studies have more often investigated experimental human models in which headache episodes are triggered, whereas data derived from spontaneous episodes of headache are sparse.[2,4]

Five-Year Milestones:

- Increase the number of biomarker studies (e.g., molecular signaling pathways, genetic, biochemistry, imaging) on spontaneous migraine attacks with or without aura.
- Increase the number of biomarker studies (e.g., molecular signaling pathways, genetic, biochemistry, imaging) on spontaneous cluster headache.

Ten-Year Milestones:

- Identify and understand how molecular signaling pathways compare between episodes of headache triggered with an experimental compound and spontaneous episodes of headache.
- Identify and understand how genetic markers compare between episodes of headache triggered with an experimental compound and spontaneous episodes of headache.
- Identify and understand how biochemistry compares between episodes of headache triggered with an experimental compound and spontaneous episodes of headache.
- Identify and understand how structural and functional imaging findings compare between episodes of headache triggered with an experimental compound and spontaneous episodes of headache.

Animal models

Research Priority #1: Refine and validate existing animal models for headache disorders and develop new models in which gaps in validation or translation exist.

There is a misperception that there is "no good animal model for migraine." This misperception is based in part upon an unrealistic expectation that the totality of a complex disease can be represented by a single animal model. Models exist that mimic components of the physiology of some headache disorders, which make them a useful basis for current work and future refinement. Current animal models for headache disorders include combinations of stimuli or experimental conditions that are intended to parallel those observed with headache disorders (e.g., nitroglycerin administration or transgenic expression of migraine genes) and readouts that may include molecular, physiological, pharmacological, and/or behavioral endpoints. Each element of each model has strengths and weaknesses and may have different utility depending on the hypothesis being tested. Some models may be better suited for developing understanding of basic mechanisms, whereas others may be better suited for therapy discovery and characterization; a better consensus should be reached on both the stimuli/experimental conditions and endpoints with respect to their mechanistic and clinical translational value. Some previously used animal models of headache have not been validated by human experience, whereas others have more substantial evidence that translates to clinical disease features including prediction of treatment effects. For some models, therapies with established clinical efficacy have a clear effect, whereas treatments that have no efficacy do not.[5] In addition, treatments that are ineffective should not be effective in the model. The use of these types of positive and negative controls is an effective way to demonstrate the predictive value of a model. Thus far, however, there are no models that have 100% predictive value. Cataloguing the results with different models has the potential to be highly useful to determine the utility of different models in different contexts.[6,7]

Five-Year Milestones:

- Produce a multi-author review/consensus statement that details different animal models, with the relevant stimuli/conditions/endpoints that are utilized in that model, including their strengths and weaknesses, and detailed description of practical issues (e.g., methodological considerations, sample size, sex effects, effects of anesthesia, cost, equipment/personnel required, throughput).
- Develop methodological standards for animal models of headache to ensure that investigators are using the most appropriate experimental conditions, minimizing invasiveness of procedures, and minimizing numbers of animals required for statistical powering of studies.
- Develop standards for validation of animal models based upon current understanding of migraine mechanisms and the established efficacy of migraine therapies.
- Develop new animal models of headache based on the most recent understanding of human headache pathophysiology derived from human models and from clinical experience with new specific therapies. These may include cell- and organoid-based models that reduce the number of animals required.
- Exploit advances in technology including molecular techniques, optogenetics, micro-electronic approaches, and machine learning

to refine existing animal models of headache and develop new models that have increased translational value.

Ten-Year Milestones:

- Characterize the effects of all the most recently approved therapeutic approaches, particularly headache disorder–specific therapies, in established and new animal models of headache.

Research Priority #2: Encourage collaborative research that enables different investigators with specific expertise and experience with different animal models/readouts to achieve synergistic results that will lead to advances in the understanding and treatment of headache disorders.

Headache disorders involve complex alterations in the central and peripheral nervous system. Animal models of headache include molecular, cellular, pharmacological, physiological, and behavioral elements. Research involving each of these elements requires specific expertise and resources. It may be impractical and inefficient for individual investigators to incorporate all these elements into research projects in their own laboratories. Effective collaboration is therefore an important priority for animal research in headache disorders. Another important aspect of collaboration is with industry partners who have historically taken on the responsibility of bringing forward new therapies for headache disorders. There is no consistent set of animal model evidence that encourages industry to "green light" the development of a given therapy, and there is no consistent mechanism for synergistic collaboration between NIH-supported researchers and industry.

Five-Year Milestones:

- Develop an infrastructure to facilitate collaborative animal model research in headache. Leverage this to generate a large multicenter database of animal model results that can be benchmarked against human clinical data, including the efficacy of therapeutic approaches.
- Develop an infrastructure for the sharing of highly specific details of animal model methods and technologies among investigators.
- Identify methods and results that are particularly important for the field and therefore warrant replication by more than one laboratory.
- Establish mechanisms for better communication of both positive and negative results with animal models in real time to provide investigators with better information to perform more efficient research.

Ten-Year Milestones:

- Develop formal mechanisms for communication/collaboration between NIH-supported researchers and therapeutic industries regarding animal models of headache.
- Develop mechanisms of communication/collaboration between NIH-supported researchers and technological industries regarding animal models of headache (e.g., micro-electronics, machine learning, "big data" approaches).

Pathophysiology

Research Priority #1: Determine the underlying pathophysiology of the non-pain symptoms of migraine and other primary and secondary headache disorders.

While we are making progress in our understanding of migraine and the chronification of migraine through peripheral and central sensitization, much less is understood about the mechanisms behind the non-headache symptoms co-occurring with headache. Associated dizziness/vertigo; nausea and vomiting; sensitivity to visual motion, light, and sound; difficulty concentrating; tinnitus; non–aura-related visual disturbances; anxiety; depression; and altered sleep architecture can sometimes be as, or more, disabling as the headache pain.[8,9] These symptoms, which may occur during the premonitory phase (prodrome), aura, headache, and/or postdrome phase, occur not only in the context of migraine, but also in new daily persistent headache, post-traumatic headache, and other headache disorders.

Five-Year Milestones:

- Determine the pathophysiology of headache-associated nausea and vomiting.
- Determine the pathophysiology of headache-associated cognitive symptoms.
- Determine the pathophysiology of headache-associated mood symptoms.
- Determine the pathophysiology of headache-associated dizziness and vertigo.
- Determine the pathophysiology of other symptoms associated with headache, such as non-aura visual disturbances, tinnitus, sensitivity to visual and auditory stimuli, and changes in sleep patterns.

Ten-Year Milestones:

- Compare the pathophysiology underlying the non-pain symptoms experienced in migraine versus other headache disorders (e.g., cluster headache, new daily persistent headache, and others) to determine if the pathophysiology of these symptoms is the same or different.
- Determine the developmental, genetic, and/or environmental influences as to why non-pain symptoms disproportionately affect some groups more than others.

Research Priority #2: Expand knowledge into the pathophysiology of head pain in migraine and other primary and secondary headache disorders.

While the brain plays a critical role in multiple aspects of migraine–head pain, full understanding of the peripheral and central

mechanisms involved in the generation and cessation of headache pain is lacking.[10] To help explore the mechanisms behind current treatments and develop novel therapeutic approaches, it is necessary to explain the processes that contribute to generating and/or perpetuating headache pain in migraine and other headache disorders.

Five-Year Milestones:

- Determine the mechanisms behind the generation of migraine attacks within the central and peripheral nervous system with a goal of better characterizing the functional networks that prepare, start, and end the processes leading to the pain of migraine and associated symptoms including the premonitory and postictal symptoms.
- Identify the central and/or peripheral mechanisms that stop or "turn off" head pain (i.e., what causes an untreated migraine attack or cluster attack to end?). In addition, determine how and why modulatory pain pathways sometimes fail, allowing headache to become chronic/persistent in some individuals.
- Identify all classes and subclasses of meningeal nociceptors, determine their role in the headache phase of migraine, and map their receptors.
- Understand the role of sensory, sympathetic, and parasympathetic involvement in the pain of migraine and other headache disorders.
- Clarify the potential role of inflammation in migraine and other headache disorders.

Ten-Year Milestones:

- Identify molecules/peptides that activate meningeal nociceptors and investigate ways to block these different activation mechanisms.
- Determine whether, and if so which, immune cells are activated before and/or during a headache attack and through which inflammatory pathways they may alter the molecular environment in the meninges, calvaria, and peri-cranial muscles.
- Identify how the central and/or peripheral mechanisms that stop headache pain can be activated or repaired in those who have developed chronic, continuous head pain (i.e., those in whom continuous head pain has been present for ≥ 3 months).

Research Priority #3: Identify and characterize genetic and epigenetic factors that influence the pathophysiology and treatment of migraine and other primary and secondary headache disorders.

Migraine and certain other primary and secondary headaches have moderate to high heritability.[11] Current headache treatments exhibit variable efficacy, and their underlying biological mechanisms remain largely unknown. Moreover, headache research is difficult due to headache's episodic nature (in most people), and absence of validated pathogenic tissue- and cell-based models. Large and powerful genetic studies of migraine, and more recently cluster headache, have identified more than 130 genetic factors associated with their risk.[12] However, much work remains to elucidate the biological consequences of the identified genetic risk factors and how these and other genetic and epigenetic factors influence the pathophysiology, clinical presentation, and treatment of migraine and other primary and secondary headache disorders.

Five-Year Milestones:

- Identify genetic biomarkers for disease risk and progression in migraine and other primary and secondary headache disorders, and whether any genetic subgroups of patients can be accurately identified based on clinical phenotype.
- Characterize existing and identify novel genetic risk factors for disease risk and migraine progression using multi-omic analyses (e.g., DNA sequence variation, DNA methylation, gene expression, proteins, and metabolites) in patient material (blood, post-mortem brain using RNA-seq, single-cell seq, epigenetics)
- Identify genetic predictors of treatment response for migraine medications.

Ten-Year Milestones:

- Identify novel drug targets using functional genomics combined with functional readouts in patients and animal models (using transgenics, electrophysiology, vascular readouts, organ-on-chip technology).
- Implement the use of polygenic risk scores as a genetic biomarker.
- Develop more refined phenotypes for genotyping, for example, the vestibular migraine phenotype, or the phenotype of those with migraine who experience continuous headache or headache attacks that last longer than 72 h (the current cut point for "status migrainosus") versus those that are shorter.

Diagnosis and management

Research Priority #1: Better understand the evolution of migraine, risk factors for chronification, and factors which predict improvement and remission by performing longitudinal studies in people with migraine with detailed phenotypic questionnaires that collect information and outcome measures regarding clinical course and comorbidities.[13,14]

Migraine is a life-long disease. We do not fully understand the factors that determine onset, remission, progression, or clinical course. Prospective longitudinal studies that include deep clinical and biological phenotyping are required.[2,15]

Five-Year Milestones:

- Investigate the natural history of migraine in children, including individuals at risk (e.g., high polygenic risk score), environment–gene interactions, and the role of migraine in biopsychosocial development.
- Create a longitudinal cohort of patients with migraine that is inclusive of ethnic, racial, and socioeconomic backgrounds which

identify factors that predict clinical course over time, including disease progression and remission.
- Reappraise the definitions of episodic and chronic migraine in the absence of diagnostic or disease severity biomarkers.
- Search for and define more objective biological measures of migraine attack phases, in the premonitory (prodrome), aura, headache, postdrome, and interictal phases, including questionnaires, biomarkers (blood-based, imaging, tissue, genetic, other omics), and technology-based assessments (e.g., digital, electrophysiological, imaging).
- Reappraise the classification and diagnostic criteria of all migraine subtypes and identify new methods for improved recognition and diagnosis in different clinical settings.
- Establish a biobank for biomarker analysis including genetic, epigenetic, proteomic, transcriptomic, exposomic, metabolomic, microbiome, and treatment response analyses, and collaborate with industry to gain access to clinical trial databases and tissue samples.
- Prioritize research involving the epidemiology, diagnosis, management, prognosis, and outcomes associated with primary and secondary headaches and identify factors that predict headache persistence even after the triggering event (e.g., traumatic brain injury, arterial dissection) has resolved.

Ten-Year Milestones:

- Harmonize regional and global headache registries to enhance collaboration across borders, enlarge sample sizes, and ensure the inclusion of evidence- and consensus-based tools and questionnaires (e.g., NINDS Common Data Elements).[16]
- Analyze the natural history and prognosis of those treated early in the course of their disease versus those who have a long duration of disease before treatment.
- Analyze long-term outcomes in people managed with over-the-counter medications versus prescription medications.

Research Priority #2: Move the migraine field toward personalized medicine by identifying predictors of treatment response, treatment adverse events, and treatment adherence. This is founded in the concept that in migraine there are different endophenotypes and pathophysiologies, and we need to connect biomarkers to clinical phenotypes and treatment response.[17,18]

Acute treatment does not currently account for the possibility of sexual dimorphism, predictive clinical factors, or predictive biological features. Selection of preventive treatments among evidence-based therapies is based on monthly headache day frequency, comorbidities, preferences regarding side effect profiles, and reimbursement. However, treatment choice does not consider person-level factors that predict treatment response based on symptom profiles or biology; this is essential for the development of precision and personalized medicine.

Five-Year Milestones:

- Identify patient-centered definitions of treatment response (acute/preventive) including the development of composite endpoints that can be utilized and validated in clinical trials.
- Define treatment refractoriness, especially for clinical trials evaluating more invasive treatments.
- Define the role of feedback systems (e.g., digital) that will drive improvement in acute and preventive treatment (e.g., monitoring of acute drug intake and warning if thresholds are exceeded).

Ten-Year Milestones:

- Develop algorithms that identify the optimal treatment for an individual patient based on clinical and biological features and that allow for early identification and discontinuation of ineffective preventive treatment based on patient report and/or feedback from electronic diary or wearable/nearable/interactive sensor technology.
- Identify personalized predictors of attacks (e.g., changes in heart rate variability, body temperature), adverse events (risk score), and response to headache treatments, including clinical endophenotypes and biomarkers (omics).

Research Priority #3: Validate short- and long-term outcome measures developed in Research Priority #2 through rigorous, prospective, international, longitudinal real-world studies. Define a range of meaningful treatment outcomes that extend beyond headache and capture the range of symptoms that disable people with migraine. Utilize simple and composite clinical trial outcomes that are applied to clinical practice.[19–22]

In clinical research we use simple outcome measures. For example, in migraine studies, acute treatment trials often use absence or reduction of pain at 2 and 24 h, while preventive treatment trials might use a ≥ 50% reduction in headache days or migraine days. However, there may be other important measures to take into consideration, such as intensity and duration of pain and other associated symptoms, as well as symptoms that may occur outside of the headache phase of an attack (e.g., prodrome, aura, postdrome, and interictal phase). Regarding adverse events, a more careful and standardized approach to the elicitation of side effects and adverse events should be implemented to account for the presence/absence of comorbid diseases (e.g., constipation in a patient with comorbid irritable bowel syndrome, mood change in a patient with concomitant depression).

Five-Year Milestones:

- Create an international multistakeholder working group to help define meaningful outcome measures for acute and preventive treatments.
- Develop clinically relevant endpoints that are feasible to use in practice and that capture symptoms relevant to patients and to migraine subtypes (e.g., cognitive, fatigue, sensory/motor function, autonomic, gastrointestinal, vestibular) and correlate with biomarker data when possible and applicable. This should include data from wearable, nearable, and interactive technologies.
- Create patient-reported outcome measures for migraine in the workplace and perform cost-effectiveness research on treatments from a workplace perspective.

Ten-Year Milestones:

- Develop composite measures that capture symptoms and burden associated with all phases of an attack as well as the interictal phase and correlate with biomarker data when possible and applicable.
- Conduct behavior change research to identify optimal approaches to enhance wellness, resilience, and adoption/adherence with disease-modifiable behaviors.
- Develop criteria and endpoints for less commonly studied subtypes of migraine (e.g., vestibular, abdominal) and other headache types.

Treatment

Research Priority #1: Develop human platform screening methods for small molecules to identify drugs that hit specified molecular targets. Develop screening platforms for devices to clarify the mechanisms of existing devices, and improve their efficacy through optimization of stimulation parameters, and to assess new devices.

Platform screening methodologies provide a bridge from targets identified in the basic science phase to molecules that can be tested in humans with headache disorders.

Five-Year Milestones:

- Identify novel molecular targets and a corresponding platform screening methodology that is suitable for identifying drugs that have the appropriate agonist and antagonist properties at the molecular target.
- Identify physiological models that can be used to test the mechanism of action of neuromodulatory devices.

Ten-Year Milestones:

- Test platform screening methodology for novel molecular targets and refine as needed.
- Test physiological models for neuromodulation devices and refine as needed.

Research Priority #2: **Develop and evaluate novel treatment paradigms**.

While new acute and preventive treatments need to be studied in current treatment paradigms (acute and preventive monotherapy), combination treatment is widely employed in some countries.[23–28] We need a broader range of studies to establish the utility of, and optimal approaches to combining more than one acute treatment, more than one preventive treatment, and acute with preventive treatments (e.g., sequential multiple assignment randomized trial [SMART] designs). We also need to address a broader range of patient-centered treatment goals. The list below offers a range of important measures that the working group has prioritized as needing further investigation.

a. Preventing progression from episodic migraine to more severe states (chronic migraine, continuous headache, or other states).
b. Designing treatments to reduce the overuse of opioids, barbiturates, and other acute treatment.
c. Identifying and managing triggers.
d. Treating, pre-emptively, predictable attacks including short-term prevention of menstrual migraine and models to predict attacks, such as sensors/algorithms/artificial intelligence, to prevent (or treat very early) in the attack.
e. Combining preventive treatments.
f. Combining acute treatments.
g. Combining acute and preventive treatments.
h. Combining drugs and devices.
i. Combining behavioral approaches with other preventive treatments.
j. Designing comparative effectiveness studies contrasting drugs, devices, behavioral treatments, and strategies of care.
k. Targeting migraine and comorbidities with unimodal or multimodal treatment (to demonstrate efficacy in subgroups and to determine if the comorbidity improves).
l. Implementing guideline-based care.
m. Optimizing strategies for combining pharmacological and behavioral treatments.
n. Developing lifestyle interventions (exercise optimization, physical therapy, diet, sleep, etc.).

These novel paradigms of treatment largely emerge from observations in clinical practice and epidemiological research. For example, we know that a substantial proportion of people with episodic migraine progress to chronic migraine. We know many risk factors that increase the probability of progression. For the most part, we do not know if risk factor modification or preventive treatment reduces the risk of progression.

Five-Year Milestones:

- Select and prioritize several novel treatment strategies (preventing progression, combining preventive treatments).
- Review literature on these novel strategies and develop protocol skeletons including eligibility criteria, primary and secondary outcomes, and statistical analysis plans with sample size calculations.

Ten-Year Milestones:

- Initiate a trial that includes a novel trial design to answer a key question in migraine management.

Research Priority #3: Develop novel patient-centered outcomes for migraine and other headaches and identify patient groups with high treatment needs.

Clinical trial outcomes have focused on reduction of headache days and pain freedom and relief along with reduction of migraine-associated symptoms. In clinical practice, these endpoints may not optimally meet the needs of clinicians and patients as they work together to identify the best treatment options or strategies.[21,22] Enrichment designs, personalized medicine approaches (based on individual patient needs and their migraine characteristics), and definition of outcomes that are most meaningful to patients are needed. Studies should include patient groups often not included in headache clinical trials. Some areas of unmet need include:

a. Multiple attack studies in episodic headache disorders to assess within-person consistency of treatment effects.[29]
b. Continuous headache disorders, which are usually excluded from randomized trials.
c. Secondary headache disorders.
d. Designs and outcomes for the paradigms in Research Priority #2.
e. Trials in special high-need populations: refractory headache, continuous headache, multiple pain comorbidities.
f. For rare headaches, improved methods for recruiting and enrolling.

Novel patient-centered outcomes will allow for improved measurement of the benefits of treatment and its risks. Including groups with special treatment needs will improve the personalization of therapy. These priorities apply to clinical science and clinical practice.

Five-Year Milestones:

- Plan enrichment trials using genetic or clinical covariates that predict treatment response.

Ten-Year Milestones:

- Launch acute or preventive trials using an enrichment design and a treatment postulated to have special benefits in the eligible population.
- Use novel secondary endpoints that highlight the benefits of treatment.

Research Priority #4: Test non-pharmacological interventions including studies focused on communication, digital intervention, patient and provider communication/collaboration and goal setting, and education focused on reduction of stigma and how this may impact the provider and patient communication.[30]

a. Behavioral
b. Neuromodulation
c. Phytotherapy
d. Diet/nutrition
e. App-based therapies/digital therapeutics[31]
f. Adherence interventions versus persistence
g. Communication studies across the spectrum of treatment
h. Education of providers and patients. Interventions to reduce stigma, enhance assessment of adherence/persistence. Collaborative setting of treatment goals and expectations.[32,33]

The management of headache disorders includes many non-pharmacologic interventions, some of which are increasingly evidence based. A comprehensive approach to management requires utilization of non-pharmacologic strategies.

Five-Year Milestones:

- Identify a prioritized non-pharmacologic intervention based on existing literature.
- Develop a randomized trial protocol that tests the efficacy, safety, and dose requirements of the intervention.

Ten-Year Milestones:

- Launch a randomized trial that tests the efficacy, safety, and dose requirements of the non-pharmacologic intervention that was prioritized based on review of the existing literature.

Inequities and disparities

Research Priority #1: Identify and detect disparities in headache health, headache care, and headache research (including clinical trials) and examine how underlying individual, provider, and system-level and/or organizational factors influence these disparities.[34,35]

First, we must understand the *scope* of the problem of disparities in headache medicine. We need to clarify whether there are true differences in the epidemiology of headache diseases across different socioeconomic, racial, and ethnic groups, or just differences in reporting and diagnosis.[36–39] We need to understand whether different groups seek and receive care for headache in different ways, and if patient or socioeconomic characteristics affect the impact of headache diseases.[40–42] We should explore whether providers of headache care reflect the backgrounds of the patients seeking care, and whether reflective representation and/or social concordance matter in headache disparities, headache research, and/or the headache health outcomes of disparate populations.[43–47] When possible, studies to address Research Priority #1 should include key stakeholders such as patients, enrolled research participants, and individuals who chose not to enroll in a research study.

Five-Year Milestones:

- Identify and define all disparate and/or underserved populations in headache medicine.
- Identify and define gaps in quality of and access to care in headache medicine.
- Identify underrepresented clinical providers and the scope of their involvement in headache medicine (i.e., clinical, academic, research, positions of leadership within headache organizations) as well as identify the impact of these providers with relation to geographic areas with patients of diverse backgrounds.

- Identify the breadth and impact of the dearth of underrepresented in medicine researchers and research participants.

Ten-Year Milestones:

- Identify reasons for patient preferences of care, including those that reflect deeply held religious and cultural beliefs as well as other beliefs, by and about such populations by the health-care system as a whole.
- Identify and define clinical care gaps and disparities rooted in modifiable barriers (such as unequal access to health-care information, low health literacy, disparate access to and/or ability to attend follow-up visits, or popular health myths).

Research Priority #2: Identify the potential determinants of gaps in health or health outcomes among disparate groups in headache medicine, which in turn can inform interventions that reduce or eliminate these differences.

Next, we must understand *why* these disparities exist, clarifying what structural, societal, and personal characteristics affect the development and diagnosis of headache diseases; what barriers affect the ability to attain successful treatment; what societal factors affect the disability caused by headache diseases; and how mismatch between provider–patient and researcher–participant cultural experiences affect care.[48] When we understand these differences, we should explore how to use the knowledge to improve care. When possible, studies to address Research Priority #2 should include key stakeholders such as patients, enrolled research participants, and individuals who chose not to enroll in a research study.

Five-Year Milestones:

- Understand the root causes of patient preferences to assist in determining the appropriateness of an intervention (both clinical and research).
- Identify how the structure of headache medicine and headache research (such as trial requirements, inclusion/exclusion criteria) may bias against the inclusion of underrepresented in medicine researchers and research participants.

Ten-Year Milestones:

- Understand how individual factors (e.g., race/ethnicity, age, culture, education, socioeconomic status, sexual orientation, gender/gender identity, comorbid conditions, etc.), provider factors (e.g., stereotypes, biases, culture, communication, etc.), system-level factors (e.g., discrimination, racism, sexism, stigma, etc.), and organizational factors (e.g., geography, continuity, availability and comprehensiveness of services delivered, leadership, staff/faculty, organizational culture, knowledge, etc.) are important in the origins of headache health disparities.
- Understand the principles of intersectionality (including but not limited to race, ethnicity, gender/gender identity, sexual orientation, age, disability, and religion) and their critical relationship in headache health and headache care disparities.

Research Priority #3: Development and implementation of interventions that reduce or eliminate disparities in headache health, headache care, and headache research.

When we understand the disparities, and why they exist, we need to test interventions to address them. Initially, these would be research studies (single and/or multi-site), but if proven successful, these strategies should be implemented broadly utilizing methods of implementation science, quality improvement, and policy efforts. Ultimately, these interventions will be validated and refined in multicenter studies, then implemented into the health-care system and supported and/or reinforced by stakeholders via updates to policies and public health campaigns; payors via coverage for the interventions; providers via education, care management, protocols, and best practices. When possible, studies to address Research Priority #3 should include key stakeholders such as patients, enrolled and non-enrolled research participants, and relevant policy leaders, from study planning through interpretation of findings.

Five-Year Milestones:

- Using the findings from Research Priority #2, interventions will be designed and tested to reduce or eliminate disparities by targeting individual, provider, and/or system-level factors. Research will utilize state-of-the-art methods of implementation among specific disparate groups (e.g., community-based settings, convenient times, allowance for consumer choice). Successful interventions will be tested in increasingly larger contexts. Interventions addressing already-demonstrated inequities with known causes may be completed in 3–5 years, though interventions based on new findings from Research Priority #2 might take 6–10 years.

Ten-Year Milestones:

- Widespread dissemination of effective strategies, customizing and adapting interventions for disparate groups, and ensuring adequate resources and technical assistance for the evaluation (systematic collection and analysis of information on all aspects of the program used to assess the impact of demonstration programs that involve multilevel interventions).

Research workforce development

Research Priority #1: Develop a pipeline.

Increasing the number of clinicians and scientists in training who have experience in headache science is a key starting priority. Many specialties and types of scientists can enter the headache field because headache medicine is not focused in one area. Neurology and other residents (primary care, anesthesia, obstetrics and gynecology, pediatrics, physical medicine and rehabilitation, emergency medicine, etc.), and social, psychological, behavioral, and basic

science trainees and degree candidates need to be aware of clinical/epidemiological, translational, psychological and behavioral, social, and basic science headache research projects. It is also uncommon for MD, MPH, PhD, EdD, PsyD, DPT, DNP, and other advanced degree students to have research interests in headache science, and we must explore and resolve how to promote its development. We need to increase the entry points to headache medicine at all levels—medical, MPH, and PhD students, residents, fellows, post-docs.[49–51] Funding mechanisms must be identified for established researchers in neighboring fields (e.g., otolaryngology, anesthesia, ophthalmology, obstetrics and gynecology, pediatrics, psychiatry, emergency medicine, behavioral medicine, psychology, sociology, social scientists) to engage in headache research. We must stress to department chairs and other leaders the importance of protected time to do headache research.

Five-Year Milestones:

- Launch a campaign to provide early stage (undergraduate, graduate, and pre-clinical) research fellowships, internships, and other education and training opportunities and experiences.[52]
- Facilitate communication between existing headache scientists with chairs of departments with neuroscience, psychology, and social science–related PhD programs, with various clinical department leadership, and residency program directors about availability of research projects.[53]
- Increase attendance and participation in meetings that focus on mentoring junior clinicians, researchers, and basic scientists in headache medicine and promote research, mentorship, and training opportunities.[54]
- Promote diversity in our pipeline by actively recruiting underrepresented populations. We need diversity in leadership, researchers, and trainees.
- Communicate the existence of headache research training grants, including those funded by federal entities, foundations, societies, organizations, and industry.
- Perform a study to understand why individuals come into the headache field, why they stay, and why they leave.

Ten-Year Milestones:

- Increase the number of MD, PhD, EdD, PsyD, and related advanced degrees (including Medical Scientist Training Program), master's degree students including MPH students, and advanced practice provider students seeking doctoral degrees who participate in headache science projects for their thesis/dissertation or other research project.
- Increase the number of headache fellowships and post-docs with a focus on research.

Research Priority #2: Develop a collaborative network.

Development and expansion of the headache research workforce through increasing collaboration and mentorship of researchers inside and outside the field of headache will be important; this can be achieved by creating a network of basic and translational science researchers in headache. To fully address rare headaches, national and international collaborations are likely needed. Many specialties in science could participate in headache research. We need to increase integration with other disciplines such as neuroimmunology, neurophysiology, non-neuronal cell biology, and pain pathway scientists. Given the high prevalence of migraine comorbidities, collaboration with clinicians and scientists in non-neurology fields (such as psychiatry, psychology, cardiology, rheumatology, ophthalmology, anesthesia, obstetrics and gynecology, hematology, otolaryngology) can be particularly useful for the study of headache disorders.

We need a single directory of headache science researchers who are accessible to undergraduate and graduate students as well as other scientists in headache medicine. We need to identify new researchers in the field of headache, including those coming from other research fields.

Five-Year Milestones:

- Establish a directory in a highly visible, easily accessible place, such as with medical societies and other places where headache researchers may be.
- Provide links to funding opportunities in a central location, such as headache society websites.
- Work with other groups and research organizations to create a cadre of researchers interested in headache science.
- Establish a central clearinghouse of mentors with different areas of expertise and promote diverse backgrounds coming together for research.
- Promote headache research that can "hook" individuals in other fields into the excitement of headache research.

Ten-Year Milestones:

- Identify mentor–mentee relationships by surveying organizations dedicated to headache medicine, including those facilitated by the workforce development program.[54,55]
- Launch a clinical trial consortium for the headache field.[56]

Research Priority #3: Provide funding and education.

Providing funding for headache research and education for trainees, clinicians, and basic scientists is essential. We need funding programs and mechanisms to promote early and mid-career development and grant writing to be competitive for applying for funded research awards and philanthropy. We need to train researchers to write high-priority and high-quality grant applications.

Five-Year Milestones:

- Launch a campaign to attract philanthropy and industry support for more research awards for early career development of headache scientists and for established scientists not primarily in the headache field but well-equipped to apply their expertise and mentorship to headache science.

- Establish a philanthropic mechanism within organizations that can support headache research and engage potential donors.[57]
- Increase research funding opportunities for mid-career headache researchers.[58,59]

Ten-Year Milestones:

- Develop a grant writing academy for mentorship on submitting high-quality fundable grants (education on grant writing, design and statistics, and grant review) with funding to support the mentorship (protected time for mentorship).[60]
- Increase the number of headache researchers who obtained career development research awards and R01 or equivalent grants.

Quality of life

Research Priority #1: Expand the behavioral headache medicine research workforce.

To achieve Research Priorities #2 and 3 (below), the headache medicine research workforce will need to expand. It is essential that scientists from a variety of disciplines (e.g., physicians, psychologists and other behavioral and mental health–care providers, allied health professionals like advanced practice providers, physical and occupational therapists, nutrition scientists, social scientists, and others) are attracted to the field of headache medicine, and that training, mentorship, and support are accessible to begin and sustain research careers in this area. This need is particularly acute for mid-career investigators, especially among women at this career stage. There are opportunities to develop infrastructure to support investigators at every career stage.

Five-Year Milestones:

- Identify high-priority gaps in the behavioral headache medicine research workforce pipeline across career stages and demographic groups.
- Establish infrastructure to support the pipeline of future headache researchers in quality of life (QOL).

Ten-Year Milestones:

- Develop strategies to grow the behavioral headache medicine workforce and to sustain these investments with attention to high-priority career stages and demographic groups, and systematically evaluate the success of these initiatives.
- Establish a model to support the research pipeline at every career stage. These programs should be supported by data on grant submissions, successes of grant awardees, and prioritized relative to identified gaps in knowledge to address headache disease burden.

Research Priority #2: Develop and test interventions designed to improve the QOL of people living with headache diseases.

It is important to people living with headache diseases, as well as clinicians, scientists, and payers, that interventions, including non-pharmacological and behavioral treatments, enhance QOL and reduce disability. Research should span from mechanistic studies to implementation projects to real-world evidence gathering, and the increasing use of technology should be leveraged to increase accessibility and reduce costs. These interventions must be designed within a structural competency framework, so that they may be effectively delivered to a range of patient populations taking into consideration variables of diversity such as age, sex, race, ethnicity, language, culture, religion, physical and/or mental abilities or impairments, and other contextual variables.[61,62]

Five-Year Milestones:

- Invest in discovery and mechanistic trials to elucidate how non-pharmacologic interventions improve QOL and other outcomes for patients.
- Develop a pipeline of well-powered phase 2 clinical trials to answer questions about required behavioral treatment components, dose, and subgroups to optimize the effectiveness of existing behavioral interventions targeting migraine and other headache diseases.
- Support the development and testing of technology-mediated treatment delivery modalities, including telehealth, web-based, app-based, virtual, and wearable technology.

Ten-Year Milestones:

- Invest in establishing the efficacy of well-established behavioral interventions and mindfulness-based interventions through fully powered phase 3 clinical trials.
- Conduct phase 2 trials necessary to identify promising interventions and evaluate required components and dose for less well-established behavioral interventions including physical activity and diet. Engage researchers with expertise in these disciplines to conduct headache research.
- Evaluate behavioral interventions to improve QOL in non-migraine headache disorders including tension type headache, post-traumatic headache, medication overuse headache, and cluster headache.
- Use adaptive intervention designs (Multiphase Optimization Strategy, SMART) to understand the effects of order and combination of behavioral, other non-pharmacological, and pharmacotherapy interventions to maximize patient QOL outcomes.

Research Priority #3: Develop a foundational understanding of the dynamic interactions between people with headache diseases and the individual, interpersonal, and social-ecological contexts that impact their QOL, headache experiences, and treatment responsiveness.

Foundational knowledge is necessary to understand what QOL entails for people living with headache diseases (i.e., what is important to patients and families) and then develop metrics that

capture these constructs with a high level of reliability, validity, sensitivity, and manageable assessment burden. Studies need to be conducted across the life span and must consider individual (e.g., age, headache type, mental health comorbidities, psychological resilience, lifestyle factors), interpersonal (e.g., interactions with caregivers, partners, children, employers, experiences of stigma and discrimination), and social-ecological contexts (e.g., race, ethnicity, gender identity, education level, income, employment status, insurance status, health-care access, disability status, language, acculturation, geographic region), as well as constructs including stigma that may span more than one target area.[61] Achieving this in a way that is robust and relevant to real-world patients and providers requires the use of a variety of methods/approaches including, but not limited to, embedding headache questions and QOL questions in population epidemiological studies, qualitative research and mixed methods approaches, longitudinal investigations across the lifespan, and diary/ecological momentary assessment/behavioral assessment studies leveraging technology.[63,64]

Five-Year Milestones:

- Identify which QOL areas matter most to patients through qualitative and mixed methods research and identify gaps between existing patient-reported outcome measures and patient-supported QOL areas.
- Identify individual, interpersonal, and/or social-ecological contexts (as defined above) that may moderate or mediate QOL for individuals with headache diseases. To achieve this, headache criteria and QOL questions can be embedded in large-scale epidemiologic studies. Longitudinal investigators that use micro- and macro-level methodologic approaches (e.g., intensive daily diary designs) should also be supported to examine concurrent and prospective inter-relationships among headache symptomatology, QOL, and candidate individual, interpersonal, and/or social-ecological moderators/mediators.

Ten-Year Milestones:

- Develop and test psychosocial interventions for improved QOL outcomes that leverage data identifying candidate individual, interpersonal, and/or social-ecological moderators/mediators of QOL and headache experiences.
- Identify, modify, or develop a core set of QOL patient-reported outcome measures that address patient-supported QOL domains validated by both state-of-the-art qualitative methods and psychometric methods. Establish that the patient-reported outcome measures are appropriate across a diverse range of individuals (e.g., race/ethnicity, gender, sexual orientation, age [child, adolescent, adult]) and can be used in a variety of research settings (e.g., clinical trials, epidemiological studies, daily diary studies).[21,22,65]
- Develop and apply novel methodological approaches for combining multiple independent headache-related datasets (raw patient-level data) to help build cumulative knowledge. Develop a core set of psychometrically robust QOL patient-reported outcome measures with input from people living with migraine and methodology guidelines for research to facilitate cross-collaborations, data aggregation/synthesis, and comparisons across research settings.

DISCUSSION

The headache research priorities described in this report are meant to help guide and focus headache research conducted within the next 10 years (Table 1). They are designed to encompass broad themes without overly restricting or dictating specific avenues of inquiry, yet they offer sufficient focus to provide tangible guidance. The milestones associated with each priority can serve as a "scorecard," allowing for assessment of research progress over time. Periodic reviews will be conducted to assess the relevance of these priorities and determine if revisions are necessary. These research priorities were identified according to current knowledge and opinions, realizing that as knowledge progresses, opinions about areas that should be prioritized will evolve. Innovation and novelty in headache research are essential. The expectation is that this set of research priorities is the first of several iterations to come.

There are several themes included in these research priorities, including the need for:

- More collaboration among research teams and individuals representing different stakeholder groups.
- Optimization, standardization, replication, and validation of research methods and models.
- Forward and reverse translation between animal and human research.
- Investigation of pain and non-pain symptoms associated with headache disorders.
- Investigation of different phases of headache attacks, including but not limited to, factors that initiate, sustain, and stop individual headache episodes.
- Identification of factors that contribute to and models that predict persistence and chronification of headache disorders, improvement or resolution of headache disorders, and treatment responses.
- Development and use of outcome measures that better reflect the total burden of headache disorders including the pain symptoms, non-pain symptoms, and ictal and interictal manifestations.
- Improved description of how currently available treatments exert their effects, identification of targets for new treatments, and investigation of optimal treatment strategies.
- Identification of disparities, understanding of why they exist, and identification of interventions to address these disparities in the headache field.
- Attraction and support of new and existing researchers from a variety of medical, psychological, behavioral, and social fields and

TABLE 1 Overview of the headache research global priorities.

Topic	Research priorities
Human models	• Identify and understand molecular signaling pathways that contribute to and are associated with the development of headache disorders, initiation of headache episodes, and evolution of headache disorders • Identify and understand alterations in biochemistry that contribute to and are associated with the development of headache disorders, initiation of headache episodes, and evolution of headache disorders • Identify and understand alterations in brain structure and function that are associated with the development of headache disorders, initiation of headache episodes, and evolution of headache disorders • Improve translation and integration between experimental human models of headache with spontaneous episodes of headache
Animal models	• Refine and validate existing animal models for headache disorders and develop new models where gaps in validation or translation exist • Encourage collaborative research that enables different investigators with specific expertise and experience with different animal models/readouts to achieve synergistic results that will lead to advances in the understanding and treatment of headache disorders
Pathophysiology	• Determine the underlying pathophysiology of the non-pain symptoms of migraine and other primary and secondary headache disorders • Expand knowledge into the pathophysiology of head pain in migraine and other primary and secondary headache disorders • Identify and characterize genetic and epigenetic factors that influence the pathophysiology and treatment of migraine and other primary and secondary headache disorders
Diagnosis and management	• Better understand the evolution of migraine, risk factors for chronification, and factors which predict improvement and remission by performing longitudinal studies in people with migraine with detailed phenotypic questionnaires that collect information and outcome measures regarding clinical course and comorbidities • Move the migraine field toward personalized medicine by identifying predictors of treatment response, treatment adverse events, and treatment adherence • Validate short- and long-term outcome measures developed in Research Priority #2 through rigorous, prospective, international, longitudinal real-world studies • Define a range of meaningful treatment outcomes that extend beyond headache and capture the range of symptoms that disable people with migraine • Utilize simple and composite clinical trial outcomes that are applied to clinical practice
Treatment	• Develop human platform screening methods for small molecules to identify drugs that hit specified molecular targets • Develop screening platforms for devices to clarify the mechanisms of existing devices and improve their efficacy through optimization of stimulation parameters, and to assess new devices • Develop and evaluate novel treatment paradigms • Develop novel patient-centered outcomes for migraine and other headaches and identify patient groups with high treatment needs • Test non-pharmacological interventions including studies focused on communication, digital intervention, patient and provider communication/collaboration and goal setting, and education focused on reduction of stigma and how this may impact the provider and patient communication
Inequities and disparities	• Identify and detect disparities in headache health, headache care, and headache research (including clinical trials) and examine how underlying individual, provider, and system-level and/or organizational factors influence these disparities • Identify the potential determinants of gaps in health or health outcomes between disparate groups in headache medicine, which in turn can inform interventions that reduce or eliminate these differences • Develop and implement interventions that reduce or eliminate disparities in headache health, headache care, and headache research
Research workforce development	• Increase the number of clinicians and scientists in training who have experience in headache science (i.e., "pipeline development") • Develop a network for collaboration and mentorship • Increase funding and educational opportunities for headache research
Quality of life	• Expand the behavioral headache medicine research workforce • Develop and test interventions designed to improve the quality of life of people living with headache diseases • Develop a foundational understanding of the dynamic interactions between people with headache diseases and the individual, interpersonal, and social-ecological contexts that impact their quality of life, headache experiences, and treatment responsiveness

backgrounds; a range of degree types and specialties; and a range of personal variables to foster diversity and strength in the headache scientific workforce.

To achieve these goals, continued growth in the headache field is needed, including the need for more headache scientists,

clinicians, and patient stakeholders, along with greater financial investment. Establishing cooperative groups and infrastructure that facilitates collaborative research and data sharing would also support attainment of these goals. To promote diagnostic standardization in human studies, investigators are encouraged to use the current edition of the International Classification of Headache Disorders and its updates, or provide sufficient clinical data to map onto, or resolve why such definitions are not being used.[66,67]

It is hoped these research priorities will provide guidance when ideating about and preparing new research proposals and will be helpful when submitting manuscripts for publication.[68] Studies that adequately help to address these research priorities, which were identified by a multistakeholder group of experts from around the world, should be considered highly significant by those evaluating research proposals and manuscripts. This does not imply that research proposals and manuscripts addressing topics that are not included in this version of the research priorities should be deemphasized, as it is likely that some important topics were unintentionally excluded from this version.

There are many strengths regarding the process by which these research priorities were developed. There was a well-defined organizational and leadership structure including the organizing and executive committees, working group chairs, and working group members. There was intentional effort to involve a diverse group of individuals in the identification of the research priorities, including, but not limited to, diversity in geographical location, stakeholder group (e.g., person with headache, clinician, pre-clinical scientist, clinical scientist, organizational representative, etc.), scientific viewpoint, and demographics. There was ample opportunity for public review and feedback, and all feedback was considered point by point for incorporation by the working groups. Of course, there are potential limitations of these research priorities. Perhaps the greatest limitation is that the identification of priorities was ultimately subjective, based on the opinions of those involved with their development and review and according to current knowledge. Although the priorities are intentionally broad, some will inherently exclude certain aspects that might be of highest priority to some individuals. For example, it might be that a research priority has emphasized migraine at the exclusion of another headache type. Although this might be justifiable based on the high population prevalence of migraine and its substantial negative impacts, individuals with less common but severe and disabling headache conditions might prioritize their headache type over migraine. Furthermore, there are likely errors of omission in this first version of the research priorities, that is, areas or topics that simply were not considered during development of these priorities despite the importance of their inclusion. Finally, the identification of research priorities was inherently guided by current knowledge and experience, with some priorities building upon current research findings and methods. At the same time, it is essential that novel and innovative research also be prioritized. Fortunately, the expectation is that these headache research priorities will be updated over the coming years, with subsequent versions and improvements expected.

In conclusion, this inaugural iteration of the headache research priorities provides guidance to the research community that should lead to finding answers and solutions for the most pressing needs in the field. Ultimately, research efforts aligned with these priorities will lead to improvements in the health and lives of the billions of people around the world with headache.

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CONFLICT OF INTEREST STATEMENT

Todd J. Schwedt: Within the prior 36 months, TJS has received compensation for consulting from AbbVie, Allergan, Amgen, Axsome, Biodelivery Science, Biohaven, Click Therapeutics, Collegium, Eli Lilly, Ipsen, Linpharma, Lundbeck, Novartis, Satsuma, Scilex, Theranica, and Tonix. He has received royalties from UpToDate. He has stock options in Aural Analytics and Nocira. Research grant funding has been received from American Heart Association, Amgen, Henry Jackson Foundation, National Headache Foundation, National Institutes of Health, Patient Centered Outcomes Research Institute, Pfizer, and Spark Neuro. **Amynah A. Pradhan**: Within the prior 36 months AAP has received a research contract from Lundbeck and has consulted for Escient Pharmaceuticals. She also receives research funding from the National Institutes of Health and the Association of Migraine Disorders. **Michael L. Oshinsky** declares no conflicts of interest. The views expressed by MLO are his own and do not necessarily reflect those of the National Institutes of Health, the Department of Health and Human Services, or the United States government. MLO's role in the development of the headache research priorities was as member of the Organizing Committee, a member of the Research Workforce Development Workgroup, and a moderator for the IdeaScale campaign. **Mitchell F. Brin**: Employee of AbbVie and recipient of salary and stock for compensation. **Howard Rosen**: Holds stock in Amgen. **Nim Lalvani**: Consulting with AbbVie. **Andrew Charles:** Served as a compensated consultant for Amgen, eNeura, Lilly, Lundbeck, and Pfizer. He is the immediate past president of the American Headache Society. **Messoud Ashina**: Personal fees from AbbVie, Amgen, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Novartis, Pfizer, and Teva. MA participated in clinical trials as the principal investigator for AbbVie, Amgen, Eli Lilly, Lundbeck, Novartis, Pfizer, and Teva. MA received a research grant from Lundbeck Foundation, Novo Nordisk Foundation, and Novartis. MA has no ownership interest and does not own stocks of any pharmaceutical company. MA serves as associate editor of the *Journal of Headache and Pain*, and associate editor of *Brain*. **Thien Phu Do:** Within the prior 36 months, TPD has received personal fees from Teva. **Rami Burstein:** Research support from the NIH, AbbVie, Modulight, Eli Lilly, and Teva. Reviewer for NINDS, holds stock options in AllayLamp and Percep. Serves as consultant, advisory board member, or has received honoraria from Allergan, Amgen, Biohaven, Brise Mutual, CGRP diagnostic, Dr. Reddy's Laboratory, ElectroCore, Eli Lilly, Escient, Johnson & Johnson, Merck, NeuroRays, Pernix, Theranica, Teva, and Ventus. CME fees from Healthlogix, Medlogix, WebMD/Medscape, and Patents 9061025, 11732265.1, 10806890, US2021-0015908, WO21007165, US2021-0128724, WO21005497. Patents: 9061025: methods for selecting headache patients responsive to botulinum toxin therapy; 11732265.1: Method and compositions for the treatment of migraine headaches, endothelial dysfunction and muscle tenderness with statin and vitamin D; US 10,766,952 B2: Methods for selecting a headache patient responsive to treatment with an anti-CGRP antibody and for reducing headache frequency in the selected patients comprising administering an anti-CGRP antibody; 10806890: Method and apparatus for managing photophobia and migraine photophobia; US2021-0015908: Methods for treating and for inhibiting progression of seizures; WO21007165: Methods for treating and for inhibiting progression of seizures; US2021-0128724: CGRP antagonists and clostridial derivatives for the treatment of cortisol spreading depression associated disorders; WO21005497: CGRP antagonists and clostridial derivatives for the treatment of cortical spreading depression associated disorders. **Amy A. Gelfand**: In the last 24 months, Dr. Gelfand has received honoraria from UpToDate (for authorship) and

from the Taiwan Headache Society for speaking. She receives payment to her institution from the American Headache Society for her role as editor of *Headache*. She receives grant support from PCORI as a member of the Steering Committee for the REACH study. **David W. Dodick**: Within the prior 5 years (60 months): Consulting: Amgen, Atria, CapiThera Ltd., Cerecin, Ceruvia Lifesciences LLC, CoolTech, Ctrl M, Allergan, AbbVie, Biohaven, GlaxoSmithKline, Halion, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Genentech, Nocira, Perfood, Praxis, AYYA Biosciences, Revance, Pfizer. Honoraria: American Academy of Neurology, Headache Cooperative of the Pacific, Headache Cooperative of New England, Canadian Headache Society, MF Med Ed Research, Biopharm Communications, CEA Group Holding Company (Clinical Education Alliance LLC), Teva (speaking), Amgen Japan (speaking), Eli Lilly Canada (speaking), Lundbeck (speaking), Pfizer (speaking), Vector Psychometric Group, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, Medica Communications LLC, MJH Lifesciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press. Non-profit board membership: American Brain Foundation, American Migraine Foundation, ONE Neurology, Precon Health Foundation, International Headache Society Global Patient Advocacy Coalition, Atria Health Collaborative, Atria Academy of Science and Medicine, Arizona Brain Injury Alliance, Domestic Violence HOPE Foundation/Panfila, CSF Leak Foundation. Research support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Henry Jackson Foundation, Patient Centered Outcomes Research Institute (PCORI). Stock options/shareholder/patents/board of directors: Ctrl M (options), Aural analytics (options), Axon Therapeutics, ExSano (options), Palion (options), Man and Science, Healint (options), Theranica (options), Second Opinion/Mobile Health (options), Epien (options), Nocira (options), Matterhorn (shares), Ontologics (shares), King-Devick Technologies (options/board), Precon Health (options/board), ScotiaLyfe (Board), EigenLyfe (Options Board), AYYA Biosciences (options), Axon Therapeutics (options/board), Cephalgia Group (options/board), Atria Health (options/employee). Patent 17189376.1-1466:vTitle: Onabotulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis (Non-royalty bearing). Patent application submitted: Synaquell® (Precon Health). **Patricia Pozo-Rosich**: Within the prior 36 months, honoraria as a consultant and speaker for: AbbVie, Almirall, Eli Lilly, Lundbeck, Novartis, Pfizer, and Teva. Her research group has received research grants from AbbVie, Novartis, and Teva, as well as Instituto Salud Carlos III, Ministerio Ciencia e Innovación—Proyectos Medicina Personalizada, EraNet Neuron, European Regional Development Fund (001-P-001682) under the framework of the FEDER Operative Program for Catalunya 2014-2020—RIS3CAT. PPR has received funding for clinical trials from AbbVie, Amgen, Biohaven, Eli Lilly, Lundbeck, Pfizer, Teva. She is the Honorary Secretary of the International Headache Society. She is on the editorial board of *Revista de Neurologia*. She is an associate editor for *Cephalalgia*, *Headache*, *Neurologia*, *The Journal of Headache and Pain*, and *Frontiers of Neurology*. She is a member of the Clinical Trials Guidelines Committee of the International Headache Society. She has edited the Guidelines for the Diagnosis and Treatment of Headache of the Spanish Neurological Society. She is the founder of www.midolordecabeza.org. PPR does not own stocks from any pharmaceutical company. **Richard B. Lipton**: Has received research support from the National Institutes of Health, the FDA, and the National Headache Foundation. He serves as consultant, advisory board member, or has received honoraria or research support from AbbVie/Allergan, Amgen, Axon, Biohaven, Dr. Reddy's Laboratories (Promius), electroCore, Eli Lilly and Company, GlaxoSmithKline, Lilly, Lundbeck, Merck, Novartis, Pfizer, Teva, Vector, and Vedanta Research. He receives royalties from *Wolff's Headache*, *8th edition* (Oxford University Press, 2009) and Informa. He holds stock/options in Axon, Biohaven, Cooltech, and Mainistee. **Jessica Ailani**: Honoraria for independent consulting from AbbVie, Aeon, Eli Lilly and Company, electroCore, GlaxoSmithKline, Ipsen, Lundbeck, Satsuma, Neurolief, Gore, Theranica, Linpharma, Pfizer, Merz, Dr. Reddy, Scilex, Tonix, Teva; honoraria for editorial services from SELF (medical reviewer) and *Current Pain and Headache Reports*; clinical trial grants paid to Medstar Georgetown from Satsuma, Parema, Ipsen, and Lundbeck. **Christina L. Szperka**: Christina L. Szperka, MD, MSCE or her institution have received compensation for serving as a consultant for Abbie, Impel, and Teva. She has received personal compensation for serving on a data safety monitoring board for Eli Lilly and Upsher-Smith. She has also received research support from the NIH NINDS (K23NS102521), the International Headache Society, and PCORI. **Larry Charleston IV**: Has received personal compensation for serving as a consultant for Allergan/AbbVie, Amgen, Amneal, Aurene, Biohaven, Haleon, LinPharma, Pfizer, and Satsuma; is on the advisory panel for Mi-Helper Inc. (stock options); and received grant/research support from the Disparities in Headache Advisory Council and Amgen. He has received CME honoraria from American Headache Society, American Academy of Neurology, BrainWeekend, Migraine360 CME Program, NeurologyWeek, and the Primary Care Education Consortium. He receives a salary as faculty from Michigan State University College of Human Medicine and Thomas Jefferson University. He is a non-compensated associate editor for *Headache: The Journal of Head and Face Pain* and serves as a non-compensated Board of Directors as Treasurer/Secretary for the Clinical Neurological Society of America. **Kathleen B. Digre** declares no conflicts of interest; KBD is supported in part by an unrestricted grant to the Department of Ophthalmology and Visual Sciences from Research to Prevent Blindness, Inc., New York, NY, USA. **Andrew F. Russo**: Within the prior 36 months, AFR has served as a consultant for Lundbeck, AbbVie, Eli Lilly, and Schedule 1 Therapeutics and has received royalties from McGraw Hill. He has patents on uses of CGRP and PACAP from Lundbeck. Research grant funding has been received from the National Institutes of

Health, Department of Veterans Affairs, and Lundbeck. **Dawn C. Buse**: Within the prior 36 months, DCB has received compensation for consulting from AbbVie/Allergan, Amgen, Biohaven, Collegium, Eli Lilly, Lundbeck, Novartis, Satsuma, Teva, Theranica, and Tonix. Research grant funding has been received from Amgen, the Henry Jackson Foundation, National Headache Foundation, and the US Food and Drug Administration (FDA). **Scott W. Powers**: Within the past 36 months, institution (Cincinnati Children's Research Foundation) has received research support from the NIH, PCORI, and CF Foundation. SWP is a member of the Board of Trustees for the American Headache Society and serves as Associate Editor for the journal *Headache*; has provided research consultation to Theranica and received personal compensation. **Cristina Tassorelli**: Consulting: AbbVie, Biohaven, Dompé, Eli Lilly, Lundbeck, Medscape, Pfizer, Teva. Speaking honoraria: AbbVie, Eli Lilly, Lundbeck, Pfizer, Teva. Research grant funding: AbbVie. Non-profit board membership: European Academy of Neurology, Headache International Headache Society, Italian Society of Neurology. **Peter J. Goadsby:** Over the last 36 months, grants from Celgene and Kallyope, and personal fees from Aeon Biopharma, AbbVie, Amgen, Aurene, CoolTech LLC, Eli-Lilly and Company, Linpharma, Lundbeck, Pfizer, PureTech Health LLC, Satsuma, Shiratronics, Teva Pharmaceuticals, Tremeau, and Vial; personal fees for advice through Gerson Lehrman Group, Guidepoint, SAI Med Partners, Vector Metric; fees for educational materials from CME Outfitters and WebMD; and publishing royalties or fees from Massachusetts Medical Society, Oxford University Press, UpToDate and Wolters Kluwer, and a patent magnetic stimulation for headache (No. WO2016090333 A1) assigned to eNeura without fee.

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