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Optimizing and Accelerating the Development of Precision Pain Treatments for Chronic Pain: IMMPACT Review and Recommendations

Robert R. Edwards[*], **Kristin L. Schreiber**[*], **Robert H. Dworkin**[†], **Dennis C. Turk**[‡], **Ralf Baron**[§], **Roy Freeman**[*], **Troels S. Jensen**[¶], **Alban Latremoliere**[‖], **John D. Markman**[†], **Andrew S.C. Rice**[**], **Michael Rowbotham**[††], **Roland Staud**[‡‡], **Simon Tate**[§§], **Clifford J. Woolf**[*], **Nick A. Andrews**[¶¶], **Daniel B. Carr**[‖‖], **Luana Colloca**[***], **Doina Cosma-Roman**[†††], **Penney Cowan**[‡‡‡], **Luda Diatchenko**[§§§], **John Farrar**[¶¶¶], **Jennifer S. Gewandter**[†], **Ian Gilron**[****], **Robert D. Kerns**[††††], **Serge Marchand**[‡‡‡‡], **Gwendolyn Niebler**[§§§§], **Kushang V. Patel**[‡], **Lee S. Simon**[¶¶¶¶], **Tina Tockarshewsky**[‖‖‖‖], **Geertrui F. Vanhove**[*****], **Daniel Vardeh**[†††††], **Gary A. Walco**[‡], **Ajay D. Wasan**[‡‡‡‡‡], **Ursula Wesselmann**[§§§§§]

[*]Harvard Medical School, Boston, Massachusetts

[†]University of Rochester, Rochester, New York

[‡]Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington

[§]Division of Neurological Pain Research and Therapy, Department of Neurology, University Hospital Schleswig-Holstein, Arnold-Heller-Strae 3, House D, 24105 Kiel, Germany

[¶]Aarhus University, Aarhus, Denmark

[‖]Johns Hopkins, Baltimore, Maryland

[**]Imperial College, London, UK

[††]UCSF, San Francisco, California

[‡‡]University of Florida, Gainesville, Florida

[§§]ICG Life Sciences, London, UK

[¶¶]Salk Institute for Biological Studies, San Diego, California

[‖‖]Tufts University, Boston, Massachusetts

[***]University of Maryland, Maryland

[†††]Abbvie Pharmaceuticals, Cambridge, Massachusetts

[‡‡‡]American Chronic Pain Association, Rocklin, California

[§§§]Department of Anesthesia and Faculty of Dentistry, McGill University, Montreal, California

Address reprint requests to Robert Edwards, PhD, Brigham & Women's Hospital, Pain Management Center, 850 Boylston St, Chestnut Hill, MA 02467. RREdwards@Partners.org, RREdwards@BWH.Harvard.edu.

[¶¶¶]University of Pennsylvania, Philadelphia, Pennsylvania

[****]Queen's University, Kingston ON, Canada

[††††]Yale University, Departments of Psychiatry, Neurology, and Psychology, New Haven, Connecticut

[‡‡‡‡]Universite de Sherbrooke, Quebec, Canada

[§§§§]Innocoll Biotherapeutics, Princeton, New Jersey

[¶¶¶¶]SDG LLC, Cambridge, Massachusetts

[‖‖‖‖]Ceres Consulting, Poughkeepsie, New York

[*****]Surrozen Inc., South San Francisco, California

[†††††]Lahey Headache Center, Boston, Massachusetts

[‡‡‡‡‡]University of Pittsburgh, Pittsburgh, Pennsylvania

[§§§§§]Department of Anesthesiology/Division of Pain Medicine, Neurology and Psychology, The University of Alabama at Birmingham, Birmingham, Alabama

Abstract

Large variability in the individual response to even the most-efficacious pain treatments is observed clinically, which has led to calls for a more personalized, tailored approach to treating patients with pain (ie, "precision pain medicine"). Precision pain medicine, currently an aspirational goal, would consist of empirically based algorithms that determine the optimal treatments, or treatment combinations, for specific patients (ie, targeting the right treatment, in the right dose, to the right patient, at the right time). Answering this question of "what works for whom" will certainly improve the clinical care of patients with pain. It may also support the success of novel drug development in pain, making it easier to identify novel treatments that work for certain patients and more accurately identify the magnitude of the treatment effect for those subgroups. Significant preliminary work has been done in this area, and analgesic trials are beginning to utilize precision pain medicine approaches such as stratified allocation on the basis of prespecified patient phenotypes using assessment methodologies such as quantitative sensory testing. Current major challenges within the field include: 1) identifying optimal measurement approaches to assessing patient characteristics that are most robustly and consistently predictive of inter-patient variation in specific analgesic treatment outcomes, 2) designing clinical trials that can identify treatment-by-phenotype interactions, and 3) selecting the most promising therapeutics to be tested in this way. This review surveys the current state of precision pain medicine, with a focus on drug treatments (which have been most-studied in a precision pain medicine context). It further presents a set of evidence-based recommendations for accelerating the application of precision pain methods in chronic pain research.

Keywords

Pain; precision; personalized; biomarker; phenotype; neuropathic; quantitative sensory testing

Chronic pain, which persists or recurs for at least 3 months,[189] is a public health epidemic. For decades, spinal pain, headache disorders, and knee pain have ranked among the top global causes of years lived with disability.[46,163] A 2018 analysis of Medical Expenditure Panel Survey data found that the proportion of U.S. adults reporting painful health conditions increased from just over 30% in 1997 to 1998 to 41% several decades later.[138] Chronic pain is notoriously difficult to "cure," is a leading global cause of reduced quality of life and carries direct and indirect costs approaching 1 trillion dollars annually in the U.S. alone.[183,204]

People with chronic pain often receive numerous treatments, with analgesic medications among the most common. However, long-term administration of analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressant medications, and opioids involves substantial risk, exemplified by the contribution of prescribed analgesics to the ongoing opioid crisis in some countries.[93] These findings, together with frustration stemming from the failure of most treatments to produce substantial benefits in the majority of patients,[45] have stimulated intensive efforts to match patients with the best treatment for them.[134,192,214] Progress in developing and implementing such precision medicine approaches has been significant in fields such as oncology, cardiology, neurology, and psychiatry,[127] though it has been somewhat slower to reach maturity for pain.[45]

Decades ago, Mitchell Max proposed that "more effective, less toxic treatments" could be developed by targeting specific pathophysiologic mechanisms in specific persons being treated for pain.[133] Precision medicine is an approach that accounts for individual variation in patient characteristics and disease mechanisms, with the primary goal of optimizing treatment outcomes.[33,127] It is a strategy that seeks to provide the right treatment to the right patient, at the right dose, at the right time, with the expectation of better health outcomes at a lower cost. We use the term precision medicine instead of "personalized medicine," which is sometimes misinterpreted as implying that unique treatments can be designed for each person.[48,49] Chronic pain is an area in desperate need of precision medicine advances, as inter-patient variability in treatment outcomes (even for efficacious treatments) is impressively broad.[57,80,81] While some variability is likely random, there is optimism that patient-by-treatment interactions can be identified.[80] In short, just as cancer is conceptualized as hundreds of (genetically) distinct diseases,[128,184] chronic pain is becoming an umbrella term encompassing overlapping conditions to which many pain-generating mechanisms contribute.

As noted in recent reviews, numerous high-quality, randomized, controlled trials (RCTs) have not produced significant overall treatment effects, despite encouraging results from early-phase drug studies.[14,45,57,79] In addition to reflecting bias in preclinical research,[35,202] such results derive from patient heterogeneity, which obscures positive treatment outcomes in certain subgroups. Within any given painful diagnosis, multiple pain mechanisms may be active to varying degrees in different patients at different time points over the course of the disease and the lifespan, leading to marked intersubject variation in treatment effects; this variability within a given pain condition is greater than that between different conditions.[66,67] Conceptually, the field generally recognizes that certain patient phenotypes are associated with differential likelihood of response to other treatments such as surgery.

For example, people with radicular leg pain and a large disc herniation are most likely to benefit from discectomy relative to those with persistent back pain who do not have those features,[114] and patients with histories of substance use disorders are least likely to be helped and most likely to be harmed by long-term opioid treatment.[47,205] However, progress toward a comprehensive precision medicine approach to managing chronic pain has been gradual.

Added to issues of mechanistic heterogeneity is the additional concern that specific mechanisms may contribute to multiple conditions, suggesting that: 1) substantial comorbidity may exist across distinct pain conditions, and 2) pain treatments may be most effective when tailored to patient phenotypes rather than pain diagnoses. This is reflected in the substantial overlap in pain diagnoses,[131] especially in older adults, who often report function-limiting pain in multiple body locations.[116,146] The high prevalence of chronic overlapping pain conditions (COPCs) highlights the presence of common mechanisms and shared phenotypes across chronic pain syndromes, which may reflect a major contribution of central factors to these conditions.[77,131] For example, someone outside the field would have no reason to suspect that irritable bowel syndrome (IBS) and temporomandibular joint disorder (TMD) would be highly comorbid. After all, the pain symptoms differ phenomenologically, they affect distinct anatomic regions, one condition is visceral in nature while the other affects primarily muscles and joints. However, IBS and TMD are in fact highly comorbid COPCs.[31] Collectively, clinical studies have revealed that comorbid pain conditions may exacerbate one another, and treatment of one may result in improvement of others.[34,82] Consequently, it is important to investigate COPCs collectively when evaluating the efficacy of potential treatments.

The aims of this comprehensive review include: 1) elucidating the challenges of taxonomy and framework that have previously been utilized for clinical trials of pain-relieving treatments; 2) highlighting specific examples of seminal precision pain medicine studies in the last several decades; 3) identifying key components of pain phenotyping that will help advance precision pain medicine; 4) summarizing the current state of knowledge in precision pain medicine; 5) developing recommendations for the design of clinical trials of pain treatments in order to continue to build an evidence base for precision pain medicine.

Methods

IMMPACT Meeting

An Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus meeting in 2016 included attendees from academia, government, pharmaceutical companies, and patient advocacy organizations. The aim of this 2-day meeting on “Accelerating the Development of Precision Pain Medicine” was to summarize the field and develop recommendations for clinical trials. Meeting organizers conducted a narrative background review of publications, and articles were circulated prior to the meeting. Titles of the meeting talks are listed in Appendix 1; meeting materials are available on the IMMPACT website: http://www.immpact.org/meetings/Immpact19/participants19.html. After the meeting, additional literature searches were incorporated into the summary of the discussions and recommendations. In light of past IMMPACT

reviews on related topics,[57] emphasis was placed on recent studies. Electronic versions of the manuscript were circulated to all authors; final agreement was achieved through discussion and iterative review of the draft manuscript. This manuscript, which focuses on foundational precision medicine approaches such as applying predictive enrichment strategies, was approved by all authors.

Challenges to creating a mechanistic pain taxonomy

Historically, pain conditions have been defined anatomically rather than on the basis of mechanisms, though this approach is steadily shifting.[189] Moreover, most chronic pain conditions may not be easily classified by predominant category (eg, nociceptive, inflammatory, neuropathic, nociplastic), and may contain multiple overlapping pain mechanisms with varying loci involving the peripheral and central nervous systems (eg, peripheral sensitization, ectopic activity, neuroinflammation, central sensitization).[197,203] An ongoing point of debate concerns what measurable phenotypic characteristics are most predictive of variability in analgesic outcomes, and what measurement approaches are best suited to evaluate these characteristics. Although we know a great deal about the general predictors of persistent pain and disability, less is known about the phenotypes that predict individual responses to specific pain treatments, and indeed, we cannot assume that these factors, or factor combinations, are the same.[56,81] Recent work has identified core domains (eg, psychosocial status, sleep, pain-modulatory capacity) that have proven to be robustly important in shaping outcomes in clinical trials of pain treatments (see[57]). As we discuss prediction studies in this review, wherever possible we focus on treatment effect modification, in which a phenotype is differentially associated with outcomes in different treatment arms. Such findings are also sometimes referred to as Heterogeneity of Treatment Effect (HTE) or moderation effects[80]; these studies are essential in facilitating precision pain medicine, which relies on identifying and harnessing differential effects across treatments in specific patient subgroups.

Caveats

Rigorous moderation studies, in which a phenotype is differentially associated with outcomes in different treatment arms (ie, most often an active and a placebo arm) are more common in certain areas (eg, pharmacologic treatment of neuropathic pain). In contrast, perhaps because controls are more challenging (or absent), there are relatively fewer trials of medical devices that examine treatment-by-patient interactions. General prediction studies abound, and some use quite sophisticated statistical approaches: For example, artificial neural networks have identified predictive factors for successful treatment with extracorporeal shock wave therapy for chronic plantar fasciitis.[221] Factors such as shorter-duration pain, higher-intensity pain, and the presence of spurs are important positive prognostic factors. However, with no control group, we cannot determine whether these are general predictive factors, or whether they are specifically important in this treatment's outcomes. Finally, we note that while most of the reviewed studies utilize pain intensity as the primary outcome, a broader range of outcomes (each of which may have unique predictors) are important to patients and should be considered in the future.[193]

Results

Biomarkers

A full examination of pain biomarker research is beyond our scope (recent reviews offer excellent summaries:[37]), but the search for pain biomarkers is an instructive example of integrating information across multiple domains towards a personalized approach to pain. Precision pain medicine overlaps with the categories of pharmacodynamic/response biomarkers (ie, biomarkers which reflect target engagement), predictive biomarkers (ie, biomarkers which can predict response to a therapy), and safety biomarkers (ie, biomarkers which reflect the potential or presence of toxicity related to a therapeutic agent). Rigorously-validated biomarkers, once they have cleared regulatory hurdles associated with the status of in vitro diagnostic (IVD) devices, have great potential to provide objective measures of pain as complements to the "gold-standard" of pain self-reports, confirm that a therapeutic intervention has reached its intended molecular target, and predict treatment responses.[37,178,188] Many pain biomarker studies have identified multimodal predictors of analgesic response to a specific treatment. For example, a recent fMRI study of people with neuropathic pain treated with ketamine revealed that high pre-treatment levels of temporal summation of pain, as well as high pretreatment dynamic functional connectivity between regions of the default mode network and descending antinociceptive brain circuits, were both associated with better analgesic response to ketamine.[20] This study was limited by the lack of a control treatment group, but the findings offer an intriguing glimpse into the potential future of precision pain medicine, involving comprehensive multimodal assessment and subsequent clustering of patients into subtypes.

Using Biomarkers/Phenotyping in Precision Pain Medicine

Peripheral Nerve Assessment—Skin punch biopsy involves taking representative sections of skin, immunohistochemically staining them to reveal intra- and subepidermal nerve fibers and quantifying the number/density of those fibers.[43] These biopsies are a critical tool in the diagnosis of small fiber neuropathy (SFN), a common source of chronic neuropathic pain. Compared to clinical examination, skin biopsy more accurately identified people with and without SFN.[42,44] Interestingly, it is not only neuropathic pain conditions that show loss of peripheral nerve fibers on skin punch biopsy. Compared with controls, people with fibromyalgia also exhibited decreased intra-epidermal nerve fiber density (IENFD).[141] People with HIV-associated peripheral neuropathy who exhibited lower IENFD at the distal leg reported more intense pain than those who had higher IENFD.[155,224] Others have reported similar findings in groups of people with SFN and diabetes,[157,179] though a direct relationship between IENFD and pain severity has not been conclusively established.[104–106]

There is some evidence that inter-patient variability in IENFD may predict likelihood of treatment benefit. In an early PHN study, participants with normal nerve fiber density and preserved sensation respond well to topical treatments.[166,167] In a more recent enrichment-design, placebo-controlled crossover trial of pregabalin for the treatment of prediabetic neuropathic pain, pretreatment IENFD was associated with treatment response.[90] Pregabalin responders (after 1 month of treatment) had a higher IENFD compared to those who were

classified as pregabalin nonresponders (compared to placebo). Collectively, IENFD has emerged as a sensitive and efficient diagnostic tool to identify individuals with SFN, and it may be useful in the early diagnosis of other neuropathic conditions.[42,43] However, further research is needed to determine whether skin biopsy can predict treatment benefit or to distinguish between people with neuropathy who will or will not experience neuropathic pain.

Brain Imaging—Magnetic resonance imaging (MRI) has opened a window into the evaluation of the human brain by allowing noninvasive study of brain structure and function.[129,154] Applying neuroimaging-based biomarkers for pain is proving be useful in numerous ways, including: diagnosis, prognosis, identifying treatment responders, identifying therapeutic targets, and defining surrogate endpoints.[126] Many of these studies use machine learning systems to work with the enormous data sets generated by imaging methods[125] to identify neural signatures associated with pain: for example, the Neurological Pain Signature (NPS) and Pain-Analgesic Network.[188,206] Neuroimaging has also been productively combined with other biomarker-based approaches such as genetics. For example, recent studies have identified brain axonogenesis as a major contributing pathway to chronic pain through a functional genomics approach combined with structural neuroimaging.[110]

A challenge for neuroimaging is to deliver actionable information at an individual level. To date, multiple studies have met this challenge,[20,120,187,191] with recent work applying whole-brain functional connectivity to develop a brain connectivity biomarker for sustained experimental pain as well as clinical pain.[126] The neural signature predicted clinical pain severity and classified patients versus controls in two independent studies of low back pain. Similar work in fibromyalgia (FM) has shown that fMRI responses to an aversive visual stimulus could distinguish not only between people with FM and healthy controls, but also between those taking pregabalin versus placebo at greater than 80% accuracy.[95] Importantly these neuroimaging predictors overlapped within the same insula region, suggesting that a specific maladaptive pattern of chronic pain-related functional brain organization could serve as the target of a successful analgesic.

Recent investigations have also sought to identify the mechanism of ketamine's analgesic effect using resting-state functional magnetic resonance imaging (rs-fMRI).[20,36,164] Persons with chronic pain were divided into ketamine responders (≥50% improvement in pain intensity) and nonresponders. Responders exhibited significantly lower functional connectivity within the default mode network (DMN), and higher connectivity between the overall DMN network and descending pain-modulatory regions (eg, the periaqueductal grey and the rostroventral medulla). This connectivity may represent an important biomarker, providing evidence that reducing an overactive ascending nociceptive system that is suppressing a strong descending modulation system is associated with ketamine benefits.[20] Some acupuncture studies have also evaluated functional connectivity in DMN regions as a predictor of outcomes. For example, connectivity between the medial prefrontal cortex (mPFC, a part of the DMN) and insula, putamen, and caudate was significantly correlated with treatment responses after 4 weeks of acupuncture treatment.[191] The insula is a key region integrating sensory processing and cognitive modulation, and it is activated

during acupuncture.[27,89] In particular, mPFC-insula connectivity was previously reported to be altered and correlated with changes in knee pain after acupuncture treatment.[29,58] It is possible that mPFC-insula connectivity may reflect patients' unique internal sensory and cognitive states (eg, reward) for acupuncture treatment, that consequently influence treatment response. In contrast, connectivity in different circuits (ie, mPFC to anterior cingulate cortex connectivity) was predictive of treatment response to sham acupuncture, suggesting that sham acupuncture may reduce symptoms in cLBP via an alternate pathway[29,89]; such work highlights the possibility that neuroimaging may allow for trial enrichment or stratification approaches that could improve assay sensitivity in clinical trials and advance the development of precision pain medicine.

Psychosocial Factors—The biopsychosocial model describes pain as a multidimensional, dynamic interaction among physiological, psychological, and social factors that reciprocally influence one another, resulting in chronic and complex pain syndromes. Psychosocial variables such as depression, anxiety, and distress are among the most robust predictors of the transition from acute to chronic pain, especially musculoskeletal pain.[56,156] Some evidence also suggests that high levels of negative affect and pain-specific distress are associated with reduced benefit from a variety of potentially pain-reducing treatments.[53,207,208] Importantly, trials of opioid analgesics have noted that elevated pre-treatment scores on measures of depression and anxiety are associated with reduced opioid analgesic benefit[101,161,207,210] within the active treatment group. Similarly, pain catastrophizing is a psychosocial construct comprised of cognitive and emotional processes such as helplessness, pessimism, rumination, and magnification of pain reports.[53,173,182] Uncontrolled studies suggest that risk factors such as catastrophizing, along with positive resilience factors, can independently predict inter-patient variation in treatment outcomes. For example, higher baseline pain resilience was associated with better quality-of-life outcomes, whereas higher baseline catastrophizing was associated with poorer outcomes following multidisciplinary treatment,[69] and similar findings have emerged from other studies.[56,60,173] There are also some moderational findings from controlled studies; for example, an RCT of transcutaneous electrical nerve stimulation (TENS) for postoperative pain reported strong effect-modification results.[158] Surgical patients were randomized to receive TENS, placebo TENS, or standard care for 6 weeks. Those in the TENS group with high baseline catastrophizing scores showed less pain reduction and reduced range of motion at 6 weeks. In contrast, there was no predictive effect of catastrophizing in the other 2 groups. Other effect modification findings have suggested that different treatments may be most effective in people reporting relatively elevated catastrophizing; for example, among women undergoing mastectomy, regional anesthesia (compared to surgery as usual with no regional anesthesia) reduced postoperative acute[226] and chronic[225] pain and opioid use to a greater degree in high-catastrophizing relative to low-catastrophizing women. Similarly, higher baseline pain catastrophizing was associated with a greater benefit of a conditioned open-label placebo intervention following spine surgery.[65]

Sleep—Pain can be both a cause and a consequence of disruption in sleep patterns. Persistent pain and sleep deficiency share a variety of mechanisms, including perturbations of opioid, monoaminergic, immune, and endocannabinoid systems.[92] Experimental, clinical,

and epidemiologic studies have suggested that sleep disruption or deprivation has a variety of negative effects such as: enhanced pain sensitivity, reduced pain inhibition, elevated chronic pain severity and disability, and increases in the frequency and impact of daily musculoskeletal pains.[62] Persistent sleep disturbance is a robust and independent predictor of chronic postsurgical pain development.[172] It is also clear that insomnia and its associated symptoms are a major contributor to poor pain-related quality of life; an IMMPACT survey found that trouble falling asleep, trouble staying asleep, and feeling tired, are 3 of the top 10 importance-rated domains for people with persistent pain.[193]

To date, several studies have shown that variation in sleep can predict pain-related outcomes. In preclinical studies, sleep-deprived animals derive reduced analgesic benefit from opioids and at least one controlled human study has shown similar effects.[180] The SPACE trial,[119] which randomized patients to opioid or nonopioid treatment, suggested that baseline sleep quality consistently predicted treatment outcomes across groups, with higher sleep disturbance scores at baseline predicting less improvement in Brief Pain Inventory (BPI) interference ($P < .001$) and BPI severity at 1-year follow-up.[115] Interestingly, a post-hoc analysis of data pooled from 16 placebo-controlled trials of pregabalin in patients with neuropathic pain conditions (ie, DPN or PHN) revealed that, among thousands of patients, one of the best predictors of pregabalin-associated pain reduction was a high degree of sleep disruption at baseline.[198,199] This small set of apparently disparate findings suggests that phenotypic measures of sleep disturbance are likely to have treatment-specific effects (eg, people with severe insomnia may benefit most from pregabalin and least from opioids), which could be identified using predictive algorithms in RCTs.

Quantitative sensory testing (QST)—QST refers to psychophysical methods used to quantify somatosensory functioning. It has been used to diagnose and monitor conditions such as sensory neuropathies,[42] probe the function of specific nerve fiber populations, investigate pain mechanisms, characterize somatosensory profiles, and measure individual variability in pain sensitivity and modulation.[2] QST can quantify the severity of positive (eg, hyperalgesia) and negative sensory phenomena (eg, hypoesthesia and hypoalgesia).[103] It has perhaps been most frequently applied to study maladaptive sensory responses in chronic pain; indeed, recent reviews highlight the extent to which pain conditions with disparate etiologies demonstrate widespread hyperalgesia.[7]

Numerous large studies have applied QST to patients with a variety of pain conditions (often neuropathic pain) in order to examine sensory profiles or subgroups.[70,84,130] Many of these studies use the German Research Network on Neuropathic Pain (DFNS) testing protocol, which is highly standardized and which assesses numerous parameters: for example, thermal and mechanical pain thresholds, temporal summation, dynamic mechanical allodynia.[165] In general, these sensory profiling studies have determined that[66,67]: 1) Most participants exhibit at least 1 sensory abnormality, which is expected, given that many diagnostic criteria for pain require positive or negative sensory symptoms/signs, 2) every measured somatosensory abnormality occurs at least occasionally across every pain condition, 3) no particular QST profile is unique to a given pain diagnosis, and 4) painful and painless neuropathies express similar clusters of QST abnormalities.[68] This last observation, that quite different neuropathies are not distinguishable on the basis of QST, but that similar

subgroups can be defined in each diagnostic group, has been especially surprising. These observed “transetiological” patterns of sensory symptoms and deficits may reflect unique pain mechanisms, which may be a fruitful target for specific therapeutic approaches.

QST has also been applied in predictive contexts. Pre-surgical individual differences in sensory profiles have shown prospective associations with acute and chronic post-operative pain across a number of procedures.[169,196] In musculoskeletal pain, QST-assessed hypersensitivity due to central pain mechanisms can impair recovery and lead to worse clinical outcomes. A recent systematic review of nearly 40 prospective studies concluded that baseline QST predicted musculoskeletal pain and disability measures, and that sensory profiling could help develop targeted interventions across a range of musculoskeletal conditions.[78] QST is sometimes combined with other phenotypic information to enhance prognosis of pain outcomes: for example, low pressure pain thresholds together with features of neuropathic pain, more widespread pain, higher patient-reported distress, and poor sleep were all predictive of persistent and worsening joint pain over 1 year in a community sample.[1] Promising findings are emerging from diverse neuropathic pain trials examining pretreatment QST responses as predictors of response to therapy.[14,15,67,153,160]

Using multinational DFNS data collected by 3 research consortia, Baron et al. conducted cluster analyses to identify and cross-validate 3 subgroups of patients with peripheral neuropathic pain[16] (see Figure 1). The sensory profiles—termed “sensory loss,” “thermal hyperalgesia,” and “mechanical hyperalgesia”—bear a striking resemblance to the 3 subgroups identified in some of the initial mechanism-focused research on post-herpetic neuralgia.[144] Moreover, similar profiles emerged in a large sample of healthy participants undergoing surrogate experimental models of nerve block, primary hyperalgesia, and secondary hyperalgesia.[200] Such QST-identified sensory phenotypes show robust temporal stability in the absence of intervention, but some abnormal sensory findings in neuropathic pain have been shown to resolve with effective disease-modifying treatment (ie, in the case of successful surgery for carpal tunnel syndrome:[109]). Recent work has also validated brief “bedside” QST, which can generally be conveniently performed in a half hour or less.[117] Importantly, the sensory phenotypes derived from QST are not likely to be amenable to assessment via patient self-report. While some questionnaire measures assessing sensory features of neuropathic pain have proven useful both as phenotyping and outcome measures (see the later “Pain Qualities” section), patient-reported neuropathic symptoms on measures such as the Neuropathic Pain Symptom Inventory (NPSI) show minimal associations with QST-assessed measures of allodynia, hyperalgesia, etc.[70,85,117]

Several trials have reported that QST-assessed indices of hyperalgesia are associated with better analgesic responses to neuropathic pain medications compared to placebo: among patients with PHN, those with mechanical allodynia had a better outcome with intravenous lidocaine than with placebo,[10] a finding that was also observed among patients with spinal cord injury pain treated with lamotrigine,[64] patients with peripheral neuropathic pain treated with botulinum toxin A,[9] and patients with HIV neuropathy or chronic visceral pain treated with pregabalin.[143,175] In painful diabetic neuropathy, an oral transient receptor potential ankyrin 1 (TRPA1) antagonist produced statistically significant improvement in pain specifically in a sub population of patients with preserved small fiber function defined

by QST.[97] To date, the majority of the positive findings involving QST-assessed phenotypes have been identified in post-hoc analyses. However, some trials have incorporated pre-specified phenotypic hypotheses into their study designs. For example, a 2014 RCT of oxcarbazepine showed effect modification using elements of the DFNS QST paradigm.[40] At baseline, patients were phenotyped into “irritable nociceptor” (ie, those with sensory gain) and “nonirritable nociceptor” groups. The irritable nociceptor group derived substantially greater benefit from oxcarbazepine compared to the nonirritable nociceptor group, with no differences in placebo effects. The number needed to treat (NNT) for 50% pain relief was 3.9 in the irritable nociceptor group, compared with an NNT of 13 in the remainder of the sample.[40] Collectively, the hypotheses presented by Baron and colleagues regarding the classes of pharmacologic treatments expected to be efficacious for each of the QST-identified subgroups of patients they identified will be a valuable guide for the design of future clinical trials[16,201] (see Table 1).

Some QST prediction work is also being done on non-pharmacologic therapies. A recent secondary analysis examined whether pressure pain tolerance predicted response to CBT or emotional awareness and expression therapy (EAET) compared to an education-based control condition.[19] The analysis revealed an interaction between treatment assignment and QST phenotype; among patients with low pain tolerance, both EAET and CBT led to small but significant improvements in pain severity compared to the education control group. Conversely, in the subset of patients with normal pain tolerance, the patients receiving EAET reported a much larger reduction in pain than the other groups. The authors suggested that QST may provide insights about individual responses to psychologically based therapies for chronic pain.[19] Interestingly, recent studies of high-frequency TENS treatment for musculoskeletal pain report that patients who are most sensitive to mechanical noxious stimuli are more likely to benefit from active TENS treatment relative to sham/placebo.[98,100,102]

Endogenous Pain Modulation—Nociceptive signals are modulated by pain-inhibitory and facilitatory processes which operate across the central nervous system and shape inter-individual variability in the trajectory of many persistent pain conditions. For instance, conditioned pain modulation (CPM) and temporal summation (TS) paradigms have been used as indices of pain-inhibitory and pain-facilitatory processesm,[2,7] respectively. Psychophysical assessment of pain facilitation is most often assessed using TS, which involves applying a series of identical noxious stimuli and measuring the increase in the percept of pain.[8] People differ broadly in their degree of temporal summation, and many persistent pain groups demonstrate increased TS relative to controls. Its neural correlates are increasingly being identified,[30,111] and TS can be reduced by a variety of centrally acting analgesic treatments, from ketamine[6] to spinal cord stimulation[59] to acupuncture[222] to exercise.[194] Recent studies of postoperative pain have highlighted the potential prognostic value of TS for predicting the development of persistent postoperative pain.[153]

In addition, CPM has emerged as a predictor of post-operative pain.[121] CPM was originally studied in animals as diffuse noxious inhibitory controls (DNIC), a physiological counter-irritation phenomenon described decades ago.[122–124] CPM reflects CNS endogenous pain-inhibitory mechanisms; a noxious stimulus applied to one body region can reduce

spinal neuronal responses (and the perception of pain) in response to a second noxious stimulus applied elsewhere on the body.[217,218] Investigations of the temporal stability of CPM have suggested that it is generally reliable and can be effectively utilized as a phenotyping measure.[108] Currently, the CPM concept is best viewed as the net effect of various facilitating and inhibiting systems exerting their activity at spinal or supraspinal levels.[136,150]

Impaired CPM and facilitated TS appear in patients with chronic musculoskeletal, visceral, and neuropathic pain conditions (for reviews, see.[7,41,78,113,153] There has been growing interest in characterizing people based on their pain modulation profiles (PMPs),[178] as inter-patient variability in pain modulation has been shown to predict clinical outcomes such as development or worsening of pain after surgery.[153] Several studies have also found that TS is a predictor of responses to COX-2 inhibitors[4] and that CPM is a predictor of responses to topical NSAID[54] as well as pregabalin[24] and duloxetine[219] treatment. Such PMP subgrouping might contribute to individualized treatment selection. For example, Yarnitsky and colleagues postulated that patients showing decrements in CPM should benefit most from serotonin-noradrenaline re-uptake inhibitors (SNRIs), which augment descending inhibition.[219] In patients with diabetic neuropathic pain who were treated with duloxetine, those with low pretreatment CPM derived substantial pain relief, while those with efficient baseline CPM did not benefit. Further, for the low CPM group, duloxetine-related changes in pain intensity paralleled changes in CPM. A placebo-controlled follow-up study also reported that CPM improved with duloxetine administration, this time in a group of migraine patients. However, it was TS rather than CPM that showed significant effect modification; higher TS predicted more pain improvement in the migraine patients receiving duloxetine, but not in those receiving placebo.[112] Since poor CPM was correlated with elevated temporal summation, as has been observed in other chronic pain studies,[132] it may be the case that clusters of patients with low CPM and high TS are most likely to respond to duloxetine versus placebo, with individual variables not necessarily emerging as significant predictors in multivariate models run in relatively small samples. Interestingly, CPM may be somewhat specific in its treatment-predictive capacity; in contrast to the SNRI findings, an RCT in patients with chronic pancreatitis suggested that pretreatment CPM was not associated with the analgesic effectiveness of pregabalin[143] and was in turn unaffected by subsequent pregabalin treatment.[23] Such specificity is expected, given the overlap between CPM mechanisms and SNRI mechanisms.[219]

Patient-Reported Pain Qualities & Characteristics—There is great interest in using electronic tools to perform real-time, frequent, “ecological” assessment of pain that has traditionally been accomplished by asking respondents for retrospective reports.[168,170] Ecological Momentary Assessment (EMA) indices of daily pain show good reliability[135] and may offer valuable supplemental information about treatment effects in RCTs,[51] though there is no firm evidence for enhanced assay sensitivity with these methods.[171] EMA also offers potential value in studies of precision pain medicine, as patients differ widely in the degree of temporal variability in their ratings of pain intensity. Several RCTs have assessed within-subject pain variability as a phenotypic predictor of trial outcomes in patients with musculoskeletal pain[94] as well as neuropathic pain[61]; in each case, people with greater

daily variability in pain intensity were more likely to be classified as placebo responders but were not more likely to respond to active medications. Such effect-modification results might suggest that people with high pretreatment variability in pain intensity (generally measured as the standard deviation of daily pain intensity ratings collected over 1 week) could be excluded from RCTs in order to minimize placebo responses and maximize assay sensitivity. Overall, it has proven challenging to identify robust predictors of placebo responses in clinical trials of neuropathic pain treatments,[86] other than variability in pain ratings.[50,57,61,190]

In addition, questionnaires measuring pain qualities (eg, “burning,” “shooting,” “aching”) may be useful in precision pain medicine. For example, patients with neuropathic pain who reported their pain as paroxysmal, deep, electrical, and radiating reported greater analgesic benefit from pregabalin (but there was no association with placebo benefits), highlighting the potential benefits of phenotyping pain qualities.[72] Similar findings emerged in a pooled post-hoc analysis of Phase 3 trials of pregabalin[70]; several subgroups of patients with specific patterns of neuropathic pain symptoms had greater pain improvement after taking pregabalin than did those who took placebo. Exploratory analyses of data from a trial of a morphine-gabapentin combination for neuropathic pain also suggested that baseline pain descriptors may be predictive of analgesic treatment response.[87,88] A trial of the sodium channel blocker oxcarbazepine noted that the subgroup of patients reporting “paroxysmal” and “burning” pain symptoms showed significantly better pain reduction with oxcarbazepine than placebo.[40] Paroxysmal and deep pain phenotypes were also associated with benefit from lidocaine patches[39] and from subcutaneous injections of botulinum toxin A.[21] Interestingly, a comparison of pregabalin and duloxetine in patients with diabetic neuropathic pain suggested that the cluster of patients with the least neuropathic pain symptoms responded better to duloxetine than to pregabalin.[22] Finally, pain duration may also play a role in shaping the relative benefits of antidepressants and anticonvulsants in neuropathic pain.[148] In a review of crossover trials, patients with shorter pain durations reported more pain improvement from antidepressant treatment, while those with longer duration responded better to anticonvulsants.[176]

Intersections of Phenotypes with Specific Treatments

Sodium Channel Antagonists—Multiple RCTs have reported that QST-assessed indices of hyperalgesia are associated with better analgesic responses to sodium channel antagonists compared to placebo: IV lidocaine in PHN,[10] lamotrigine in central neuropathic pain,[64] and oxcarbazepine in patients with peripheral neuropathic pain conditions.[40] Moreover, recent efforts at back-translation of these studies have produced exciting results.[45] For example, in a rat model of neuropathy, spontaneous activity in the thalamus was substantially attenuated by spinal lidocaine, as well as intraplantar lidocaine and systemic oxcarbazepine.[147] Intraplantar injection of oxcarbazepine’s active metabolite licarbazepine replicated the effects of systemic oxcarbazepine, supporting a peripheral locus of action.[147] These findings suggest that ongoing activity in primary afferent fibers drives spontaneous thalamic firing after spinal nerve injury; the inhibitory effects of both lidocaine and oxcarbazepine suggest that this rat model of neuropathy, involving a partial ligation of spinal nerves, resembles the irritable nociceptor patient subgroup identified in human studies.

Like oxcarbazepine, lacosamide is a nonselective sodium channel blocker and also reduced evoked spinal neuronal responses in an experimental rat model.[18] Prior negative trials in neuropathic pain may stem from a lack of patient stratification rather than lack of efficacy as such. A recently registered trial will attempt to address this by investigating whether a similar drug-by-sensory phenotype interaction exists.[28] A multimodal genetic, electrophysiological, and sensory profiling approach has already showed promise for treatment selection; several recent studies support that patients with Nav1.7 variant-driven small fiber neuropathies can benefit from lacosamide treatment.[38,139]

Calcium Channel Antagonists—The $\alpha 2\delta$−1/2 ligands pregabalin and gabapentin have seen steady increases in use across the globe (eg,[223]). Their effects have been comprehensively characterized in rodent injury models, and both gabapentin and pregabalin attenuate ongoing pain and evoked hypersensitivity through central mechanisms, particularly where central sensitization is present.[13,14,213] However, many patients do not derive substantially greater benefit over placebo, with NNTs in the range of 5 to 6.[145] This may be at least partly attributable to the fact that, in animal models, the gabapentinoids are particularly effective at inhibiting high-intensity mechanically-evoked neuronal responses.[13] There is some evidence from human studies that pregabalin may have similarly selective effects. Post hoc analysis of clinical trial data revealed that pregabalin did not separate from placebo in patients with HIV neuropathy, but provided pain relief in a subgroup characterized by severe mechanical hyperalgesia.[175] This is consistent with Baron and colleagues' proposal that central sensitization may be the predominant pathophysiological mechanism for this mechanically sensitive patient phenotype.[16] Consistent with the features of this QST-derived sensory profile, analysis of a separate pregabalin trial concluded that analgesia corresponded with preserved large fiber function and poorer outcomes were observed with loss of fibers.[96] In addition, post-hoc analysis of questionnaire and bedside QST data in a series of 5 pregabalin trials in neuropathic pain revealed that patient-reported hyperalgesia on the Neuropathic Pain Symptom Inventory was associated with a significantly better response to pregabalin than to placebo in both primary and confirmatory analysis, and that the presence of severe punctate hyperalgesia, moderate-to-severe cold hyperalgesia, and moderate-to-severe temporal summation to tactile stimuli were all associated with a better response to pregabalin over placebo.[21,70] Collectively, these disparate studies suggest that pregabalin is likely to be differentially effective in reducing neuropathic pain in patients who demonstrate a mechanically sensitized sensory profile, characterized by at least moderate hyperalgesia.

Opioids—Psychosocial factors are known to be strong predictors of opioid-related outcomes, with high levels of distress, negative effect, and catastrophizing predicting less opioid analgesia, more side effects, and a greater propensity to misuse opioids.[12,55,76,99,107,210] Most of this work involves general prediction studies, though several trials have identified differential response to opioid vs. placebo as a function of psychosocial status.[101,207, 209] Previous QST findings have suggested that the magnitude of CPM is lower for opioid users than nonusers, suggesting that long-term opioid use might dampen the functioning of endogenous pain-inhibitory systems.[55,132,159] Interestingly, several recent experimental studies have found that acute opioid administration may enhance

endogenous pain inhibition,[3,140] though other reports of short-term administration have suggested minimal effects.[185] Further work has indicated that higher levels of pre-treatment CPM are associated with enhanced morphine analgesia (measured as a reduction in experimental pain sensitivity) in patients with chronic low back pain as well as healthy adults.[25] Collectively, these findings may suggest that the impact of opioid use on indices of pain inhibition shows a biphasic time course, with acute potentiation of CPM followed by long-term decrements of CPM in persistent opioid users. To the extent that endogenous pain-inhibitory systems exert a modulatory influence upon sensitization processes,[5,52,91,215] opioid-induced disruption of CPM might compromise the expected association between pain inhibition and pain facilitation, as a recent study has observed.[132] Collectively more precision medicine data from opioid trials is necessary in order to determine which phenotypic patient characteristics are associated with relatively better or worse pain-related outcomes associated with opioid treatment.

NSAIDs—Most reviews and meta-analyses of NSAID effects have focused on features of the specific medications themselves (eg, comparing drugs, or dosages, or durations of treatment) rather than patient-level characteristics as predictors of analgesic responses to NSAIDS, though one recent individual patient meta-analysis of topical NSAIDS did report superior benefit over placebo in women relative to men.[149] Collectively, we know relatively little about QST's role in the prediction of NSAID-associated pain relief, but there is some evidence that, contrary to some of the neuropathic pain treatments, a less favorable, more sensitized pain modulation profile is associated with reduced responsiveness to NSAID treatment. For example, after 3 weeks of treatment with NSAIDs and paracetamol in patients with knee osteoarthritis, high TSP was associated with a lower likelihood of response.[151] Furthermore, in contrast to the duloxetine findings, better CPM was associated with better analgesic effects of topical NSAIDs for painful knee osteoarthritis and with better response to NSAIDs and paracetamol in patients with knee osteoarthritis.[54,152] Both of these were uncontrolled "general prediction" studies, highlighting the preliminary stage of the NSAID data.

SNRIs—An RCT in diabetic neuropathic pain revealed that patients with the lowest burden of neuropathic pain symptoms responded better to duloxetine than to pregabalin,[22] and QST studies have also suggested that patients with poor CPM and elevated temporal summation (ie, those with relatively maladaptive pain modulation profiles[132] are most likely to respond to duloxetine.[112,219] Given the prior findings of a review in painful polyneuropathy (ie, the benefits of antidepressant treatment over placebo are significantly greater in those who have experienced pain for less than 3 years[176]), it appears important to consider the duration of patient-reported pain symptoms as a potentially important factor as well. Finally, recent neuroimaging studies have suggested that predictive brain biomarkers of placebo responses differ from the predictive brain biomarkers of duloxetine responses, generating hope that personalized treatment algorithms will eventually be possible.[186,187]

Recommendations (see Table 2)

Test for heterogeneity of treatment effect

Before examining (differential) prediction of outcomes in different groups in RCTs, it would ideally be important to demonstrate statistically that patients vary significantly (over and above the "natural" fluctuations that occur in outcome variables such as pain intensity) in their response to intervention. It seems obvious that such variability would be significant, given that a sizable percentage of patients respond even to placebo treatments,[86,149] but not all treatments produce definitive statistical evidence of heterogeneity. For example, a recent analysis of 4 multiperiod crossover trials of fentanyl treatment for cancer pain revealed firm evidence of heterogeneity (ie, significant treatment-by- patient interactions) for at least 3 of the trials.[80] That is, patients differed from one another in their differential response to fentanyl compared to placebo, and those individual differences persisted across treatment episodes. In contrast, a meta-analysis of an education-focused behavioral treatment (Pain Neuroscience Education) revealed insufficient evidence for inter-patient variation (over and above random variation over time) in treatment response.[211] These disparate findings highlight the potential importance of evaluating response heterogeneity before undertaking resource-intensive precision pain medicine approaches to evaluate predictors of inter-patient variation in treatment responsiveness.

Select validated phenotyping measures

In a 2016 review, we offered recommendations for including phenotypic factors (and validated phenotyping measures) for Phase 2 and 3 trials of chronic pain treatments.[57] Additional advances have been made in some of the fields: for example, we recommended considering the DFNS QST battery for QST phenotyping, and that recommendation remains solidly evidence-based. Since then, though, further work has been done on brief, less resource-intensive "bedside" QST protocols that can generally be conveniently performed in a half hour or less.[117] Such assessments may be less burdensome and more feasible to apply in multisite trials and could be considered in place of the full DFNS battery. It is also recommended that investigators strongly consider including assessment of commonly-assessed phenotypes that are not necessarily the primary phenotypic factors that are being studied: for example, pain variability, sleep, mood. Over time, this will help to promote additional precision pain medicine investigations, allow for pooling of data, etc.

Carefully consider sample size requirements

In order to rigorously show the ability of a phenotype to predict response to active treatment, an RCT with a prespecified primary analysis that tests the significance of the difference between the effect sizes in the 2 subgroups must be conducted. This is accomplished by testing for treatment-by-phenotype interactions. Powering a trial to test such interactions generally requires quite large sample sizes.[81,201] For example, if the subgroups are of equal size (50:50 allocation) and the Standardized Effect Sizes (SESs) in the subgroups are 0.2 and 0.5, respectively (ie, an SES of 0.35 for the overall treatment effect), the total sample size required to demonstrate a significant treatment-by-subgroup interaction (for this subgroup difference in SES of 0.3) is over 1,300 participants.

Consider crossover, or N-of-1 trials

The sample sizes required to detect treatment-by-phenotype interactions are far more reasonable in crossover designs.[80,81] For example, in the hypothetical investigation above (phenotypic subgroups of equal size (50:50 allocation), with SESs of .2 and .5), if we assume a moderate (r = .4–.6) within-patient correlation in treatment effects, only around 300 to 400 patients are required to achieve 80% power (in contrast to over 1,300 patients in the parallel-design study). Multiperiod crossover N-of-1 trials require even smaller samples, have been facilitated by the broad adoption of mobile data collection platforms (e.g., smartphones), and have been used in both recent and older studies to assess individual treatment responses.[17,118,142,174,220] Additional design for consideration include enriched enrollment randomized withdrawal designs; these have been routinely used, especially for opioid trials,[137] though it is not clear whether such trials provide greater power for subgroup analyses than standard non-withdrawal designs.[71]

Consider stratified allocation

While past trials have performed post-hoc analyses, we recommend 50:50 stratified allocation based on a defined phenotype. This approach will maximize power to detect phenotype-by-treatment interactions (eg, see:[66] and[81]). Some ongoing trials in neuropathic pain appear to be taking this type of approach. For example, a recently described phase 2, proof-of-concept, phenotype-stratified study is enrolling patients with peripheral neuropathic pain who will be randomized to a 12-week treatment with lacosamide or placebo.[28] The primary objective is to compare change in daily ratings of average pain intensity in patients with and without the irritable nociceptor phenotype.

Back-translation

When possible, consider back-translation (also termed reverse translation) approaches which can help to confirm effects and targets and localize where in the nervous system drug effects are unfolding.[14,45,162] Reverse translation, also called bedside–to–benchtop research, begins with clinical experiences or clinical research findings, and works backward to uncover the mechanistic basis for these observations. For example, Rice and colleagues have proposed a back-translational approach involving classifying animal models of neuropathic pain by their sensory response profiles, which would be defined on the basis of human QST studies (eg, sensory loss, thermal hyperalgesia, mechanical hyperalgesia).[162] Collectively, progress in the area of precision approaches to treatment of chronic neuropathic pain with sodium channel antagonists appears to have been substantively facilitated by back-translational work.[14,28,147,216]

Consider phenotypic clusters

It may eventually be prudent to utilize cluster-based approaches to define phenotypes (since seemingly disparate characteristics are often inter-correlated:[11,77,177]). This is an area where modern multivariable and machine-learning approaches that overcome the limitations of single-variable prediction studies may be invaluable, as has been demonstrated in the Precision Psychiatry literature.[32,195,212] Advanced machine-learning algorithms should be

developed along with digital phenotyping and other data-rich measurement techniques; these are at present being most frequently applied in the area of neuroimaging.[37,129]

Implement dynamic measurement

To advance precision pain medicine more rapidly, we may need frequent, dynamic measurement of predictors.[127] Though investigators often assume that a disorder's pathophysiology is well-known, such that a static baseline marker can reliably predict treatment effects, a treatment course in neuro-behavioral conditions is a complex, evolving interplay between a patient and their treatment. Dynamically assessed phenotypic changes, which may occur as patient behavior and neurobiology evolve during the course of treatment, may provide more robust individual prediction of pain treatment outcomes.[26,73–75,83]

Summary & Conclusion

In the field of pain, many treatments are available but most are only partially beneficial for a subset of patients, and the consequences of poor pain control are frequently dire, including severe suffering, disability, and elevated mortality. Numerous stakeholders would benefit tremendously from our ability to identify, for a given patient, the available intervention(s) most likely to yield the best response. While challenges abound,[63] and the slow pace of findings to date suggests that success in the goal of matching patients to treatments has been elusive, the accelerating success of precision medicine in other disciplines offers reason for optimism.[32,127,181] The tremendous heterogeneity among patients with persistent pain, and the disappointing, negative results of many analgesic trials may be harbingers of a future in which patients are comprehensively phenotyped (in addition to being diagnosed), then are managed according to an empirically-supported algorithm that matches those patient profiles to the optimal combination of treatments.[57,66] We hope that this summary of the current state of precision pain medicine, as well as evidence-based recommendations for implementing these methods in research, can facilitate the further development and indeed the acceleration of precision medicine in chronic pain management.

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Appendix 1.: IMMPACT Precision Pain Medicine Meeting Talks

1. Precision Pain Medicine: Accomplishments of the Past 25 Years, and Prospects for the Next 10 (Clifford Woolf).
2. Preclinical Research Obstacles and Opportunities in Developing Precision Pain Medicine: An Overview (Andrew Rice).

3. Clinical Research Obstacles and Opportunities in Developing Precision Pain Medicine: An Overview (Michael Rowbotham).
4. Precision Medicine at the NIH (William Riley).
5. Rare vs Common Gene Variants as Guides to Pain Mechanisms and Drug Development (Alban Latremoliere).
6. Sodium Channels as Targets for Precision Pain Medicine: Preclinical Perspectives (Simon Tate).
7. Sodium Channels as Targets for Precision Pain Medicine: “Irritable Nociceptors” and Other Phenotypes in the Design of Clinical Trials (Troels Jensen).
8. COX Inhibitors and NGF Antibodies as Targets for Precision Pain Medicine (Nathaniel Katz).
9. Descending Inhibition as a Target for Precision Pain Medicine (Roland Staud).
10. Signs, Symptoms, and Comprehensive QST: A Perspective from the German Research Network on Neuropathic Pain (Ralf Baron).
11. Signs, Symptoms, and Bedside QST: $\alpha 2$-δ and Other Targets (Roy Freeman).
12. Non-pharmacologic Treatments in Precision Pain Medicine: Rationale for Splitting (Stratifying) vs. Lumping (Dennis Turk).
13. What Else Needs to be Included When Phenotyping is Considered? (Robert Edwards).

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Perspective:

Given the considerable variability in treatment outcomes for chronic pain, progress in precision pain treatment is critical for the field. An array of phenotypes and mechanisms contribute to chronic pain; this review summarizes current knowledge regarding which treatments are most effective for patients with specific biopsychosocial characteristics.

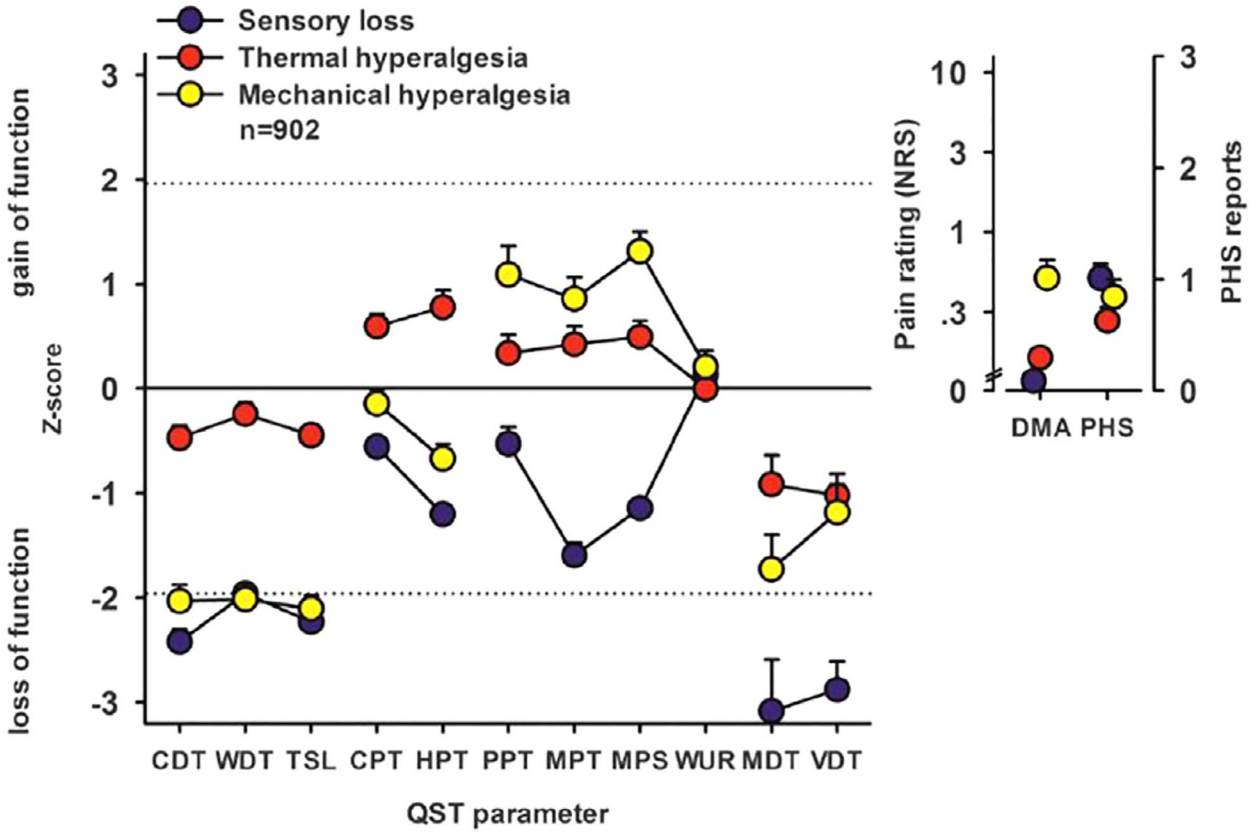

Figure 1.

DFNS-assessed 3-cluster sensory profiles (Adapted with permission from Baron et al., 2017). Cluster analysis results: Sensory profiles of the 3 clusters presented as mean z scores ± 95% confidence interval for the test data set (n = 902). Positive z scores indicate positive sensory signs (hyperalgesia), whereas negative z values indicate negative sensory signs (hypoesthesia and hypoalgesia). Dashed lines: 95% confidence interval for healthy subjects. Insets show numeric pain ratings for dynamic mechanical allodynia (DMA) on a logarithmic scale (0–100) and frequency of paradoxical heat sensation (PHS; 0–3). Blue symbols: cluster 1 “sensory loss” (42% of sample). Red symbols: cluster 2 “thermal hyperalgesia” (33% of sample). Yellow symbols: cluster 3 “mechanical hyperalgesia” (24% of sample). CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; NRS, Numerical Rating Scale; PPT, pressure pain threshold; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

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Table 1.

(Adapted from Vollert et al., 2017). Predicted Benefits of Different Analgesic Classes in 3 DFNS-defined Subgroups

Cluster Characteristics, Hypotheses About Underlying Pathophysiology, and Expected Treatment Efficacy			
	Sensory Loss	**Thermal Hyperalgesia**	**Mechanical Hyperalgesia**
Sensory profile			
Sensory Loss	Touch, thermal, pain	None	Mostly thermal
Hyperalgesia	None	Mostly cold & heat	Mostly pressure & pain
DMA	Little	Little	Much
PHS	Much	Little	Little
Pathophysiology			
Sensory Loss	Small & large fibers	—	Mostly small fibers
Hyperalgesia	—	Peripheral sensitization	Central sensitization
Ongoing Pain	Ectopic activity	Spontaneous activity	Ectopic activity
Predicted Findings			
IENFD	Loss	None	Mild loss
CCM	Loss	None	Mild loss
Peripheral MRI	Damage	None	Mild damage
LEP	Reduction	Normal or gain	Mild reduction
RIII	Reduction	Normal or gain	Gain
μENG	Denervation	Sensitization	Little denervation
Predicted Efficacy			
NSAIDS	—	(+)	—
Botox		+	
Topical capsaicin		+	
NMDA antagonist			+
SNRI	++	+	+
Gabapentinoid	+	+	++
Sodium channel blocker	+	++	++
Opioid	++	+	+

CCM, confocal corneal microscopy; DMA, dynamic mechanical allodynia; IENFD, intraepidermal nerve fiber density; LEP, laser-evoked potentials; μENG, microneurography; PHS, paradoxical heat sensation; RIII, nociceptive flexion reflex; SNRI, serotonin-norepinephrine reuptake inhibitor.

Table 2.

Recommendations for Precision Pain Medicine Studies

	Recommendation	Benefit
1.	Test for heterogeneity of treatment effect	Confirms an adequate degree of inter-patient variation in treatment responsiveness to test phenotype-by-treatment interactions.
2.	Select validated phenotyping measures	Maximizes precision in quantifying phenotypes of interest. Facilitates comparison of findings across studies (that use validated measures).
3.	Carefully consider sample size requirements	Testing for phenotype-by-treatment interactions often requires large samples. Adequately powering a trial is essential in minimizing Type II error.
4.	Consider crossover, or N-of-1 trials	Offers much greater power (i.e., greatly reduced sample size requirements) when examining subgroup/phenotype differences in treatment response.
5.	Consider stratified allocation based on phenotypes	Maximizes power to detect phenotype-by-treatment interactions. When possible, implement 50:50 (i.e., equal group sizes) stratified allocation.
6.	When possible, implement back-translation approaches	Facilitates confirmation of hypothesized treatment targets and localization of drug/treatment effects in the nervous system.
7.	Plan for phenotypic clustering	Reduces concerns related to testing multiple, correlated, individual variables. Enhances power by minimizing the need for multiple comparison corrections.
8.	Implement dynamic measurement in trials	Accounts for naturally-occurring phenotypic variability over time, increases reliability of phenotyping measurements.