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Are we closer to achieving precision medicine for migraine treatment? A narrative review

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Abstract

Background: The term 'precision medicine' encompasses strategies to optimize diagnosis and outcome prediction and to tailor treatment for individual patients, in consideration of their unique characteristics. The greater availability of multi-faceted datasets and strategies to model such data have made precision medicine increasingly possible in recent years. Precision medicine is especially needed in the migraine field since the response to migraine treatments is not universal amongst all individuals with migraine.

Objective: To provide a narrative review describing contributions to achieving precision medicine for migraine treatment.

Methods: A search of PubMed for English language articles of human participants published from 2005 to January 2024 was conducted to identify articles that reported research contributing to precision medicine for migraine treatment. The published literature was categorized and summarized according to the type of data that were included: clinical phenotypes, genomics, proteomics, physiologic measures, and brain imaging.

Results: Published studies have investigated characteristics associated with acute and preventive treatment responses, such as nonsteroidal anti-inflammatory drugs, triptans, onabotulinumtoxinA, and anti-calcitonin gene-related peptide

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monoclonal antibodies, in patients with episodic or chronic migraine. There is evidence that clinical, genetic, epigenetic, proteomic, physiologic, and brain imaging features might associate with migraine treatment outcomes, although inconsistencies for such findings clearly exist.

Conclusions: The published literature suggests that there are clinical and biological features which associate with, and might be useful for predicting, migraine treatment responses. To achieve precision medicine for migraine treatment, further research is needed that validates and expands on existing findings and tests the accuracy and value of migraine treatment prediction models in clinical settings.

Keywords

headache, migraine, precision medicine, genomics, proteomics, imaging, prediction, treatment, personalized medicine

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Introduction

Differences in genetic, epigenetic, biological, and environmental characteristics can influence the optimal treatment approach for individual patients. This understanding has led modern medicine to an era of 'precision medicine', which can be defined as 'a patient-centric vision with therapeutic choices driven by the identification of specific predictive biomarkers of response to avoid ineffective therapies and reduce adverse effects,' (1) or as 'providing the right treatment at the right time to the right person and taking into account patients' health history, genes, environments, and lifestyles' (2,3). The precision medicine approach goes beyond treating the disease and instead prioritizes treating the patient. Precision medicine aims to deliver comprehensive, personalized care tailored to the individual needs of each patient (4).

Adopting a precision medicine approach to migraine treatment could reduce the time required to find effective and tolerable treatment. Traditional approaches to migraine management have often relied on a one-size-fits-all model in which acute and preventive treatments are recommended based on knowledge obtained from large groups of people with migraine, such as cohorts enrolled into clinical trials. Although such data are essential for establishing the safety and efficacy of migraine treatments, they typically contribute little to determining which treatment is best suited for each individual patient. Introducing a precision medicine approach to migraine treatment would be a paradigm shift, addressing the unique aspects of each patient and their disease, and ultimately better alleviating migraine-associated burden (5–7).

Precision medicine in the context of migraine treatment might rely on a diverse array of data types that contribute to a more nuanced understanding of individual patient profiles. Clinical data, including medical history, comorbidities, ictal and interictal migraine characteristics, and prior treatment responses, might be vital for tailoring migraine treatment recommendations. Clinical data that could contribute to precision medicine might be captured through patient interviews, questionnaires, and migraine diaries. Genomic information is likely to be crucial for understanding migraine susceptibility, symptomology, and comorbidity with other traits and conditions (8). Genomic and epigenomic data are likely to be useful for understanding the risk of migraine progression and for selecting migraine therapies. Pharmacogenomic data, which investigates genetic variants impacting drug response, can help clinicians select amongst medications to reduce side effects and maximize treatment effectiveness (9). Measurement of blood or saliva biomarkers, such as ictal and interictal neuropeptides, may pave the way for selecting treatments that target the underlying pathophysiology of an individual person's migraine disease (10,11). Real-time monitoring of physiological parameters, made possible by collecting digital health data from wearables and mobile devices, potentially facilitates the objective measurement of migraine attack onset and resolution, appropriate timing of treatment administration, and responses to such treatments. Neuroimaging data, including structural and functional imaging, might identify specific brain regions involved in an individual's migraine pathophysiology and indicate the severity of migraine disease, potentially assisting with making treatment decisions (12). Machine learning and artificial intelligence algorithms can assist in evaluating large, multifaceted, complex datasets to develop predictive models for migraine treatment responses (13).

We hope that advances in precision medicine will transform migraine treatment from a one-size-fits-all approach to a more personalized and targeted strategy. Overall, precision medicine has the potential to revolutionize migraine therapy by allowing for the selection of specific treatments that are most likely to be effective for an individual patient.

Methods

Search strategy

PubMed was searched for English language articles of human participants published from 2005 to January 2024.

The titles, abstracts, and/or manuscripts were reviewed by each author group and those deemed to be original and most relevant to understanding progress made in achieving precision medicine for migraine treatment were selected for inclusion. Search terms are included in Online Supplement 1. For *phenotypic data* that might contribute to precision medicine in migraine treatment, 29 articles were identified. After reviewing all the abstracts, 23 were chosen for inclusion. One additional article (14), which was included in the reference list of another (15), was included given the relevance to precision medicine. For *genomics* and *other 'omics'*, 735 articles were identified and screened, and 105 and 480 articles were included and excluded, respectively. Review of the other 150 articles resulted in conflicting decisions regarding their inclusion, which was resolved by a third author; ultimately, 45 of these articles were included for full-text screening. In total, 150 articles were included in full-text screening and 31 articles that are relevant to this manuscript's topic were included. Six additional articles, included in the reference lists of the 31 articles, were also included. For *physiologic measures*, 24 articles were identified; after further review, 14 were chosen for inclusion. Three of these articles (15,–17) are discussed in the *phenotypic data* section. For *brain imaging*, 80 articles were identified, of which 11 articles were selected after review.

Results

Phenotypic data

Published studies have investigated patient and migraine characteristics associated with acute and preventive treatment responses (Table 1).

Acute treatment. Ezzati et al. analyzed data from 2224 participants with episodic migraine (EM) enrolled in the American Migraine Prevalence and Prevention (AMPP) (14) study to investigate predictors of treatment response to over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs), caffeine combination products, acetylsalicylic acid, and acetaminophen (14). The achievement of adequate pain freedom at 2 h was associated with a lower pre-treatment average headache pain intensity, lower Migraine Disability Assessment Scale (MIDAS) grade, less depression, and lower Migraine Symptom Severity Scale score. Another analysis of the AMPP study of 8233 individuals with EM revealed that a higher BMI was associated with inadequate 2-h pain-free response to acute medications, which was theorized to be due to a pro-inflammatory state associated with obesity, and consistent with another study focused on triptan response (23,24).

A prospective diary study in Italy collected data from three consecutive migraine attacks for which frovatriptan was used for acute treatment. Frovatriptan was found more likely to be effective in patients experiencing unilateral pain, phonophobia, cranial autonomic symptoms, and prodrome symptoms (18). A Japanese study of 60 patients with migraine found that older age and absence of periorbital/deep orbital pain were factors significantly associated with triptan response (19). Other potential predictors of response have been identified, including lower baseline pain severity as a predictor of sumatriptan response (20), no prior triptan use as a diclofenac potassium response predictor (21), and psychiatric characteristics as NSAID response predictors (22).

Furthermore, presence of allodynia symptoms, defined as the sensation of pain in response to a normally non-nociceptive stimulus, has been reported as a negative predictor of acute treatment efficacy (23,25); however, the results are not consistent, with another study reporting cutaneous allodynia as a positive predictor for response to NSAIDs (14).

Preventive treatment. Several studies have investigated the phenotypic predictors of the response to onabotulinumtoxinA (BoNT-A), with varying results. For example, medication overuse (MO) has been noted as both a positive (27) and negative predictor (26). A lower number of monthly headache days (MHD) (27) was considered a positive predictor of response, and longer duration (28) and depressive symptoms (26) were listed as negative predictors, but these findings were not reproduced in other reports. One study revealed that a combination of age at migraine onset, opioid use, anxiety, and MIDAS score, was significantly associated with BoNT-A response (29). Regarding the 'wearing-off' of response (i.e., a clinical response with a duration shorter than 10 weeks), a longitudinal study of 193 patients found no significant demographic or baseline headache characteristics to be predictive (30). An Italian study of 115 patients found that more recent onset of CM and a greater number of headache-free days at baseline were predictors of sustained response to BoNT-A over several treatment cycles (31).

There are numerous recent publications describing predictors of response to anti-calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) (32,–43). Typically, these studies defined responders as those experiencing ≥50% reduction in monthly migraine days (MMDs) or monthly headache days (MHDs) after three to six months of CGRP mAb treatment compared to baseline. Other studies have used HIT-6 score reduction (32) or MO resolution (38) as outcomes, while others have focused on specific populations such as those 65 years of age or older (36) or patients who experienced treatment failure with ≥4 preventive medications (34). Several treatment response predictors have been identified across some of these observational real-world studies. For example, at least five studies noted that fewer numbers of previous preventive treatments are a positive predictor of response

Table 1. Main findings on clinical characteristics associated with acute and preventive migraine treatment responses.

Author	Year	Treatment	Predictors of Treatment Response
Ezzati (14)	2023	NSAIDs, CCP, ASA, Acetaminophen	Lower average headache pain intensity, less cutaneous allodynia, lower MIDAS grade, less depression, lower MSSS
Viana (18)	2021	Frovatriptan	Unilateral pain, presence of phonophobia, presence of one or more cranial autonomic symptoms, presence of one or more premonitory symptom
Ishii (19)	2012	Triptans	Older age, absence of pain location (periorbital, deep orbital)
Diener (20)	2004	Sumatriptan	Lower baseline pain severity and disability, absence of vomiting
Lipton (21)	2017	Diclofenac potassium	No prior triptan use
Lu (22)	2020	NSAIDs	Shorter disease duration, lower headache intensity, lower frequency, absence of anxiety, absence of depression, and absence of sleep disorder
Lipton (23)	2016	Acute treatment	Cutaneous allodynia predicted inadequate response (2 h and 24 h) and inadequate sustained pain freedom (24 h) to acute treatment.
Saracco (24)	2014	Frovatriptan, rizatriptan, zolmitriptan, almotriptan	Pain-free rates at 2 h were higher in non-obese group than obese group. Pain-relapse rate at 48 h was similar in both groups with frovatriptan, however, it was significantly higher in obese group with rizatriptan, zolmitriptan, and almotriptan.
Cady (25)	2009	Almotriptan	Presence of allodynia-associated symptoms did not influence efficacy of almotriptan for 2 h pain freedom, 2 h pain relief, sustained pain relief, and need for rescue medication use.
Schiano di Cola (26)	2019	BoNT-A	Absence of depressive comorbidity, absence of medication overuse
Ornello (27)	2022	BoNT-A	Presence of medication overuse, lower number of MHD
Eross (28)	2005	BoNT-A	Migraine duration
Martinelli (29)	2023	BoNT-A	Response: older age at migraine onset, higher anxiety subscore in HADS Non-Response: opioid use, higher MIDAS score
Quintas (30)	2019	BoNT-A	None
Ornello (31)	2020	BoNT-A	More recent onset of CM and more headache free days at baseline
Zecca (32)	2023	Erenumab	Absence of hypertension
Zecca (33)	2022	Erenumab	At least 50% reduction in migraine days: non-significant results At least 75% reduction in migraine days: older age at migraine onset, fewer failed preventive medications, higher baseline MIDAS
Eghtesadi (34)	2021	Erenumab	None
Ihara (35)	2023	Erenumab, Galcanezumab, Fremanezumab	Older age, fewer number of prior treatment failures, absence of immuno-rheumatologic disease history
Gonzalez-Martinez (36)	2023	Erenumab, Galcanezumab, Fremanezumab	EM, lower number of baseline MHD
Barbanti (37)	2022	Erenumab, Galcanezumab, Fremanezumab	At least 50% response, HFEM: Unilateral pain, unilateral cranial autonomic symptoms At least 50% response, CM: Unilateral pain, unilateral cranial autonomic symptoms, allodynia, no obesity At least 75% response, HFEM: Unilateral pain, unilateral cranial autonomic symptoms At least 75% response, CM: Unilateral pain, unilateral cranial autonomic symptoms, allodynia 100% response: non-significant results
Caronna (38)	2021	Erenumab, Galcanezumab	Medication overuse resolution: lower baseline pain severity
Argyriou (39)	2023	Fremanezumab	50–74% response: HFEM, strict unilateral pain, pain location in the ophthalmic trigeminal branch At least 75% response: Allodynia
Yalinay Dikmen (40)	2023	Galcanezumab	Previous failures of 2 or fewer preventive medications
Vernieri (41)	2022	Galcanezumab	Lower body mass index, fewer failed preventive treatments, more frequent unilateral pain, medication overuse at baseline, good response to triptans
Lee (42)	2023	Galcanezumab	

(continued)

Table 1. (continued)

Author	Year	Treatment	Predictors of Treatment Response
			Accompanying symptoms of migraine, absence of everyday headache, absence of depression
Kim (43)	2023	Galcanezumab	Absence of CM, fewer prior failures
Pensato (44)	2022	Erenumab	Allodynia was negative predictor for erenumab response in patients with CM with MOH.
Pijpers (45)	2023	Detoxification for MOH	Absence of allodynia predicted reversion from CM to EM after detoxification for MOH.
Messina (46)	2020	Candesartan	Younger age, longer disease duration, and absence of daily headaches
Lee (47)	2007	Topiramate	Paresthesia

*The same cohort was used for these two analyses. CM: chronic migraine; NSAIDs: nonsteroidal anti-inflammatory drugs; CCP: caffeine combination products; ASA: acetylsalicylic acid; BoNT-A: onabotulinumtoxinA; MIDAS: migraine disability assessment scale; MSSS: migraine symptom severity scale; MMD: monthly migraine days; HADS: hospital anxiety and depression scale; EM: episodic migraine, HFEM: high-frequency episodic migraine; rNMS: repetitive neuromuscular magnetic stimulation.

(33,35,40,41,43). Lower headache frequency, measured as lower baseline MHDs (36), absence of everyday headache (42), presence of EM (36,39), or absence of CM (43), have all been associated with treatment response. Other characteristics consistently identified to be positively associated with treatment response include unilateral pain (37,39,41), lower body mass index (41), and absence of obesity (37). Other studies have identified unique predictors of treatment response that warrant further investigation, such as the absence of immune-rheumatologic disease history (35), absence of hypertension (32), and presence of non-headache symptoms that characterize the migraine attack including nausea, vomiting, and photophobia (42). Previous studies on allodynia revealed mixed results. A real-world study of erenumab found pre-treatment allodynia symptoms were associated with non-response (44). Additionally, a study of CM with MO showed that the likelihood of remission to EM after treatment was higher in patients without pre-treatment cutaneous allodynia symptoms as assessed by the ASC-12 (45). However, two studies (37,39) showed that baseline self-reported allodynia was positively associated with response to CGRP mAbs.

There have also been several reports on conventional treatment options. A real-world study including 253 patients found that candesartan response was positively associated with younger age and longer disease duration and negatively associated with experiencing daily headaches (46). For topiramate, paresthesias, which are a relatively common side effect of topiramate, predicted good response (47).

Summary: Phenotypic data

Numerous studies have sought to identify phenotypic predictive factors for response to acute and preventive migraine treatments. Though many studies have identified predictive factors, due to varying results from study-to-study, no firm conclusions can yet be made.

Genomics and other '-omics'

Advances in genomic technology and understanding of the complex molecular mechanisms underlying migraine have provided valuable insights into genetic predictors of treatment response. The key findings from studies that contribute to precision medicine approaches for migraine treatment using 'omics' data are presented below (Table 2).

Genomics

Acute treatment. In the recent few decades, genome-wide association studies (GWAS) have found variants, mostly single nucleotide polymorphisms (SNPs), that are associated with susceptibility to migraine (69–74). This finding suggests that treatment outcomes could potentially be different according to patients' genetic profiles. A polygenic risk score (PRS) study identified an association between an increased migraine risk score with a positive response to triptans, with an odds ratio (OR) of 1.25 (95% confidence interval [CI] = 1.05–1.49) (49), but found no significant association between PRS with response to analgesics or preventive treatments. Another study (50) utilized risk scores based on SNPs to predict headache response to triptans in migraine without aura, revealing that the alleles at *TRPM8 rs6724624* and *FGF6 rs1024905* were inversely associated with the risk of inconsistent responses to triptans. Additional gene polymorphisms of the serotonin transporter gene *SLC6A4*, and specifically the *STin2 VNTR*, also confer a higher risk of inconsistent response to triptans (51). In a study assessing triptan response, a collective burden of 1 to 12 SNPs increased the odds ratios (ORs), ranging from 1.3 to 2.6, for treatment success with triptans (52). Specifically, the variant *rs2651899* in *PRDM16* exhibited a significant association with triptan efficacy, showing an OR of treatment success at 1.3, while a higher aggregate genetic score correlated significantly with triptan efficacy, yielding an OR of success up to 2.6. Combined analyses of triptans and ergotamine strengthened this association.

Table 2. Main findings on genomic and proteomic factors associated with acute and preventive migraine treatment responses.

Author	Year	Category and Specific Biomarker	Treatment	Main Findings
Chase (48)	2024	Polygenic risk scores	CGRP mAb	Non-responder: *rs12615320-G* in *RAMP1* and *rs4680-A* in *COMT*. Lower mean genetic risk score than responders, fraction of responders increased with genetic and polygenic risk score percentile.
Kogelman (49)	2019	Polygenic risk scores	Migraine specific acute treatment	Increase in PRS associated with positive migraine-specific acute treatment response, OR 1.25 (95% CI = 1.05–1.49)
Cargnin (50)	2019	Genetic risk score	Triptans	Genetic risk score including susceptibility risk alleles at *TRPM8 rs6724624* and *FGF6 rs1024905*: inversely associated with risk of inconsistent response to triptans, OR, 0.62 (95% CI = 0.43–0.89)
Terrazzino (51)	2010	Genetic risk score	Triptans	*STin2 VNTR* polymorphism of serotonin transporter gene: higher risk of inconsistent response to triptans
Christensen (52)	2016	SNPs	Triptans	OR of treatment success with triptans, 1.3–2.6: depending on genetic load of 1–12 SNPs associated with migraine (*rs2651899* in *PRDM16*)
Moreno-Mayordomo (53)	2019	CALCA and TRPV1	BoNT-A	Polymorphic variations of *CALCA* and *TRPV1* genes: correlate with positive outcome of OnabotulinumtoxinA in female CM
Mehta (54)	2023	Epigenomics	Medication Overuse Discontinuation	CM-MO: reduction in DNA methylation at an intronic CpG site (*cg14377273*) within the *HDAC4* gene was associated with MHD 50% response 12 wks following the withdrawal of acute medication. Lower baseline DNAm at a CpG site (*cg15205829*) within *MARK3* was associated with MMD response at 12 weeks.
Kogelman (55)	2021	RNA sequences, differential expression analysis	Sumatriptan	Serial blood sample after subcutaneous sumatriptan: differentially expressed genes within the serotonergic synapse (KEGG pathway hsa04726) between sumatriptan responders and nonresponders was investigated: No overall difference but significantly different gene DE: *BRAF* ($P = 3.79 \times 10–4$)
Alpuente (56)	2022	CGRP	N/A	Photophobia and phonophobia more associated with CGRP dependent attacks than non-CGRP dependent attacks
Cernuda-Morollón (57)	2014	CGRP, VIP	BoNT-A	Interictal CGRP threshold 72 pg/mL, prediction of response to BoNT-A in 95% of cases; CGRP level above threshold multiplies the probability of response by 28.
Greco (58)	2020	CGRP, miR-382-5p and miR-34a-5p	Medication Overuse Discontinuation	CM-MO: detoxification decreased CGRP levels and miRNAs expression
Lee (59)	2018	CGRP	Preventive Medications	Higher serum CGRP concentration did not predict treatment response in CM
Alpuente (60)	2022	CGRP	Erenumab	12 wks erenumab: Higher pretreatment salivary CGRP levels: higher probability of having at least 50% response in EM, but not in CM.
Bellamy (61)	2006	CGRP, VIP	Sumatriptan	Sumatriptan resulted in decreased levels of salivary CGRP and VIP, which correlated with relief of symptoms
Cady (62)	2014	CGRP	BoNT-A	Decrease in interictal salivary CGRP levels for subjects receiving onabotulinumtoxinA

(continued)

Table 2. (continued)

Author	Year	Category and Specific Biomarker	Treatment	Main Findings
Cady (63)	2009	CGRP	Rizatriptan	Increased level of saliva CGRP predicted response to rizatriptan.
Sarchielli (64)	2006	CGRP, neurokinin A, VIP	Rizatriptan	decrease in CGRP and NKA levels one hour after rizatriptan administration in responders. VIP levels were also significantly reduced at the same time
Zagami (65)	2014	PACAP	Sumatriptan	Elevated PACAP in the external jugular vein during headache, that was reduced 1 h after treatment with sumatriptan 6 mg, and further reduced interictally.
Tuka (66)	2013	PACAP	N/A	Lower PACAP-38-like immunoreactivity in interictal plasma of migraine compared with HC. Elevated levels in ictal period relative to attack-free period. Negative correlation between interictal levels and disease duration.
Han (15)	2015	PACAP	N/A	Lower interictal plasma PACAP levels in migraine than TTH and healthy controls. Interictal PACAP levels negatively correlated with duration of CM.
Hirfanoglu (67)	2009	TNF alpha	Preventive Treatments	Migraine, 77 children, Cytokine levels (tumor necrosis factor a, interleukin-1b, interleukin-6) decreased and leptin levels increased after treatment (cyproheptadine, amitriptyline, propranolol, orflunarizine)
Coveli (68)	1992	TNF alpha	Propranolol	Serum TNF level normalized after three months of propranolol

CGRP mAb: anti-calcitonin gene-related peptide monoclonal antibodies; CGRP: calcitonin gene-related peptide; CM: chronic migraine; MO: medication-overuse; PRS: polygenetic risk score; CI: confidence interval; OR: odds ratio; SNP: single nucleotide polymorphisms; HM: hemiplegic migraine; MMD: monthly migraine days; MHD: monthly headache days; NKA: neurokinin A; VIP: vasoactive intestinal peptide; PACAP: pituitary adenylate cyclase activating peptide; N/A: not applicable.

Preventive treatment. A retrospective study identified characteristics associated with the response to CGRP mAbs, emphasizing the role of genetic factors in predicting treatment efficacy (48). More specifically, in 198 genotyped patients, non-responders were associated with *rs12615320-G* in *RAMP1* (OR [95% confidence interval]: 4.7 [1.5, 14.7]), and *rs4680-A* in *COMT* (0.6 [0.4, 0.9]). Non-responders had a lower mean genetic risk score than responders (1.0 vs. 1.1; $t(df) = -1.75(174.84)$, $p = 0.041$), and the fraction of responders increased with genetic and polygenic risk score percentile. Moreno-Mayordomo et al. identified polymorphisms in *CALCA* and *TRPV1* genes that correlate with positive treatment outcomes in female CM patients receiving BoNT-A (53).

Epigenetic alterations and medication withdrawal. Longitudinal genomic analysis demonstrated that alterations in DNA methylation are associated with reduced migraine and headache days after medication withdrawal treatment in patients with CM and MO (54). These results show that a decrease in *HDAC4* DNA methylation status over time, as well as an initial low *MARK3* DNA methylation status, are both linked to treatment efficacy. This offers evidence for the involvement of pathways connected to chromatin structure and synaptic plasticity in the progression of headaches and suggests a potential role for epigenetic mechanisms in migraine pathophysiology and treatment response. Epigenetic alterations can also result from the use of specific medications. Sumatriptan acts as a serotonin receptor (5-HT1B/D) agonist. Serial blood samples collected after subcutaneous sumatriptan treatment were analyzed to identify the genes within serotonergic synapses. No overall difference was found between sumatriptan responders and non-responders. However, the gene, *BRAF* was found to be significantly differentially expressed (55). Additionally, the '5HT1 type receptor mediated signaling pathway' was found to be enriched among the top expression quantitative trait loci.

Other biomarkers. In addition to genomics, salivary and plasma biomarkers of migraine have been investigated. Studies of CGRP, vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), and others are introduced.

Measurement of salivary CGRP might distinguish between CGRP-dependent and CGRP-independent migraine attacks

(56,75). In one study, patients were divided into two categories based on the extent of change in CGRP between the preictal and ictal phases: CGRP-dependent (79.6%) and non-CGRP-dependent migraine attacks (20.4%). Symptoms such as photophobia and phonophobia were notably linked to the former group. Although yet to be proven, presumably, CGRP-dependent attacks would be more responsive to CGRP-targeting therapies. Other studies have identified elevated CGRP and peripheral microRNAs (miR-382-5p, miR-34a-5p) associated with CM with MO compared to EM patients ($p = 0.003$ for all comparisons) (11,58). CGRP plasma concentrations also displayed a significant positive correlation with miR-382-5p and miR-34a-5p across the entire population. In the CM with MO subgroup, detoxification notably reduced CGRP levels and miRNA expression.

A comparison between responders and non-responders to detoxification revealed that the former exhibited significantly higher CGRP levels at baseline and decreased expression of miR-382-5p following detoxification. The association between baseline CGRP levels and treatment response with erenumab has been investigated (60), which showed that elevated salivary CGRP levels before treatment were significantly linked to a greater likelihood of experiencing a $\geq 50\%$ reduction in headache frequency among individuals with EM, but not in those with CM. Following 12 weeks of erenumab treatment, salivary CGRP levels among patients across all migraine frequency ranges became comparable. However, this convergence was not observed in patients with concurrent depressive symptoms, potentially providing insights into the more challenging nature of treating CM with concomitant mood disorders. Salivary CGRP might also be useful for predicting treatment response to triptans and BoNT-A (57,62,63).

In summary, various investigations have highlighted elevated CGRP levels in venous blood, saliva, and tear fluid among migraine patients compared to healthy controls, especially during migraine attacks, suggesting CGRP as a potential migraine biomarker. Yet, conflicting findings and methodological challenges mar the reliability of CGRP measurements in migraine studies (59). Indeed, inconsistent differences in CGRP levels between CM and EM further complicate interpretation. Additionally, CGRP's involvement extends beyond migraine to non-migraine pain disorders like cluster headaches and osteoarthritis. Therefore, many authors suggested that, presently, CGRP levels lack justification as a migraine diagnostic or severity marker. Further, previous evidence should be interpreted carefully given the challenges with measuring CGRP and variation in sampling methods (i.e., venous blood, saliva, and tear fluid). Nevertheless, measurement of CGRP concentration holds promise as a future biomarker for predicting therapeutic responses, notably to anti-CGRP migraine medications (76).

Similarly, VIP (61,64) has been suggested to serve as a therapeutic marker for triptan therapy and BoNT-A efficacy, particularly in CM (57). PACAP also shows promise as a therapeutic marker for triptan therapy (65,77). Human clinical studies have consistently shown increased plasma PACAP-38 levels during the ictal phase of migraine, specifically during spontaneous migraine attacks, in comparison to the interictal period (65,66). Notably, interictal plasma PACAP concentrations were significantly lower in people with migraine than in healthy controls or those with tension-type headache (15,65,66). Additionally, PACAP levels in the external jugular vein decrease with migraine headache improvement following sumatriptan treatment. Lower PACAP levels were observed between attacks compared to during attacks, indicating a potential correlation with migraine phases (65).

There is evidence that tumor necrosis factor alpha (TNF-α), high sensitivity c-reactive protein, and adiponectin could serve as biomarkers for predicting and/or monitoring migraine treatment efficacy (67,68). Together, these findings underscore the potential for a diverse set of biomarkers being associated with treatment responses, monitoring disease progression, and tailoring migraine therapies to individual patient needs (11).

Summary: Genomics and other '-omics'

Genomic studies demonstrate the potential for PRS, SNPs, and epigenetic alterations as predictors of migraine treatment response. In addition, measurement of peptides, such as CGRP, might assist with determining which peptide(s) are driving a person's migraine attacks and thus with selection amongst migraine medications. However, existing results must be interpreted carefully due to challenges with measuring each biomarker and varying methodologies between published studies.

Physiologic measures and brain imaging

Studies have explored relationships between physiological measurements, measurements of pain thresholds, and brain imaging data with treatment outcomes (Table 3).

Acute treatment. One study investigated the relationship between brain resting state functional causal connectivity between the anterior cingulate cortex and visual cortex and response to NSAIDs (16). Compared with responders to NSAIDs, the non-responders showed a different causal connectivity between bilateral anterior cingulate cortices with the lingual gyrus. For sumatriptan, two studies identified possible neuroimaging characteristics associated with a good response. In one study, in which diffusion tensor imaging was used to measure brain structural connectivity, pre-treatment local connectivity of the thalamic nuclei differed between sumatriptan responders and non-responders (78). In another study, greater left hippocampal volume was a predictor of response to sumatriptan: 84.6% of

Table 3. Main findings on physiologic and brain imaging features associated with acute and preventive migraine treatment responses.

Author	Year	Topic	Treatment	Predictors of Treatment Response
Wei (16)	2024	Functional connectivity	NSAIDs	In NSAID nonresponders compared with responders, causal connectivity from bilateral ACC to LG was increased and connectivity in the opposite direction was decreased. Compared with the healthy controls, nonresponders had heightened causal connectivity from ACC to LG, right IOG, and left superior occipital gyrus, however, diminished connectivity patterns from LG and right IOG to ACC were observed.
Lee (78)	2023	Structural connectivity	Sumatriptan	Global structural connectivity differed between newly diagnosed migraine patients and healthy controls. Local structural connectivity differed significantly between responders and non-responders to sumatriptan.
Wu (79)	2022	Hippocampal volume	Sumatriptan	Larger left hippocampal volume predicted response to sumatriptan.
Ashina (80)	2023	Allodynia	Galcanezumab	Non-ictal cephalic allodynia identified galcanezumab responders with nearly 80% accuracy and non-responders with nearly 85% accuracy, while non-ictal extracephalic allodynia did so less accurately.
Peng (81)	2022	Pain threshold	Galcanezumab	Pre-treatment heat pain threshold at the forearm predicted galcanezumab response.
Nowaczewska (82)	2021	Cerebral blood flow	Erenumab	Baseline Vm in right cerebral arteries and basilar artery is reduced in erenumab responders compared with non-responders. This difference normalized after erenumab treatment with significant increase in Vm of cerebral arteries.
Nowaczewska (83)	2022	Cerebral blood flow	Erenumab Fremanezumab	Baseline Vm in MCAs were significantly lower in responders. $\geq$ 50% reduction in MMD was significantly negatively associated with Vm in right MCA.
Chuang (84)	2023	Heart rate variability	Flunarizine	CM had reduced heart rate variability compared to healthy controls. Patients with normal heart rate variability were likely to be superior responders to flunarizine.
Ahmed (17)	2023	White matter hyperintensities	Ibuprofen Topiramate	Patients who did not respond to ibuprofen and topiramate had higher frequency of WMHs and higher WMHs Scheltens score. Vomiting, dizziness, and migraine with aura were significant predictors for developing WMHs.
Bumb (85)	2013	White matter lesions	BoNT-A	No difference between responders and non-responders to BoNT-A for age, age at onset, gender, attack duration, frequency, aura, white matter lesions, and size of white matter lesions.
Basedau (86)	2022	Functional MRI	Erenumab	Galcanezumab decreased hypothalamic activation in all patients. The reduction was greater in responders.
Fu (87)	2022	Functional MRI	Transcutaneous vagus nerve stimulation	Seventy predictive features involved in trigeminal cervical complex/rostral ventromedial medulla, medial prefrontal cortex, temporal gyrus, middle cingulate cortex, and insula were identified to predict the reduction in attack frequency after transcutaneous VNS in patients with migraine without aura.

(continued)

Table 3. (continued)

Author	Year	Topic	Treatment	Predictors of Treatment Response
Feng (88)	2022	Resting-state functional MRI	Transcutaneous auricular vagus nerve stimulation	Baseline fALFF features involved in thalamocortical circuits, default mode network, and descending pain modulation system may predict response to transcutaneous auricular VNS in patients with migraine without aura.
Nahman-Averbuch (89)	2021	Resting-state functional connectivity Conditioned pain modulation	Cognitive behavioral therapy	Greater baseline functional connectivity between the right amygdala and frontal gyrus, anterior cingulate cortex, and precentral gyrus was related to response to CBT. Response to CBT was related with less efficient baseline conditioned pain modulation response at the trapezius but not at the leg.

NSAIDs: nonsteroidal anti-inflammatory drugs; CCP: caffeine combination products; fMRI: functional magnetic resonance imaging; ACC: anterior cingulate cortex; LG: lingual gyrus; IOG: inferior occipital gyrus; HFEM: high-frequency episodic; CM: chronic migraine; EM: episodic migraine; MOH: medication overuse headache; Vm: mean blood flow velocity; MCA: middle cerebral artery; WMHs: white matter hyperintensities; BoNT-A: onabotulinumtoxinA; fALFF: fractional amplitude of low frequency fluctuation; MRI: magnetic resonance imaging; MMD: monthly migraine day; VNS: vagus nerve stimulation.

those with a hippocampal volume >4032.6 mm^3 responded to sumatriptan, whereas 42.1% of those with a smaller hippocampal volume were responders (79).

Preventive treatment. Using quantitative sensory testing (QST) to determine the presence of interictal allodynia before the administration of galcanezumab, a study demonstrated that pre-treatment presence of allodynia was associated with a worse clinical response after three months of treatment. In a separate study, higher pre-treatment heat pain thresholds on the forearm (demonstrating less sensitivity to the stimulus) predicted response to galcanezumab (80,81).

Studies using transcranial Doppler to compare changes in cerebral blood flow have found that the pre-treatment mean blood flow velocity value in the middle cerebral artery is significantly lower in responders than in non-responders to erenumab (82). A larger study including both erenumab and fremanezumab also found consistent results (83). Additionally, a study of CM patients found that those with a normal heart rate variability had a better response to flunarizine compared to those with a reduced heart rate variability, which is suggestive of autonomic dysfunction (84).

Two previous studies have investigated the usefulness of brain white matter hyperintensities (WMHs) for predicting treatment response. One study showed that the higher the WMH burden, including larger size, higher number, and higher Scheltens score, the more likely to have a poor response to ibuprofen and topiramate, though the results should be carefully interpreted given that potential confounding factors were not adjusted (17). On the other hand, another study found that neither the presence nor size of WMHs predicted the effect of BoNT-A (85).

Additionally, a brain functional MRI study investigated 26 migraine patients, who were imaged before and a few weeks after galcanezumab treatment. Response to galcanezumab was associated with baseline activity of the spinal trigeminal nucleus and its coupling with the hypothalamus (86).

Two studies investigated the prediction of neuromodulation effectiveness using the fractional amplitude of low-frequency fluctuation (fALFF) measurements obtained with functional brain MRI. In patients undergoing transcutaneous vagus nerve stimulation (tVNS), migraine attack frequency reduction was correlated with pre-treatment fALFF of the trigeminal cervical complex/rostral ventromedial medulla, prefrontal cortex, temporal gyrus, middle cingulate cortex, and insula (87). The other study also demonstrated that the efficacy of transcutaneous auricular VNS can be predicted by pre-treatment fALFF in several brain regions, including prefrontal cortex and posterior cingulate gyrus (88).

A study investigating predictors of treatment response to eight weeks of cognitive behavioral therapy in adolescents, found that resting-state functional connectivity and conditioned pain modulation (CPM) measures before treatment could be used as predictors (89). This study revealed that a reduction in headache days was correlated with functional connectivity between regions in the right amygdala, precentral gyrus, anterior cingulate cortex, and frontal lobe, and a lower CPM response.

Summary: Physiologic measures and brain imaging

Several studies of cutaneous pain thresholds and structural and functional brain imaging identified predictive factors for migraine treatment response. However, like with the other data modalities discussed above, validation studies are needed to confirm study findings.

Discussion and conclusions

Evidence suggests that there are phenotypic, genomic, proteomic, physiologic, and brain imaging features that might associate with response to migraine treatments. However, the literature includes studies with conflicting results and there is a lack of validation studies. As the available evidence is rapidly expanding, it is reasonable to assume that migraine treatment could, in the upcoming years, be tailored to the individual using a precision medicine approach. Such an approach would shorten the time required for patients to receive an effective treatment, thereby reducing migraine burden and treatment-associated frustration.

To assess the progress towards achieving precision medicine in migraine treatment, the limitations of published studies should be carefully considered. For example, some of the studies included in this article used a retrospective design and included relatively small cohorts of patients, raising the possibility of recall and selection bias, and leading to uncertainties about the generalizability of study results. There are conflicting results regarding the nature of associations between certain features with treatment outcomes. Additionally, it is critical to note that features which are associated with treatment response are not found exclusively in responders or non-responders. Published studies commonly report patient and headache characteristics that are observed more frequently in treatment responders as predictive factors; however, sometimes these characteristics are also seen in non-responders. Furthermore, the cost and ease by which data can be collected needs to be considered when developing migraine treatment prediction models, since the goal is for such models to be available and used in a clinical setting.

To achieve precision medicine for migraine treatment, existing findings need to be confirmed and validated. In addition to investigating associations between treatment response with patient features, future studies with prospective designs should focus on pre-treatment prediction of treatment responses. Published studies often identified predictors of response to an individual treatment type, such as a single migraine medication. Although that could be useful clinically, treatment prediction models that consider more than one treatment and help to select amongst those treatments would be even more useful in the clinical setting. For example, it would be particularly practical to have a model that considered multiple migraine preventive or acute medications simultaneously and determined which of the medications was most likely to be effective for an individual patient. Overall, the published literature demonstrates advancements and feasibility of achieving precision medicine for migraine treatment. Continued work is needed to reach this most important goal.

Key findings

- A precision medicine approach to migraine treatment would tailor treatment recommendations according to individual patient characteristics and would reduce the time needed to find effective and tolerable treatments.
- There are clinical, genomic, proteomic, physiologic, and brain imaging features that might associate with responses to acute and preventive migraine treatments.
- Further research is needed to develop models that accurately predict migraine treatment responses and tolerability, and that assist with choosing amongst treatment options.

Author contributions

Authors of this manuscript include attendees and faculty from the 2023 International Headache Academy (iHEAD) education conference held in Seoul, South Korea. Authors were divided into five groups: 1) introduction; 2) overview of data types contributing to precision medicine in migraine management; and summaries of progress in achieving precision medicine in migraine management using 3) phenotypes, 4) genomics and other 'omics', and 5) physiological measures and brain imaging. The output from the five groups was then combined and all authors reviewed, revised, and approved the final manuscript.

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Supplemental material

Supplemental material for this article is available online.

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