Precision medicine: the emerging approach to the chronic pain patient

Chronic pain is a major public health issue. Its management mandates a multidisciplinary clinical assessment. Over the past decades, the individual variation in response to analgesic medication has been shown to be tightly mediated by the pharmacogenetic profile. Better understanding of the molecular basis of pain complemented by gradual unraveling of genotype–phenotype associations hold important implications for clinical utility and safety in the field of pain management. However, as the pain community embraces the accumulation of genomic data, it is worthwhile analyzing the caveats of a pure gene-derived approach and consider the many environmental factors that affect the highly complex phenomenon of pain.

KEYWORDS: analgesics ■ chronic pain ■ genomics ■ individualized medicine ■ personalized medicine

Ohad Oren*[1,2] & Jacob Ablin[1,3]

[1]Institute of Rheumatology, Tel Aviv Sourasky Medical center, Tel Aviv, Israel
[2]The Ruth & Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel
[3]Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel
**Author for correspondence: ohadoren@gmail.com*

Chronic pain continues to pose a major, unmet challenge for modern medicine. It is an important global healthcare issue affecting approximately 12–30% of the population [1]. The implications of chronic pain on patients' mental health, overall functioning and productivity are far reaching. When inadequately treated, chronic pain adversely affects quality of life, diminishes ability to engage in meaningful daily activities, impacts on social and employment status, and acts as potent psychological stressor often leading to depression [1,2]. Persistent pain is frequently a sequel of preceding acute severe pain, emphasizing initial individualized treatment as a means to improve clinical outcomes [3]. In a recent survey, 40% of respondents expressed dissatisfaction with the effect of treatment on their pain [2]. Almost half of the patients with cancer are undertreated for pain, according to an analysis of 26 studies [4]. An inadequate systematic approach to chronic pain often results in suboptimal symptomatic management, affecting millions of individuals, according to WHO [5]. Pain relief, an important patient right in and of itself [6], has yet to be fully realized for many patients [7].

Chronic pain encompasses two broad categories: chronic noncancer pain and chronic malignant pain. Chronic noncancer pain is commonly associated with musculoskeletal/orthopedic conditions (e.g., osteoarthritis, rheumatoid arthritis and tendinitis) or neuropathic processes (e.g., diabetic neuropathy, carpal tunnel syndrome and complex regional pain syndrome) [5]. When pain is secondary to musculoskeletal etiologies, it is considered to be mainly nociceptive in character; inflammatory and mechanical factors are considered to be major contributors to such pain. Neuropathic conditions, the end result of malfunction of the peripheral and/or CNS, may accompany nerve injury due to multiple etiologies [8].

Other causes of chronic noncancer pain include visceral pain (distention of hollow organs), sickle cell anemia and fibromylagia. The latter is characterized by widespread pain and prominent hyperalgesia. The pain symptom of fibromyalgia patients is often challenging to treat and is compounded by the coexistence of additional debilitating symptoms, such as fatigue and dyscognition [8]. Chronic malignant pain may result either from the underlying disease or the treatment administered, and is not infrequent in elderly populations. Compared with pain associated with malignancy, noncancer pain has been less meticulously researched. Although nonmalignant conditions are the more prevalent category of chronic pain, this group of conditions appears to be under-represented both in the literature relating to guidelines and management, as well as in the allocation of recourses directed at providing comprehensive treatment for such patients.

In view of the unmet challenges of chronic pain management, the personalized approach holds particular appeal in this field. Personalized pain management is destined to play an increasingly major role in the clinical interaction with pain patients; thus, constant vigilance is required on the part of physicians involved in the care of pain patients in order to stay abreast of the developing science involved and in order to incorporate novel

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capabilities into clinical practice in a timely, safe and evidence-based manner.

Combining clinical analysis with state-of-the-art molecular understanding of pain, precision medicine, by virtue of a sophisticated tailor made approach, is destined to result in better clinical outcomes and reduced healthcare spending [9].

The multifaceted nature of pain

Development of chronic pain involves a complex interaction between peptides, neurotransmitters and membrane receptors at different levels of the peripheral and/or CNS. Detailed mechanistic understanding of cellular events leading to chronic pain has yet to be fully achieved. However, it is believed that hypersensitivity to pain hinges on both peripheral and central sensitization components. At the peripheral level, accumulating data show that tissue injury, in the context of inflammation, neuropathic processes or nociceptive stimulation, results in alteration in tissue metabolite level (e.g., potassium, substance P and prostaglandins) [10]. Such local metabolic disequilibrium leads to a complex downstream cascade that includes both cyclic-AMP-dependent and independent pathways. Various downstream signal mediators (e.g., bradykinin, leukotriens and prostaglandins) alter the activation threshold of the nociceptive terminal and result in heightened sensitivity to pain [11,12]. Central sensitization, by contrast, typically accompanies neuropathic, inflammatory or functional pain [11]. Resulting in hypersensitivity to pain, central sensitization is a physiologically complex phenomenon, its components include tactile allodynia, temporal summation, after sensations, and conditioned pain modulation (CPM) [13,14]. Central sensitization is the result of a multistep process at the secondary afferent neurons of the dorsal horn. Acute tissue injury brings about massive release of regulatory peptides. This, in turn, results in depolarization of plasma membrane and neutralization of the magnesium-induced block of *N*-methyl-D-aspartate receptors [13]. Further modification of neural transmission occurs through the action of calcium–calmodulin-dependent kinases [15]. Alterations in cellular environment and adjacent neural structure coupled with changes to the functional properties of afferent neurons have been hypothesized to contribute to enhanced pain sensitivity in central sensitization. These dynamic biological modifications lend support to the concept of pain plasticity [16], whereby unrelieved pain may result in structural alteration of nervous tissue. Chronic pain may, therefore, be considered not merely a symptom, but a disease in itself.

The different types of pain observed can be divided into nociceptive, neuropathic and functional (also termed dysfunctional or central). Nociceptive pain, from a teleological perspective, serves as an alarm system that informs the individual about the presence of potentially-damaging stimuli. Thermal, chemical or mechanical stimuli activate primary afferent nociceptors residing within the peripheral nervous system. Second-order projection neurons conduct the signal to the brain stem, thalamus and cortex where cognitive recognition of the pain occurs. Descending pathways, which are critical modulators of pain perception, may inhibit transmission of the pain signal through the action of endogenous opiates and various neurotransmitters [17]. Unlike the nociceptive form, neuropathic pain results from a primary lesion or dysfunction in the nervous system itself. There are many conditions associated with neuropathic pain, including infectious, ischemic and metabolic processes, but also trauma, malignancy and the effects of malnutrition [101]. Diabetic and postherpetic neuropathy are two salient examples of neuropathic pain conditions. A complex entity defined by the predominant fiber type affected, neuropathic pain may occur spontaneously (stimulus-independent pain) or in response to sensory activation (stimulus-evoked pain) [18]. Functional pain, in which no peripheral pathology or neurologic deficit can be found, results from abnormal responsiveness or function of the CNS. Patients suffering from fibromyalgia, irritable bowel syndrome and temporomandibular joint disorder, all share such centrally originating pain [19,20].

Neurobiological studies have started to shed light on distinct mechanisms that account for different types of pain [21,22]. The ultimate goal of these molecular endeavors would be to move from the current empirical therapeutic approach to personalized targeting of the predominant mechanism responsible for pain. An approach that is tailored to the pertinent etiological pain component and the genetic make-up of a given individual would require comprehensive command of individual traits and needs if satisfactory pain relief is to be achieved.

Pain in elderly patients

Tackling chronic pain in a patient-specific fashion begins with recognition of certain features that affect the treatment of pain. Elderly patients comprise a unique group exhibiting distinct clinical and biochemical traits that may complicate the management of pain. Barriers to appropriate management of chronic pain

in the elderly include under-reporting of pain, cognitive and communication problems, and unique drug metabolism issues. First, elderly individuals often regard pain a normal part of aging. Some misinterpret symptoms as resulting from a coexisting disease, while others have communication problems. Cognitive impairment, secondary to delirium or dementia, poses additional barriers to the reliable assessment of pain in this population. The result is that pain is profoundly under-reported by elderly individuals. Second, older patients exhibit distinct pharmacodynamic and pharmacokinetic properties that translate into different medication half-life, onset of action and rate of elimination. Analgesic regimens must be carefully dose- and route-adjusted to an elderly individual's characteristics and needs. In addition, older patients are more likely to suffer from comorbid medical conditions, such as cardiovascular disease, diabetes or renal dysfunction, for which they receive treatment that may interact with that directed at pain [23]. A case in point is the use of NSAIDs, whose rate of complications increases dramatically in individuals older than 65 years of age [25,26], especially its gastrointestinal, renal and hematological adverse effects. A patient-centered approach, beginning with judicious selection of analgesics and continuing with careful monitoring for adverse reactions and, if indicated, coprescribing of protective agents (e.g., proton-pump inhibitors for patients at high risk for peptic ulcer disease), is vital for effective management of pain in elderly patients.

Fibromyalgia & fibromyalgianess

Patients with rheumatic disorders often suffer from concomitant fibromyalgia. A prototypical central sensitization syndrome, fibromyalgia is most responsive to a combination of nonpharmacological interventions, such as graded exercise, together with medications capable of affecting central pain processing, such as serotonin–norepinephrine reuptake inhibitors (SNRIs) and $\alpha 2\delta$ subunit voltage-dependent calcium channel agonists (e.g., pregabalin) [26]. Concomitant nonpharmacological modalities are exceedingly important in the management of fibromyalgia and include warm water-based treatment, movement meditative treatments and cognitive–behavioral therapy [27].

Some patients with or without specific other rheumatic diseases, failing to meet strict diagnostic criteria for fibromyalgia, have been shown to manifest varying levels of pain and disability. This symptom construct has been coined 'fibromyalgianess' [28]. The presence of fibromyalgia-like symptoms in patients with rheumatic disorders predicts good response to centrally acting medications and, thus, has important implications for the management of pain. Rheumatologists and other physicians treating such patients must constantly stay alert to the possibility of various pain mechanisms overlapping in the individual patient over time. Incorrectly attributing fibromyalgia-like symptoms to an underlying inflammatory process will lead to inadequate therapeutic response, such as increasing the dose of potentially harmful anti-inflammatory medications. On the other hand, correctly identifying and treating fibromyalgia symptoms in such patients will lead to improved outcomes, functional preservation and patient satisfaction.

Malignant pain

Pain is reported by 50–70% of patients afflicted with cancer [102]. Historically, adequate pain relief was thought to be achieved in less than half of cancer patients. A quarter of these patients succumbed to their disease while suffering from pain [103]. In many cases, multiple analgesics are administered before a reasonable degree of pain control is achieved. The complexity of targeting a multitude of pain components in the same individual, with potentially deleterious medication adverse effects, is challenging. Moreover, opioids, and specifically morphine, often have undesirable effects, an example being opioid-induced hyperalgesia. A paradoxical effect of opioid therapy, opioid-induced hyperalgesia is a pronociceptive condition that occurs in patients on chronic treatment with opioids. Opioid-induced hyperalgesia is increasing in prevalence as more patients are being treated long term with opioids. This complication should be kept in mind in any patient with failed opioid therapy, and should be addressed with patients even before starting an opioid [29]. Optimization of pain management in the cancer patient requires familiarity with different classes of analgesics and their potential toxicity. For example, NSAIDs inhibit platelet function and may lead to gastric ulceration and bleeding. For chemotherapy-treated cancer patients with previous gastrointestinal bleeding or nausea and/or vomiting, NSAIDs may not be ideal [30]. Morphine, the standard opiate for cancer pain, is metabolized primarily in the liver; however, it is secreted (along with its metabolites) through the kidneys. Therefore, it should be used with extra caution in cancer patients with underlying renal insufficiency [30]. For patients lacking enteral access for analgesia or those experiencing

nausea and vomiting, a transdermal patch of fentanyl has been embraced by palliative medicine specialists as an alternative opioid [31].

Various other general medical conditions influence the treatment of pain. Obesity is more prevalent in patients with rheumatologic conditions, particularly knee osteoarthritis and carpal tunnel syndrome, than in patients with no rheumatic disorders [32]. Higher BMI has been correlated with more tender points and physical dysfunctioning and lower quality of life in patients with fibromyalgia [33]. The management of obese patients with chronic pain is compounded by the weight-gain potential of some of the medications (e.g., amitriptyline and pregabalin). In the case of hypertension, medications that may interfere with blood pressure control include NSAIDs and SNRIs. When treating patients with a history of psychiatric impairments, particularly substance abuse, an attempt should be made to avoid using cannabinoids, which may lead to psychosis. Similarly, SNRIs should be carefully administered to patients with psychiatric comorbidities, as they may increase the risk of suicidal ideation. As stressed before, patients with chronic pain should be assessed using a systematic and holistic approach.

Patients with pain differ in their personal values, self perception and cultural background. Therefore, it is incumbent upon the treating physician to explore the identities and social worlds of his or her patients [34]. Such an approach, called the narrative perspective, is becoming increasingly recognized in the field of fibromyalgia [34]. Learning more about the individual through listening to storytelling, trying to appreciate the 'insider perspectives', the exact meaning and social impact an illness has, is valuable. It may allow the care provider to bolster relations with the patients, while helping inform treatment approach.

Individual variation to drug response: the genetic component

Patients with pain display marked variability in their response to analgesics. Such heterogeneity in drug effect is not obvious when analyzing entire populations, but is uncovered when focusing on individuals. In the case of morphine, a subset of patients gains no benefit when administered the medication; however, they would show clinical improvement upon switching to another opioid regimen. The varying degree of analgesia induced by opioids is just one reflection of the individualized response to pain medications; another is the extent of adverse effects, an important issue as it frequently precludes use of drugs, and may result in disability or even death.

Associations between gentotype and analgesic response are presented in Table 1 [35–44].

Plasma level of metabolites is tightly regulated by enzymatic biotransformation processes. One of the most thoroughly-researched pathways in opioid metabolism is the CYP2D6 system. Several opioids, including codeine, tramadol and oxycodone, are dependent on the CYP2D6 enzyme for bioactivation. These opioids undergo *O*-methylation, converting inert prodrug to active metabolites with potent μ-receptor activity [45]. Dozens of *CYP2D6* polymorphisms have been described [46]. The impact of these gene variations on patient phenotype can be divided into several groups: poor metabolizers, intermediate metabolizers, extensive metabolizers and ultrarapid metabolizers. Among Caucasian individuals, 10% are poor metabolizers, while 3% are ultrarapid metabolizers [40,47]. The former generate only small amounts of active metabolites and, thus, may achieve insufficient analgesia, while the latter are at higher risk for toxic effects [42,47]. Some opioids display narrower interindividual variability and, thus, may be safer to use. These include morphine, oxymorphone and hydromorphone, the three being *O*-demethylated metabolites. Serious consequences may result from inadvertent opioid overdose. These are best illustrated by a case of neonatal death ascribed to ingestion of codeine by a mother who was an ultrarapid metabolizer [48]. Opioid toxicity is also increased by copy number variation, which alters drug metabolism and response. In some cases, 13 functional copies of the *CYP2D6* gene have been identified in the same patient, theoretically increasing efficacy though with an added risk of toxicity.

A broad family of enzymes playing an important role in the metabolism of approximately one half of all known medications is CYP3A. Among opioid substrates of CYP3A are fentanyl and oxycodone, which require either CYP3A4 or CYP3A5 for their metabolism [41]. Studies have pinpointed numerous functional polymorphisms in the genes coding for CYP3A4/CYP3A5. A particular genetic polymorphism, namely the *CYP3A4*1G*, has been shown to reduce CYP3A activity and fentanyl requirements following surgery [42]. CYP3A4 and CYP3A5 are believed to affect the perception of pain in a synergistic fashion. Polymorphisms in genes coding for the two enzymes have additive effects and markedly influence postoperative analgesia.

UGT2B7 is the hepatic isoenzyme primarily responsible for the metabolism of morphine. The

catalytic activity of UGT2B7 yields two products from morphine: morphine-3-glucoronide and morphine-6-glucoronide. The former has weak affinity to opioid receptors and may induce a neuroexcitatory response (jerks, herperalgesia and allodynia) [49]. The latter has analgesic properties that, animal studies have revealed, are even more potent than those of morphine. Several genetic variations have been shown to be in correlation with morphine/metabolite ratios [50]. However, a clinical impact directly attributable to any polymorphism in the *UGT2B7* gene has yet to be defined.

The *ABCB1* gene regulates the expression of an important membrane transporter, the P-glycoprotein. Also termed the *MDR* gene, is novel pumping machinery that governs the transport of drugs across the blood–brain barrier. P-glycoprotein influences the concentrations of drugs and their metabolites, and is also related to development of central adverse reactions. Recent studies have found an association between the *ABCB1* 3435T allele and lower morphine consumption and greater pain relief in the oncology setting [38,39]. Two alleles of the *ABCB1* gene, 2677A and 3453T, have shown protective effect against nausea and vomiting, with the first also correlating with less mental status changes [51,52].

Several genetic variants of the μ-opioid receptor gene (*OPRM1*) have been studied. Several investigators have been successful in delineating an association between the exonic A118G single-nucleotide polymorphism of the *OPRM1* gene and increased morphine requirements in cancer or postoperative patients. A meta-analysis, however, showed only weak statistical significance [38,53,54]. The physiological function of *OPRM1* gene alleles and their relation to the individual opioid response remains to be elucidated.

The link between unique nucleotide patterns and specific clinical response continues to be investigated. Nevertheless, it is unclear how identification of functional genetic variants would change the therapy of pain patients. The presence of pharmacogenetic data for the individual patient seems a logical and potent accessory that would enhance our ability to improve outcomes. However, the practical utility of genotype–phenotype associations remains unknown (see the 'From the analgesic ladder to pharmacogenetics: a complex translation' section). One multicenter study examined the role of genotyping in pain patients treated with opioids [39]. Researchers identified imprints of all gene variants known to affect pain in a group of patients. They then tried to establish a correlation between distinct alleles and opioid dosing, pain score and side effects. The conclusions were that the laboratory effort to define genetic variants was not justified [39]. Only few alleles possessed sufficiently strong associations with the studied markers that could make them suitable for guiding treatment of patients.

Table 1. Summary of associations between genotype and analgesic response in patients with pain.

Gene	Polymorphism	Clinical effect	Ref.
OPRM1	rs1788871 (A118G)	Increased morphine requirements	[36,37]
ABCB1	rs1045642 (C3435T) rs1045642 (C3435T)	Decreased morphine requirements Increased pain relief with morphine	[38] [39]
CYP2D6	Poor metabolizers (codeine)	Decreased analgesia	[40]
CYP3A	*CYP3A5*3* and *CYP3A4*1G*	Decreased fentanyl requirements	[41,42]
COMT	rs4680 (G472A)	Decreased morphine requirements	[43]
TNF	rs1800629 (G308A)	Decreased pain relief	[44]
IL6	rs1800795 (G174C)	Increased dose requirements	[44]

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From the analgesic ladder to pharmacogenetics: a complex translation

To simplify the pharmacological approach to patients with pain, WHO devised, in 1986, an analgesic ladder [104]. At the core of this practical guide is a gradual stepping up of therapeutic intensity adapted to a patient's subjective experience of pain. The ladder was originally developed for cancer patients, and was divided into three steps. The first step, aimed at patients with mild pain, comes with a recommendation to use NSAIDs or acetaminophen (with an optional use of an 'adjuvant'). The second step, intended to treat mild-to-moderate pain, encourages use of weak opioids (e.g., codeine and tramadol) with or without agents mentioned in the first step. The third step, aimed at moderate-to-severe pain, supports the use of morphine with or without agents used in the first step [104]. Despite having provided a model to help standardize the management of (cancer) pain, the WHO three-step analgesic protocol lags behind present day scientific understanding of pain. The utility of the second step of the ladder has been intensively debated, with some studies showing insufficient, time-limited efficacy [55]. The role of weak opioids for mild-to-moderate pain also remains to be determined [56]. Another issue relates to medications included under the 'adjuvant analgesic' category, many of which are currently indicated as first-line therapy for different types of pain. Thus, the place adjuvant medications should

assume in the care of pain patients needs to be redefined.

Tailoring the unique molecular action of a medication to the cellular origin of an individual's pain holds great promise for improving clinical outcomes. Nevertheless, the road to gene-based interventions is bumpy and there are many caveats along the way. First, the perception of pain is a highly complex trait to accurately assess: it is subjective by nature and encompasses a multitude of phenotypes. From a research perspective, it is remarkably difficult to extrapolate data from animal models to humans. Second, pain is influenced not only by our genetic repertoire, but also by various environmental factors. Gender, ethnicity and the noxious stimulus itself affect the pain tolerance threshold, which makes an association between genotype and pain perception even more complex. For instance, females carrying the G118 allele of the *OPRM1* gene tend to have higher thermal pain ratings than those not having that allele, whereas males expressing that allele tend to have lower pain rating compared with males who do not [57]. Moreover, different ethnic groups vary by the specific nucleotide substitutions responsible for determining pain threshold. A polymorphism of the *OPRM1* gene (A118G) associated with pain–pressure sensitivity that is common in Caucasian populations is distinct from those found in Han Chinese individuals (IVS2 and A31G) [58]. In real life, concomitant use of medications often alters the activity of different CYP450 systems. A compilation of all medications known to inhibit CYP2D6 activity can be found online [101]. The implied message is that the genetic influence on pain is not exclusive and has tight and crucial collaterals. We must, therefore, apply special caution when interpreting results of genetic trials, whether they pertain to pain or not.

Starting to do this are the Clinical Pharmacogenetics Implementation Consortium guidelines. This practical tool has been created to inform therapy with codeine based on results of *CYP2D6* genotyping [59]. Its underlying pharmacodynamic/pharmacokinetic rationale is tailoring of an appropriate opioid-based analgesic to a patient's genotypic profile, with the end result being more effective analgesia and lower risk of systemic toxicity. The guidelines endorse using a noncodeine analgesic in patients who are ultrarapid metabolizers of the *CYP2D6* gene (to minimize adverse effects) and in those who are poor metabolizers (to avoid medication ineffectiveness) [59]. It is recommended to use a standard starting dose of codeine in patients with *CYP2D6* intermediate/extensive metabolizer phenotype [59]. The guidelines provide useful information to facilitate physicians' comprehension of pharmacogenomic data. They offer a calculated tone towards selection and/or dosing of codeine. Specifically, they reiterate the evidence base at the core of the recommendations, mentioning the specific experimental model used to show relation between genotype and drug metabolism/response [59]. They also pinpoint the technical hurdle resulting from the diverse laboratory methods that are used to determine patients' phenotypes and encourage the incorporation of an activity score based on the specific allele combination to classify patients according to phenotype

Psychophysical correlations as a bridge to personalized treatment

Several studies have focused on pain modulation patterns as potential predictors of medication efficacy. A group of investigators attempted to delineate patient subsets distinguished by pathophysiology of pain [7]. They utilized the concept of CPM, an indicator of the integrity of descending pain inhibition pathways. In most chronic pain states, administration of two simultaneous painful stimuli results in pain inhibition. Impairment of such inhibitory control is characteristic of several chronic pain populations. The researchers delivered a train of painful stimuli to patients with neuropathic pain, using a protocol termed temporal summation. Patients were then started on treatment with duloxetine. The investigators looked for an association between pain modulation patterns and responsiveness to medication [60]. Their working hypothesis was that duloxetine, a SNRI, induces different clinical effects in patients with normal CPM, compared with those showing altered baseline CPM. The results confirmed the researchers' theory: patients with lower pain inhibitory capacity had a greater response to duloxetine than those with normal CPM [60]. A point-of-care assessment of pain modulation may, therefore, elicit important data for drug selection in patients with neuropathic pain. Tackling interindividual variability in the response to a neuropathic medication, this study exposes the pain modulation mechanism as a quantifiable pathophysiological factor underlying the perception of pain. Should other drugs that decrease sensitization be similarly correlated with pharmacological efficacy, we may anticipate an array of nongenetic, psychophysical tools to enrich our decision-making armamentarium when encountering patients with chronic pain. Experimental

pain measures may well serve as a bridge to the genetic tailor-made approach to chronic pain of the future. Simpler to perform and interpret, these clinical assessments may help predict pain intensity and guide treatment strategy.

Conclusion & future perspective

Genotype-driven patient assessment and its direct implication on clinical practice represent a paradigm shift in the approach to chronic pain. Determination of genetic traits would, in the future, be a pain-specialist's microsurgical means of directing therapeutic strategies. Treatments would be selected based on the probable mechanism leading to pain so that a patient's likelihood of gaining clinical benefit is enhanced. However, it is worthwhile remembering that genetic code determination is not *sine qua non* with a personalized approach to pain. Subsets of individuals who are expected to respond favorably to a given medication can also be identified through nongenetic technologies.

It is important to note that, unlike most common medical conditions (e.g., hypertension, diabetes and chronic kidney disease) encountered by internal medicine specialists, the pain complex still relies primarily on self-reported symptoms. It is still missing inherent clinical or laboratory biomarkers that would provide objective evidence of symptom intensity or help define the natural history of a disease. We currently have no clear-cut tools to identify patients more likely to progress from acute pain to relentless chronic pain. We cannot tell which patients are going to develop related cognitive or physical comorbidities at a later point in time. Moreover, our studies overwhelmingly neglect the pivotal influence that environmental factors have on chronic pain. Until we augment our understanding of the complex intertwining gene–environment relations, we will not be able to perfect our discoveries and innovations in the field of pain. Together with more nuanced pain-related recognition of psychological, physiological and molecular processes, personalized medicine should soon be the holy grail of the management of chronic pain. Until we are there, the enigmatic puzzle of chronic pain should continue to occupy our thoughts and stimulate our curiosity.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Chronic pain is a leading cause of disability in the adult population.
- Appropriate classification of pain (e.g., nociceptive, neuropathic and functional) is grounded on pathophysiological understanding and is necessary for proper management of symptoms.
- Clinicians must apply a systematic approach to the management of patients with pain, taking into account diverse factors, such as age, weight, medications and physical and psychiatric comorbidities, but also the individual's values and social world.
- Individual pharmacogenomics properties govern both the beneficial and the detrimental effects of analgesic medications, and can be assessed by genotyping relevant *CYP* alleles, although its impact on clinical outcomes remains to be determined. Novel bedside psychophysical tests may help define the mechanism and nature of an individual's pain in some cases, yielding data that could potentially be integrated with that derived from more sophisticated gene-based assays.

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