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Potential biomarkers for persistent and neuropathic pain therapy

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ABSTRACT

Persistent, in particular neuropathic pain affects millions of people worldwide. However, the response rate of patients to existing analgesic drugs is less than 50%. There are several possibilities to increase this response rate, such as optimization of the pharmacokinetic and pharmacodynamic properties of analgesics. Another promising approach is to use prognostic biomarkers in patients to determine the optimal pharmacological therapy for each individual. Here, we discuss recent efforts to identify plasma and CSF biomarkers, as well as genetic biomarkers and sensory testing, and how these readouts could be exploited for the prediction of a suitable pharmacological treatment. Collectively, the information on single biomarkers may be stored in knowledge bases and processed by machine-learning and related artificial intelligence techniques, resulting in the optimal pharmacological treatment for individual pain patients. We highlight the potential for biomarker-based individualized pain therapies and discuss biomarker reliability and their utility in clinical practice, as well as limitations of this approach.

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1. Introduction

The FDA defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention" (Biomarkers Definitions Working Group, 2001). Biomarkers for pain therapy, ideally, would predict onset and intensity of pain, the risk of development toward persistent pain, and could be used as readouts for the optimal and individual pharmacological treatment of pain patients. Although persistent and neuropathic pain usually consist of both a neurological and an inflammatory component, there is rarely a systemic inflammatory response. The site of inflammation is usually locally restricted, which makes it difficult to determine a systemic plasma or serum derived biomarker for neuropathic pain. Moreover, the inflammatory contribution to neuropathic pain depends on its etiology and

Abbreviations: BDNF, *Brain-derived neurotrophic factor*; CGRP, calcitonin-gene related peptide; CYP, Cyotochrome-P_{450}-oxygenase; EpOME, Epoxy-octadecenoic acid; FZD, Frizzled Receptor; GABA, γ-aminobutyric acid; GDNF, Glial cell-derived neurotrophic factor; HODE, Hydroxy-octadecadienoic acid; HTR, serotonin receptor; IL, interleukin; KCNS, Potassium Voltage-Gated Channel Modifier; KCNK, two-pore-domain potassium channel; LPAR, Lysophosphatidic Acid Receptor; NGF, nerve growth factor; OPRM, Opioid Receptor Mu; P2X, *Purine* gated ion channel; PGE_2, Prostaglandin E_2; pNF-H, phosphorylated high-molecular-weight neurofilament heavy subunit; SCN, Sodium Voltage-Gated Channel; SNP, single nucleotide polymorphism; TNF, tumor necrose factor; TRPA, transient receptor potential ankyrin; TRPM, transient receptor potential melastatin; TRPV, transient receptor potential vanilloid.

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may profoundly differ, for instance in nerve injury neuropathies versus toxic neuropathies.

It may be more appropriate, therefore, to test for various types of biomarkers. These could include plasma- or CSF-molecules, as classical biomarkers, but also single nucleotide polymorphisms (SNPs) in genes that are related to pain pathophysiology as genetic biomarkers. Moreover, quantitative sensory testing (QST), as a sensory biomarker, would provide information on the quality of pain, its intensity and distribution. The collective information from these different biomarkers, processed to obtain an individual patient pain profile, can then be used as the basis for a decision on an individual pharmacological treatment.

In addition, determining differential activity in distinct brain regions by modern imaging has revealed potential biomarkers in persistent pain. The role of brain imaging, however, in the identification of biomarkers has recently been reviewed (Davis et al., 2017; Morton, Sandhu, & Jones, 2016). Here, we focus on biomarkers in plasma and CSF as well as genetic and sensory biomarkers in chronic inflammatory and neuropathic pain states.

2. Plasma biomarkers

The ideal biomarker would be a chemically stable small molecule, easily quantifiable in the plasma of patients, the concentration of which could be used to predict the onset, persistence and drug susceptibility of the patient's pain state. Unfortunately, we are still far away from such a scenario. Ideally, a biomarker for pain would be specific for pain rather than being regulated by the pathophysiologic context of which pain is merely a symptom (Kringel et al., 2018). Thus, a biomarker for rheumatic pain should ideally be associated with the pain and not with the underlying inflammatory processes in the joint. However, this distinction is currently barely possible. Defining threshold concentrations for a plasma molecule as a surrogate endpoint is particularly difficult in neuropathic pain because these concentrations may differ profoundly depending on the etiology of the particular pain state. For most neuropathic pain states with mixed neurological and inflammatory contributions, it may be more promising to measure a panel of several different small molecules or peptides and to determine patterns of these molecules to predict the severity of a neuropathic pain state or to suggest a pharmacological treatment. For other neuropathic pain states, a defined analyte may be easier to determine. For example, in toxic neuropathies, a metabolite of the toxic substance that causes the neuropathy may be measured in the plasma. The concentrations of the toxic metabolite can then be related to its rate of catabolism and it may be used as surrogate marker to predict duration and severity of neuropathic pain.

Nonetheless, in recent years, several molecules have been identified in the blood of pain patients that are altered during persistent or neuropathic pain states and thus, may serve as biomarkers.

2.1. Lipid mediators

During inflammation, cyclooxygenase 2 (COX-2) oxidizes arachidonic acid to generate prostanoids. Particularly prostaglandin E_2 (PGE_2) is detectable at increased concentrations in the plasma during inflammation and inflammatory pain, during which it causes sensitization of peripheral sensory neurons (Ricciotti & FitzGerald, 2011; St-Jacques & Ma, 2014). For example, in patients with postoperative pain, the plasma concentrations of PGE_2 are rapidly elevated after surgery (Buvanendran et al., 2006; Takada et al., 2007). Non-steroidal anti-inflammatory drugs, which are widely used for the treatment of inflammatory pain, prevent excessive synthesis of PGE_2 and markedly reduce prostanoid plasma concentrations (FitzGerald, 2003; Takada et al., 2007). Plasma concentrations of PGE_2 and ratios of PGE_2 to other prostanoids, such as thromboxane B2, have previously been suggested as biomarkers to predict effective treatment doses of NSAIDs in patients suffering from rheumatoid arthritis (Huntjens, Danhof, & Della Pasqua, 2005).

However, the degree of inflammation and the contribution of inflammatory mechanisms to persistent and neuropathic pain states strongly depend on their etiologies (Ji, Xu, & Gao, 2014). This restricts the potential use of PGE_2 and other inflammatory mediators as biomarkers only to pain states with a strong inflammatory component, such as pain during rheumatoid arthritis. Moreover, recent work also suggested a potential role for PGE_2 in the resolution of systemic inflammation via the production in the gut of IL-22 (Duffin et al., 2016). In this case, increased plasma concentrations of PGE_2 may be mistaken as reflecting a proinflammatory state. Therefore, a profile of various inflammatory markers is needed to determine the exact inflammatory state of the patient and to predict potential treatment efficacy.

Apart from prostanoids, the oxidized linoleic acid metabolites 9,10-EpOME (9,10- epoxy-9Z-octadecenoic acid) and 9-HODE (9-hydroxy-10E,12Z-octadecadienoic acid) have recently been proposed by us as potential biomarkers for chemotherapy-induced neuropathic pain (CINP), a toxic neuropathy and severe side effect of widely used cytostatics (Park et al., 2013) (Hohmann et al., 2017; Sisignano et al., 2016). In animal studies, the generation of these hydroxylipid biomarkers could be directly correlated with the nociceptive response and vice versa with its pharmacological inhibition. Future studies are needed to determine the potential role of these signaling lipids as biomarkers of pain.

2.2. Nerve growth factor (NGF)

The nerve growth factor NGF belongs to the family of neurotrophins and binds mainly to two receptors in peripheral sensory neurons, the TrkA-receptor homodimer and a heterodimer of TrkA and $p75^{NTR}$ (Sofroniew, Howe, & Mobley, 2001). Activation of these receptors results in the initiation of signaling cascades in sensory neurons. These involve activation of the PI3K-AKT pathway and ERK-phosphorylation, as well as activation of the protein kinases PKCγ and PKA, leading to sensitization of ion channels, such as TRPV1, and subsequently to enhanced nociceptive activity and inflammatory pain (Denk, Bennett, & McMahon, 2017; Woolf, Safieh-Garabedian, Ma, Crilly, & Winter, 1994). NGF produces hypersensitization in human experimental pain models (Munkholm & Arendt-Nielsen, 2017), and elevated NGF levels were found in the plasma of patients suffering from persistent inflammatory pain states, such as bladder pain syndrome (Chen et al., 2016), chronic prostatitis (Watanabe et al., 2011) and chronic migraine (Jang, Park, Kho, Chung, & Chung, 2011). Moreover, increased NGF was found in synovial fluid from arthritis patients (Halliday, Zettler, Rush, Scicchitano, & McNeil, 1998). Indeed, treatment of patients suffering from pain induced by osteoarthritis of the knee with tanezumab, a humanized antibody against NGF, markedly reduced pain in these patients in a randomized placebo-controlled clinical trial involving 450 patients. This indicates that anti-NGF-therapy may be beneficial in the treatment of osteoarthritis induced pain (Lane et al., 2010). However, initial hopes were dampened, because of clinical complications with anti-NGF-treatment. Preclinical data also suggested central nervous toxicity of the anti-NGF-treatment, which led the FDA to put all clinical development of NGF-antibodies on hold for five years. This moratorium was lifted in 2015 after dose-restrictions for anti-NGF-antibodies were set for further clinical trials (Mullard, 2015). Despite the beneficial effects of anti-NGF-therapy in pain induced by osteoarthritis, its effects in neuropathic pain are controversial (Bramson et al., 2015; Wang et al., 2014). Notably, plasma NGF concentrations seem to vary between neuropathic pain states, indicating that the contribution of NGF to each specific neuropathic pain state differs depending on the neuropathic pain etiology (Chang, Hsu, Hottinger, & Cohen, 2016). This led to the hypothesis that anti-NGF-therapy is only beneficial in reducing neuropathic pain when plasma NGF concentrations in the specific neuropathic pain state are elevated. Consequently, assay of plasma NGF concentrations

may be used as a companion diagnostic tool to predict efficacy of anti-NGF-therapy and to suggest adequate dosing.

2.3. Tetrahydrobiopterin (BH_4)

A study in 2006 correlated a genetic variant of the gene encoding for GTP cyclohydrolase (GCH1), carried by about 2 percent of the population, with decreased risk for developing persistent pain. A major product of GCH1 activity is tetrahydrobiopterin (BH_4), an important biochemical cofactor, that is essentially required, for instance for the synthesis of aromatic amino acids and nitric oxide. Further studies confirmed that the levels of BH_4 in sensory neurons of animals and in blood from patients seem to correlate with pain sensitivity, thus making it a promising marker for pain intensity in patients (Latremoliere et al., 2015; Tegeder et al., 2006). However, the range of plasma concentrations of BH_4 that separate its physiological functions from those clearly associated with increased pain sensitivity in patients has yet to be determined.

2.4. Cytokines

2.4.1. Interleukin 6 (IL-6)

In a clinical study, the recovery of 110 patients who suffered from lumbar radicular pain was monitored for one year. The authors observed that high levels of IL-6 in the serum were associated with worse recovery (Schistad et al., 2014). Moreover, patients who developed postherpetic neuralgia (PHN), a neuropathic pain syndrome that may follow *Varicella zoster* infection (Johnson & Rice, 2014), seem to have higher levels of IL-6 in the plasma compared with patients who do not develop post-infective neuralgia (Zhu, Liu, An, & Chen, 2009). However, the increase in circulating IL-6 levels seems to depend on the etiology of neuropathic pain. Thus, in a clinical study comparing patients with painful neuropathies and patients with non-painful neuropathies, the authors failed to observe any difference in IL-6 levels in patients. Only patients with severe neuropathy showed higher circulating IL-6 levels than those with mild neuropathy (Ludwig, Binder, Steinmann, Wasner, & Baron, 2008). In pain syndromes with a stronger inflammatory component, pro-inflammatory cytokines such as IL-6 may be more promising as biomarkers. In a meta-analysis covering 25 articles with 1255 patients suffering from fibromyalgia syndrome (FMS), the authors conclude that FMS patients had higher serum levels of IL-6 than the controls (Uceyler, Hauser, & Sommer, 2011). It should also be born in mind that IL-6 is a non-specific marker of inflammatory responses and fever and is also increased in blood during inflammation in the absence of pain.

2.4.2. Tumor necrosis factor alpha (TNFα) and interleukin 2 (IL-2)

A study published in 2001 reported up-regulated TNFα expression by human Schwann cells in patients with painful neuropathies (Empl et al., 2001). Similar results were obtained in a study from 2007, that identified increased mRNA and protein levels of both TNFα and IL-2 in the blood of 58 patients with painful neuropathy, compared with patients with non-painful neuropathy or healthy subjects (Uceyler, Rogausch, Toyka, & Sommer, 2007). Similar results were obtained in a study from 2001 in which TNFα expression by human Schwann cells was found to be up-regulated in patients with painful neuropathies (Empl et al., 2001). Again, TNFα as a fundamental mediator of inflammation, is not only raised in the blood of patients suffering from a painful condition.

Although IL-6 or TNFα may be useful serum biomarkers, more data is needed. Moreover, neuropathic pain patients need to be stratified in clinical trials according to their pain syndrome and not to their disease symptoms. This should permit identification of pain syndromes in which IL-6 or TNFα concentrations are specifically and significantly altered and define threshold concentrations of these cytokines as risk factors for increased intensity of pain.

2.5. CGRP (calcitonin gene related peptide) in peripheral blood of migraine patients

A migraine attack starts with increased trigeminal nerve activity, followed by release of CGRP, a neuropeptide that causes vasodilation and neurogenic inflammation (Edvinsson & Uddman, 2005; Ho, Edvinsson, & Goadsby, 2010). Indeed, humanized antibodies against CGRP or its G-protein-coupled receptor are considered as promising novel therapeutics for the pharmacological treatment of migraine (Diener, Charles, Goadsby, & Holle, 2015). Recently conducted randomized and placebo-controlled trials report that treatment of chronic migraine patients with the CGRP antibody fremanezumab or the recently approved CRGP receptor-inhibiting antibody erenumab, reduced migraine frequency (Silberstein et al., 2017; Tepper et al., 2017). In a further clinical study involving 103 female patients suffering from chronic migraine, defined as 15 or more headache days per month for at least 3 months, the CGRP concentrations in peripheral blood of migraine patients were significantly higher compared with healthy control subjects. Interestingly, these concentration differences were observed between the migraine attacks and could thus, be used as a predictive risk biomarker for subsequent migraine attacks (Cernuda-Morollon et al., 2013). The results also indicate that plasma concentrations of CGRP in migraine patients may be used as a predictive biomarker for the efficacy of anti-CGRP-therapy. However, a recent study involving 106 episodic and 50 chronic migraine patients concludes that serum CGRP concentrations did not reflect pain intensity or susceptibility to migraine treatments and did not correlate with changes in monthly headache frequency (Lee, Lee, Cho, Kang, & Chung, 2018). The discrepancy between these studies may be explained by differences in the study protocols and the use of plasma versus serum for CGRP measurement. Moreover, the release of CGRP caused by triggering the trigeminal nerve is known to be transient and the time window of elevated systemic CGRP concentrations may be narrow, so that the time point of peak CGRP concentrations can easily be missed. It may thus, be useful to analyze systemic CGRP concentrations over a period of time to identify potential peak concentrations within migraine attacks.

2.6. pNF-H (phosphorylated high-molecular-weight neurofilament heavy subunit)

The phosphorylated high-molecular-weight neurofilament heavy subunit pNF-H is a cytoskeleton protein subunit that is abundant in sensory neurons and may be a candidate serum biomarker for axonal damage (Hayakawa et al., 2012). However, in neuropathic pain, its role as a biomarker for neuronal damage remains controversial. In a clinical study published in 2015, involving 76 breast cancer patients who suffered from chemotherapy-induced neuropathic pain (CIPN), the authors observed elevated serum levels of pNF-H which increased in a cumulative, dose-dependent manner (Natori et al., 2015). However, in another study with 71 CIPN patients, the authors concluded that pNF-H is not useful as a biomarker of CIPN (Sumitani et al., 2016). The mechanisms of CIPN differ profoundly depending on the cytostatic drug or treatment regimen that is used (Sisignano, Baron, Scholich, & Geisslinger, 2014). It may therefore, be necessary to stratify the patients into groups with the same cytostatic treatment to conclusively evaluate the usefulness of pNF-H as a biomarker for CIPN (Fig. 1, Table 1).

3. CSF biomarkers – cytokines, neurotrophins and neurotransmitters

As stated above, finding a systemic biomarker to clearly distinguish between a physiological and a pathophysiological pain state is difficult. However, the cerebrospinal fluid (CSF) may be a more promising matrix to analyze for potential biomarkers than the blood. It is in direct contact with the CNS and because of its small volume, enrichment occurs of small molecules, peptides or proteins that are released from CNS

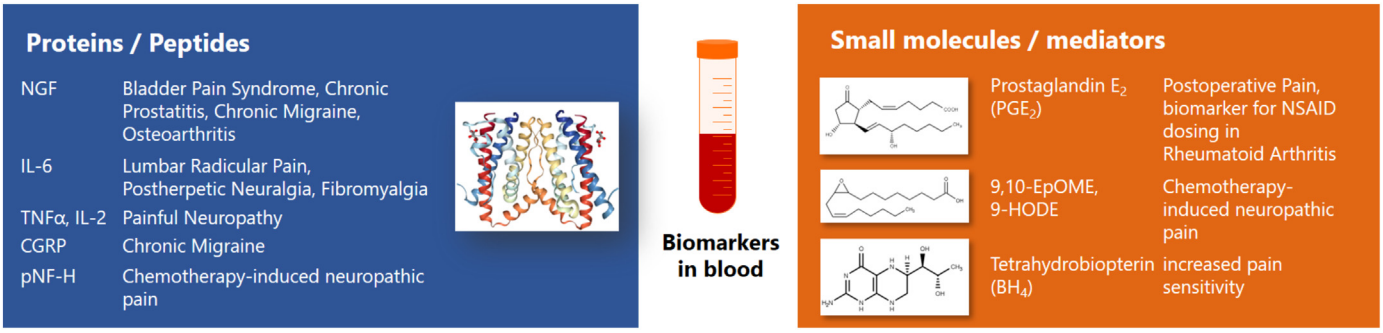

Fig. 1. Potential biomarkers in blood. Left: proteins and peptides, such as growth factors and cytokines. Protein structure: human Interleukin 6, PDB: 1ALU from Somers *et al.,* (Somers, Stahl, & Seehra, 1997). Right: small molecules, such as lipid mediators and the cofactor BH_4. Structures of Prostaglandin E_2, 9,10-EpOME and BH_4 are shown and were drawn with MarvinSketch v16. For schematic drawings Scientific Illustration Toolkits from Motifolio were used. Abbreviations: NGF: nerve growth factor; IL-6: Interleukin-6; TNFα: Tumor necrosis factor alpha; CGRP: calcitonin-gene related peptide; pNF-H: phosphorylated high-molecular-weight neurofilament heavy subunit

neurons or immune cells (Sakka, Coll, & Chazal, 2011). Indeed, CSF is currently used to determine biomarkers for Alzheimer's Disease (Mattsson et al., 2009).

There are several reports of small molecules, peptides or proteins that are present in the CSF at increased levels in persistent or neuropathic pain patients. For example, the glial cell line-derived neurotrophic factor (GDNF) and IL-8 were increased in the CSF of persistent pain patients. However, the levels in the blood did not show any differences compared with the control subjects (Lundborg, Hahn-Zoric, Biber, & Hansson, 2010). This indicates that concentration changes in these molecules during persistent pain may be too subtle to detect them systemically in the blood and that the CSF allows more focused analysis.

In a study with 39 patients suffering from lumbar disc herniation, IL-8 was increased in the CSF of patients with symptoms of shorter duration, indicating locally acute rather than prolonged inflammatory responses shortly after disc herniation (Brisby, Olmarker, Larsson, Nutu, & Rydevik, 2002). Another group investigated the CSF levels of neurotrophins and neurotransmitters in 20 patients with chronic migraine. They found increased CSF concentrations of the pronociceptive excitatory neurotransmitter glutamate, as well as the growth factors NGF and BDNF (*brain-derived neurotrophic factor)* in the pain patients compared with control subjects (Sarchielli et al., 2007). Increased concentrations of NGF as well as the neuropeptides, substance P and CGRP, were observed in the CSF of patients suffering from chronic daily headache (CDH) (Sarchielli, Alberti, Floridi, & Gallai, 2001). Moreover, in a study comparing 19 migraine patients with healthy controls, increased CSF levels of the neurotransmitter GABA were found in the migraine patients (Bigal et al., 2008) (Table 1). Thus, while clearly increased markers of pain states can be detected in the CSF, it remains to be seen how selective these are for the various types of pain. (Fig. 2, Table 1)

Table 1
Potential blood and CSF biomarkers of pain.

Molecule	Type of mediator	Indication	Reference(s)
Blood biomarkers			
Prostaglandin E_2 (PGE_2)	Lipid metabolite	Increased rapidly in the plasma during postoperative pain after surgery	Buvanendran et al. (2006); Takada et al. (2007) Huntjens et al. (2005)
		Prognostic biomarker to predict effective treatment doses of NSAIDs in patients suffering from rheumatoid arthritis	
9,10- EpOME, 9-HODE	Lipid metabolites	Potential biomarkers for Chemotherapy-induced neuropathic pain	Hohmann et al. (2017); Sisignano et al. (2016)
Nerve Growth Factor (NGF)	Protein	Increased in the plasma of patients suffering from • bladder pain syndrome • chronic prostatitis • chronic migraine	• Chen et al., (2016) • Watanabe et al. (2011) • Jang et al. (2011) Halliday et al. (1998)
		Increased levels in synovial fluid of arthritis patients	
Tetrahydrobiopterin (BH_4)	Biochemical cofactor	Potential prognostic biomarker for increased pain sensitivity	Latremoliere et al. (2015); Tegeder et al. (2006)
Interleukin 6 (IL-6)	Cytokine	Lumbar radicular pain, Postherpetic Neuralgia, Fibromyalgia	Johnson & Rice (2014); Ludwig et al. (2008); Schistad et al. (2014); Uceyler et al. (2011); Zhu et al. (2009)
TNFα, IL-2	Cytokines	Painful Neuropathy	(Empl et al. (2001); Uceyler et al. (2007)
CGRP	Peptide	Chronic Migraine	Cernuda-Morollon et al. (2013)
pNF-H	Protein	Chemotherapy-induced neuropathic pain	Hayakawa et al. (2012); Natori et al. (2015); Sumitani et al. (2016)
CSF-biomarkers			
GDNF	Growth factor	Persistent Pain	Lundborg et al. (2010)
IL-8	Cytokine	Persistent Pain, inflammation after lumbar disc herniation	Brisby et al. (2002)
NGF, BDNF	Protein	Chronic Migraine	Sarchielli et al. (2007)
NGF, substance P, CGRP	Protein, Neuropeptides	Chronic daily headache (CDH)	Sarchielli et al. (2001)
Glutamate	Neurotransmitter	Chronic Migraine	Sarchielli et al. (2007)
GABA	Neurotransmitter	Chronic Migraine	Bigal et al. (2008)

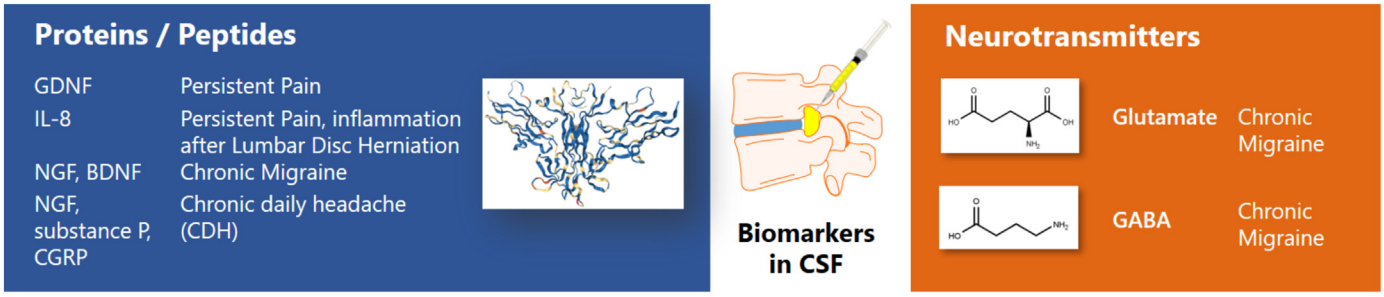

Fig. 2. Potential biomarkers in cerebrospinal fluid (CSF). Left: proteins and peptides, such as growth factors and cytokines. Protein structure: human nerve growth factor (NGF) 6, PDB: 1WWW from Wiesmann *et al., (Wiesmann, Ultsch, Bass, & de Vos, 1999)*. Right: neurotransmitters Glutamate and GABA, Structures were drawn with MarvinSketch v16. For schematic drawings Scientific Illustration Toolkits from Motifolio were used. Abbreviations: GDNF: glial cell line-derived neurotrophic factor; BDNF: Brain-derived Neurotrophic Factor; CGRP: calcitonin-gene related peptide; GABA: *gamma-aminobutyric acid.*

4. Genetic biomarkers

4.1. Ion channel gene SNPs

Genetic biomarkers can be used for special pain syndromes that are correlated with single nucleotide polymorphisms (SNPs) in sodium, potassium or calcium channel or transmitter transporter genes that are important for neuronal function, action potential generation and transmission. An example is a point mutation (2564A>G) in the *TRPA1* (transient receptor potential ankyrin 1)-gene. that leads to an exchange of amino acids in the resulting protein (N855S). The mutation leads to a drastic increase in channel activity in patients with familial episodic pain syndrome (FEPS1) (Kremeyer et al., 2010). In another study, point mutations in the *TRPV1* and *TRPA1* genes were associated with sensory changes in neuropathic pain patients (Binder et al., 2011). Moreover, point mutations in the gene encoding for TRPV4 (transient receptor potential vanilloid 4) have been related to congenital distal motor neuropathy and Charcot–Marie–Tooth disease type 2C (CMT2C), both of which are inherited diseases that involve degradation of motor and sensory neurons (Landoure et al., 2010; Nilius & Voets, 2013). A recent publication also identified TRPV1 expression in brain microglia under physiological conditions. At the onset of neuropathic pain, however, TRPV1 seems to be expressed in neurons, indicating an expression shift of TRPV1 in different brain cell types during early neuropathic pain in mice. TRPV1 expression in neurons in the brain may thus, be an early marker for neuropathic pain (Marrone et al., 2017). However, these expression changes cannot be identified in patient blood samples. Thus, further research is needed to elucidate the role of increased TRPV1 expression in CNS neurons during neuropathic pain.

Apart from TRP channels, nucleotide receptors and potassium channels are important for the regulation of neuronal excitability and mutations in their genes may have consequences for the activity of peripheral sensory neurons. In the gene encoding for the nucleotide receptor P2X7, which is an ionotropic ATP-gated receptor expressed in sensory neurons, a SNP was identified in two patient cohorts with persistent pain caused by mastectomy or osteoarthritis that is associated with lowered pain intensity (Sorge et al., 2012). Additionally, a SNP in a gene for the potassium channel subunit KCNS1 causes an exchange of amino acids and decreased activity of the protein, which may result in increased hypersensitivity of peripheral sensory neurons and increased pain perception in patients (Costigan et al., 2010).

The highest number of known SNPs that are related to painful syndromes are found within genes encoding for voltage gated sodium channels, such as $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ (encoded by the genes *SCN9A, SCN10A* and *SCN11A*) which are predominantly expressed in peripheral sensory neurons (Bennett & Woods, 2014).

Several mutations have been identified in these genes, that lead to amino acid exchange, to altered activity and kinetics of these ion channels and to alterations in amplitude and frequency of action potentials in peripheral sensory neurons (Waxman, 2013). Some of the mutations have been identified as gain of function mutations, causing inherited pain syndromes due to excessive activity of the ion channels and hyperexcitability of peripheral sensory neurons (Brouwer et al., 2014; Waxman, 2013). For example, several gain-of-function mutations in the gene of $Na_v1.7$ were identified in patients with small fiber neuropathy and several missense mutations were identified in the gene of $Na_v1.9$ in patients with peripheral neuropathy (Faber et al., 2012; Huang, et al., 2014). Likewise, two SNPs have been identified that cause exchange of amino acids in the $Na_v1.8$ channel (L554P and A1304T). This results in increased activity of the channel and may lead to increased pain intensity in patients with painful neuropathy (Faber et al., 2012). In contrast, other mutations in sodium channel genes seem to reduce pain perception. Recently, a gain of function mutant in the gene of $Na_v1.9$ was identified, that causes loss of pain perception due to constant depolarization of $Na_v1.9$ expressing sensory neurons (Leipold et al., 2013). The various sodium channel SNPs have been reviewed in detail elsewhere (Bennett & Woods, 2014; Brouwer et al., 2014).

Once specific SNPs are associated with a pathophysiological phenotype in pain syndromes, the respective ion channel or receptor can be specifically modulated with a selective drug. Recently, SNPs causing a gain of function mutation in the sodium channel $Na_v1.7$ were identified in patients with inherited erythromelalgia (IEM), a pain syndrome that causes a strong sensitization of sensory neurons. The subsequent treatment of two patients who carry this mutation, with the sodium channel blocker carbamazepine alleviated neuropathic pain (Geha et al., 2016). Of course, the patient number was too low to draw conclusions from this form of therapy, but the study indicates that genetic biomarkers may be useful for the assessment of treatment of neuropathic pain in patients. Similarly, patients with FEPS1 will probably benefit from an individualized therapy with one of the many novel TRPA1 antagonists under current clinical development (Weyer-Menkhoff & Lotsch, 2018).

4.2. SNPs in genes for G-protein coupled receptors (GPCRs)

Despite the large number of G-protein coupled receptors that can modulate nociceptive processing, as well as peripheral and central sensitization (Pan et al., 2008), only a few alterations are known in their genes that may lead to a different phenotype in pain perception and persistence.

Several SNPs have been reported in the gene for the serotonin-receptor 2A (encoded by *HTR2A*) that may be associated with higher susceptibility to rheumatoid arthritis (Kling et al., 2008). In a study on 49 healthy individuals, a SNP was identified in the gene for the sister serotonin-receptor 1A (encoded by *HTR1A*). This SNP seems to be associated with reduced thermal pain, as carriers of the G-allele of the *HTR1A* SNP rs6295 have reduced pain in response to mild thermal stimuli (Lindstedt et al., 2012). Apart from neurotransmitter receptors, little is known about SNPs in other GPCRs that may be responsible for altered

nociceptive processing. Interestingly, in a study on 368 patients, a SNP in the gene for the LPA1-receptor 1 (formerly EDG2) was found that may be correlated with increased susceptibility to knee osteoarthritis (Mototani et al., 2008). LPA1R is a receptor for the lysophospholipid lysophosphatidic acid (Blaho & Hla, 2011) and several lipid GPCRs have already been shown to modulate pain hypersensitivity in inflammatory and neuropathic pain states (Hohmann et al., 2017; Ji et al., 2014; Shimizu, 2009). This finding indicates that SNPs in lipid GPCRs may be equally important genetic biomarkers as SNPs in ion channel genes.

4.2.1. Opioid receptors

Well-known G-protein coupled receptors involved in pain and analgesia include opioid and cannabinoid receptors, both families being targets for endogenous pain modulating compounds and at least partly effective exogenous analgesic drugs. Opioid signaling is triggered by endogenous opioid peptides comprising endorphins, enkephalins and dynorphins. These endogenous opioids show receptor preferences and dynorphins preferentially bind κ-opioid receptors, whereas enkephalins and endorphins bind both μ-, and δ-opioid receptors (Dhawan et al., 1996). The existence of opioid binding sites in the brain was established in 1973 (Pert & Snyder, 1973) and subsequently attributed to various different physiological systems. In both peripheral (Kobal, 1985; Stein, 1995) and central (Bushnell et al., 1999; Lee, Wanigasekera, & Tracey, 2014; Price, 2000) areas of the nociceptive system, activation confers an effective nocifensive mechanism. However, the expression of opioid receptors is not just restricted to the nocifensive system. Activation of opioid receptors in the *Area postrema* causes respiratory depression (Lötsch, Dudziak, Freynhagen, Marschner, & Geisslinger, 2006) and their activation in brain areas associated with the reward system (Borras et al., 2004) is involved in addiction (Bond et al., 1998; Kirson et al., 2014; Wand et al., 2002). Activation of opioid receptors in the gastrointestinal tract causes constipation (Mosińska, Zielińska, & Fichna, 2016), and their activation in the hypothalamic–pituitary–adrenal (HPA) axis is involved in stress responses (Drolet et al., 2001). This widespread importance of opioid signaling is the basis for several genetic effects associating variants in opioid receptor genes with pain and with wanted and unwanted effects of opioid analgesics.

The major human opioid receptor genes, *OPRM1*, *OPRK1* and *OPRD1*, located on chromosomes 6, 8, and 1, encode for the three major (μ, κ, δ) opioid receptors, respectively. In addition, the *SIGMAR1* gene, located on chromosome 9 and coding for σ_1-opioid receptors, belongs to this class although σ_1-opioid receptors are not activated or blocked by opioid peptides or naloxone. Historically, though, they have been categorised as opioid receptors (Martin, Eades, Thompson, Huppler, & Gilbert, 1976) and are targets of some drugs classified as opioids, such as pentazocine (Narayanan, Bhat, Mesangeau, Poupaert, & McCurdy, 2011) or dextromethorphan (Werling, Keller, Frank, & Nuwayhid, 2007). Nevertheless, as most currently clinically used opioid analgesics are μ-opioid receptor agonists, genetic biomarkers have been sought mainly in the sequence of the human *OPRM1* gene. The most pronounced genetic effect is conferred by the 802T>C *OPRM1* SNP, which abolished opioid signaling almost completely *in vitro* (Befort et al., 2001; Koch et al., 2000). However, this variant was found only in a single family. By contrast, a more common *OPRM1* variant, 118A>G SNP, has an allelic frequency ranging from 1% in Africans to almost 50% in some Asian ethnicities, (https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1799971). It is associated with both reduced opioid receptor signaling efficiency (Befort et al., 2001; Oertel et al., 2009) and expression (Zhang, Wang, Johnson, Papp, & Sadee, 2005), the latter probably due to a genetic-epigenetic interaction as the variant introduces a CpG methylation site into the *OPRM1* gene (Oertel et al., 2012). The variant has been shown to decrease the sensory perception of pain in human experimental settings (Fillingim et al., 2005; Lötsch, Stuck, & Hummel, 2006) and to reduce the analgesic effects of opioids in both experimental (Oertel et al., 2010; Oertel, Schmidt, Schneider, Geisslinger, & Lötsch, 2006; Skarke, Darimont, Schmidt, Geisslinger, & Lötsch, 2003) and clinical settings (Klepstad et al., 2004). Consistent with the widespread importance of the opioid system, the 118A>G variant also reduces opioid effects on pupil constriction (Lötsch et al., 2002), ameliorates respiratory depression (Oertel et al., 2006) and opioid-induced sedation (Lötsch et al., 2002) and interferes with addiction such as that to nicotine (Kong, Deng, Alston, Kong, & Wang, 2017) or ethanol (Pratt & Davidson, 2009) or with stress responses (Wand et al., 2002). However, its utility as a biomarker for pain or for the response to opioid therapy is insufficient. Meta-analyses of its predictive value judged the evidence for this as poor (Walter & Lötsch, 2009) or insufficient (Carmen Walter, Doehring, Oertel, & Lötsch, 2013). Only when including comparatively newer studies performed in Asians, was the predictive role judged more positively (Somogyi et al., 2016).

However, even when accepting the greater importance of the 118 A>G SNP for an Asian ethnic background, because of its higher frequency, the variant is unlikely to provide a satisfactory biomarker for pain or opioid analgesia. The reason for this is its small effect size (Doehring et al., 2011) and the confounding effects of concomitant variants in the opioid receptor or other genes which partly counteract its regulation (Lötsch, Fluhr, Neddermayer, Doehring, & Geisslinger, 2009). Even among the opioid receptor genes, other variants, summarized previously (Lotsch & Geisslinger, 2005), contribute further modulation of opioid related phenotypes. This emphasizes the need for broader approaches to the genetic modulation of pain and analgesia, recently facilitated by the availability of next generation sequencing and the development of data science tools to exploit the vast amount of data available for clinical associations. In a recent analysis of patients with particularly high clinical demands for opioid analgesia (≥ 400 mg daily oral morphine equivalents), the 118A>G variant was found to be unimportant. But a combined biomarker set, composed of the 34 most informative markers in the *OPRM1*, *OPRK1*, *OPRD1* and *SIGMAR1* genes revealed a pattern of genotypes that identified, with a k-nearest neighbor (kNN) classifier, the high-opioid demanding phenotype with a diagnostic accuracy of 80.6 ± 4 % (Kringel et al., 2017).

4.3. SNPs in other genes

Several studies indicate the involvement in chemotherapy-induced neuropathic pain of SNPs in genes encoding for metabolic or transport proteins (Cavaletti, Alberti, & Marmiroli, 2011). Among these metabolic proteins, CYP-epoxygenases are important proteins for the degradation of xenobiotics and SNPs in the genes encoding for CYP2C8 and CYP3A4 may be associated with the intensity of paclitaxel-induced neuropathic pain in patients (Leskela et al., 2011). Paclitaxel is metabolized via CYP2C8 and possibly also via CYP3A4 or CYP3A5 (Wang et al., 2014). The SNPs in these genes may modulate CYP-activity, thereby decreasing the metabolism of paclitaxel. This can result in accumulation of paclitaxel in sensory neurons and may increase its cytotoxic effects. Indeed, CYP-epoxygenases of the subfamily 2J have also been connected with paclitaxel-induced neuropathic pain in rodent models by increasing oxidized lipid synthesis and subsequent sensitization of TRPV1 in sensory neurons (Sisignano et al., 2016). Collectively, these data indicate that CYP epoxygenases are crucial for paclitaxel metabolism and paclitaxel-induced neuropathic pain.

A 2012 study involving 855 subjects, found that SNPs in the gene *FGD4*, which encodes for a Rho-GTPase guanine nucleotide exchange factor involved in the regulation of the cytoskeleton, and to a lesser extent in the genes *EPHA5* and *FZD3,* were strongly associated with onset and severity of paclitaxel-induced peripheral neuropathy (Baldwin et al., 2012). Indeed, Rho kinase has previously been connected with increased neuropathic pain as a result of phosphorylation of myristoylated alanine-rich C-kinase substrate (MARCKS) and the subsequent increase in nNOS activity in spinal cord neurons (Tatsumi et al., 2005). Although EphrinB receptors have been associated with persistent pain in rodent studies and Ephrin B1 seems to be responsible for

Table 2
Potential genetic biomarkers of pain.

Gene	SNP location and consequence	Associated clinical pathology	Reference(s)	Gene product(s)
TRPA1	A2564G, causes amino acid exchange: N855S ➔ increased channel activity	Familial-episodic pain syndrome (FEPS)	Kremeyer et al. (2010)	TRPA1, ligand-gated calcium channel
TRPA1	G710A (rs920829) causes amino acid exchange: E179K	Paradoxical heat	Binder et al. (2011)	TRPA1, TRPV1 ligand-gated calcium channels
TRPV1	A 911G (rs8065080) causes amino acid exchange: I585V	Cold hypoalgesia Less heat and pinprick hyperalgesia		
TRPV4	C805T and G806A, cause amino acid exchange: R269C and R269H ➔ increased channel activity	Charcot-Marie-Tooth disease type 2C (CMT2C)	Landoure et al. (2010)	TRPV4, ligand-gated calcium channel
P2X7	G952A (rs7958311), causes amino acid exchange: R270H ➔ decreased channel activity	pain after mastectomy, osteoarthritis	Sorge et al. (2012)	P2X-Purinoceptor 7, ligand-gated calcium channel
KCNS1	A1862G (rs734784), causes amino acid exchange: I489V ➔ increased channel activity	lumbar back pain with disc herniation, limb amputation	Costigan et al. (2010)	$K_v9.1$, subunit of a voltage-gated potassium channel
SCN9A	Several SNPs associated with different pain syndromes.		reviewed in Waxman (2013)	$Na_v1.7$, voltage-gated sodium channel
SCN10A	T1661C and G3910A cause amino acid exchange: L554P and A1304T ➔ increased channel activity	Painful peripheral neuropathy	Faber, Lauria, et al. (2012)	$Na_v1.8$, voltage-gated sodium channel
SCN11A	• T1142C and T3473C cause amino acid exchange: I381T and L1158P ➔ increased channel activity • T2432C causes amino acid exchange: L811P ➔ decreased channel activity	• Painful peripheral neuropathy • Loss of pain perception	• Huang, et al. (2014) Leipold et al. (2013)	• $Na_v1.9$, voltage-gated sodium channel
• *OPRM1* several SNPs including rs1799971 (A118G), a widespread variant in asian ethnicities that is associated with reduced opioid receptor signaling and reduced analgesic efficacy of opioids.			• reviewed in (Lotsch & Geisslinger, 2005)	• mu-oipioid-receptor, G-Protein coupled receptor
HTR2A	SNP rs6313 causes amino acid exchange: T102C	Rheumatoid arthritis	(Kling et al., 2008)	Serotonin-(5-hydroxytryptamine)-receptor 2a, G-Protein coupled receptor
HTR1A	Carriers of the G-allele of the *HTR1A* SNP rs6295 have reduced pain in response to mild thermal stimuli	Thermal Pain	(Lindstedt et al., 2012)	Serotonin-(5-hydroxytryptamine)-receptor 1a, G-Protein coupled receptor
LPAR1 (formerly EDG2)	The SNP rs6295 is associated with higher susceptibility for developing Osteoarthritis	Osteoarthritis	(Mototani et al., 2008)	Lysophosphatidic acid receptor, G-Protein coupled receptor
CYP2C8 *CYP3A4*	The SNPs rs11572080, G>A causing amino acid exchange R139K and the SNP rs1113129, G>C in *CYP2C8* As well as the SNP rs776746, A>G in *CYP3A5* are associated with onset and severity of paclitaxel-induced peripheral neuropathy	Paclitaxel-induced neuropathic pain	(Leskela et al., 2011)	Cytochrome-P_{450}-Oxygenases, isoforms 2C8, 3A4
1. *FGD4* 2. *EPHA5* 3. *FZD3*	1. rs10771973 G>A; 2. 2. rs7349683 C>T3. rs 10771973 G>T associated with higher incidence of paclitaxel-induced peripheral neuropathy	Paclitaxel-induced neuropathic pain	(Baldwin et al., 2012)	1. FYVE, RhoGEF and PH domain containing 4, 2. Ephrin receptor A5, tyrosine kinase 3. Frizzled Class Receptor 3, G-Protein coupled receptor
GSTP1	SNP causing amino acid exchange I105V may be associated with increased intensity of oxaliplatin-induced neuropathic pain	Oxaliplatin-induced neuropathic pain	(Boige et al., 2010; Cavaletti et al., 2011; McLeod et al., 2010)	Glutathione S-Transferase P 1
*ERCC*1	SNPs rs1161, rs11615 and rs3212986 may be associated with increased intensity of chemotherapy-induced neuropathic pain, however, these associations are controversial.	Chemotherapy induced neuropathic pain	(Cavaletti et al., 2011; Goekkurt et al., 2009; Inada et al., 2010)	Excision repair cross-complementation group 1, DNA repair protein
AGXT	SNPs rs2032582 and rs2032582 may be associated with increased intensity of chemotherapy-induced neuropathic pain, however, these associations are controversial.	Chemotherapy induced neuropathic pain	(Cavaletti et al., 2011; Gamelin et al., 2007; Kanai et al., 2010)	Alanine-glyoxylate aminotransferase
CEP72	SNP TT rs 924607 in the promoter region of *CEP72* associated with increased intensity of vincristine-induced neuropathic pain respectively	Vincristin-induced neuropathic pain	(Diouf et al., 2015)	Centrosomal protein 72, protein of the leucine-rich-repeat (LRR) superfamily
1. *SNPs in genes encoding CYP2C8, CYP3A4, ARHGEF10, LIMK2, EPHA4, SLCO1B1* and *TUBB2A* associated with taxane-induced peripheral neuropathy 2. *SNPS in genes encoding FARS2, ACYP2* and *TAC1* associated with oxaliplatin-induced-peripheral neuropathy 3. *SNPS in genes encoding CEP75* and *CYP3A5* associated with vincristin-induced-peripheral neuropathy		Chemotherapy induced neuropathic pain	(Cliff et al., 2017)	1. Cytochrome-P_{450}-Oxygenases, isoforms 2C8, 3A4, Rho guanine nucleotide exchange factor 10, LIM domain kinase 2, Ephrin receptor A4 (tyrosine kinase), solute carrier organic anion transporter family member 1B1, tubulin beta 2A class IIa (cytoskeleton), 2. phenylalanyl-tRNA synthetase 2 (mitochondrial), acylphosphatase 2, tachykinin precursor 1 3. centrosomal protein 75, Cytochrome-P_{450}--Oxygenase, isoform 3A5
SLC24A3, *KCNK5*, *TRPM8*, *REST*, *GJA1*, *YAP1*, *PRDM16*, *LRP1*, *MRVI1* and	migraine		(Gormley et al., 2016),	solute carrier family 24 member 3

Table 2 (*continued*)

Gene	SNP location and consequence	Associated clinical pathology	Reference(s)	Gene product(s)
	several more were identified in a meta-study identifying 38 gene loci associated with increased susceptibility for migraine		reviewed in (Nyholt, Borsook, & Griffiths, 2017)	(sodium/potassium/calcium exchanger), potassium two pore domain channel subfamily K member 5, Transient receptor potential melastatin 8 (ligand-gated calcium channel), RE1 silencing transcription factor, gap junction protein, alpha 1, yes-associated protein 1 (transcriptional regulator), PR/SET domain 16, LDL receptor related protein 1
	microRNA 30c-5p was found elevated in plasma and CSF of patients suffering from neuropathic pain after ischemia (n=25)	neuropathic pain after ischemia	(Tramullas et al., 2018)	Increased miR30c-5p associated with reduced expression of TGFβ-receptor (transforming growth factor beta)

synaptic plasticity by association to postsynaptic NMDA receptors (Vasileiou, Adamakis, Patsouris, & Theocharis, 2013), the role of the Ephrin A5 receptor in pain is not clear.

In contrast, there are several reports concerning the involvement of Frizzled receptors in persistent pain from rodent models. In these studies, the Wnt/frizzled/β-catenin signalling pathway in sensory neurons and astrocytes was connected with nerve-injury induced neuropathic pain, causing increased production of the proinflammatory cytokines IL-18 and TNFα (Y. K. Zhang et al., 2013). Moreover, neuronal frizzled 3 seems to be particularly involved in sensitization processes of sensory neurons during cancer pain in rodents (Simonetti et al., 2014).

There is controversy about SNPs resulting in amino acid exchanges in glutathione S-transferase P1 (*GSTP1*). A large study involving 520 patients revealed that the SNP resulting in the exchange of Ile105 with Val in GSTP1 protein is associated with increased intensity of oxaliplatin-induced neuropathic pain (McLeod et al., 2010). However, another study with a similarly high number of patients failed to confirm the association between the SNP and pain intensity (Boige et al., 2010). There have also been contrasting results concerning the contribution to the intensity of chemotherapy-induced neuropathic pain of SNPs in genes for DNA excision repair (*ERCC*1) and alanine-glyoxylate aminotransferase (*AGXT*) (Cavaletti et al., 2011) (Table 2). Till now, more than 70 genes have been identified that are potentially associated with chemotherapy-induced neuropathic pain. However, only 22 of these were identified in unbiased genome wide association studies (reviewed in (Argyriou, Bruna, Genazzani, & Cavaletti, 2017)) and the identified genes differ profoundly, depending on the chemotherapeutic agent. For example, 13 genes have been identified that make a potential contribution to peripheral neuropathic pain caused by paclitaxel or oxaliplatin, but only one gene overlaps with pain induced by both drugs (*GSTP1*) (Argyriou et al., 2017). *GSTP1* encodes for a protein that conjugates glutathione to xenobiotic substances in an unspecific manner, thereby accelerating their degradation. Although *GSTP1* has been implicated in the detoxification of cisplatin (Peklak-Scott, Smitherman, Townsend, & Morrow, 2008), no such involvement in persistent pain has been reported so far. Similarly, there is no report of a connection between *ERCC1* or *AGTX* and persistent pain states. *ERCC1* encodes a protein that seems to be critically involved in nuclear excision repair of damaged DNA and in homologous recombination (Al-Minawi et al., 2009) and the gene product of AGXT (Alanine-glyoxylate aminotransferase) is an enzyme in amino acid metabolism.

Moreover, a SNP in the promoter region of the *CEP72* gene that encodes a protein involved in microtubule synthesis seems to be associated with increased risk and occurrence of vincristine-induced peripheral neuropathy (Diouf et al., 2015). Authors of a recent meta-analysis concluded that SNPs in the genes *CYP2C8, CYP3A4, EPHA4*, *ARHGEF10,* and *TUBB2A* are particularly associated with taxane-induced peripheral neuropathy, whereas *FARS2, ACYP2* and *TAC1 are associated with oxaliplatin-induced neuropathy while CEP75* and *CYP3A5 are associated with vincristine-induced peripheral neuropathy, respectively (Cliff* et al., 2017*)*. As mentioned above, CYPs and Ephrin receptors have been associated with chemotherapy-induced neuropathic pain in the past. The gene *ARHGEF10 encodes for a r*ho Guanine-nucleotide exchange factor 10 previously found to be important for proper neuronal conductivity and myelination of peripheral nerves (Verhoeven et al., 2003). SNPs in its gene may alter activity of the protein, which may accelerate demyelination and increase neuronal damage, hyperexcitability and pain after chemotherapy. Likewise, the gene *TUBB2A* encodes for a tubulin subtype which is a major component of the cytoskeleton which is important for structural integrity and axonal transport in sensory neurons (Kapitein & Hoogenraad, 2015). Paclitaxel interacts with tubulin by stabilizing and preventing its depolymerization (Xiao et al., 2006). In this regard, it seems reasonable that SNPs in the *TUBB2A* gene may accelerate microtubule breakdown and neuronal damage in sensory neurons, contributing to pain hypersensitivity.

Although no role for acylphosphatase 2 (encoded by *ACYP2*) or centrosomal protein 75 (encoded by *CEP75*) has been reported in persistent pain, FARS2 and TAC1 do appear to be involved in neuropathic pain states. *FARS2* encodes for a mitochondrial phenylalanyl-tRNA synthetase and since it is known that oxaliplatin causes mitochondrial damage (Jaggi & Singh, 2012), it is possible that SNPs in *FARS2* modulate mitochondrial activity and may enhance mitochondrial stress and subsequent neuronal damage caused by oxaliplatin. The gene *TAC1 encodes for a tachykinin precursor that is necessary for the synthesis of the proinflammatory neuropeptide substance P. This peptide is known to be produced and released from sensory neurons and to be critically involved in neurogenic inflammation in persistent pain states (Chiu, von Hehn, & Woolf,* 2012*). The mutation in the TAC1 gene may cause increased maturation and release of substance P and may thus, enhance neurogenic inflammation and pain after oxaliplatin treatment.*

These data indicate that stratification of chemotherapy-induced neuropathy in the respective treatment group and including high numbers of individuals in the study is the most appropriate approach in identifying individual genetic biomarkers for each chemotherapeutic drug causing neuropathy.

Similarly, in migraine, a recent meta-analysis of a large cohort involving 375,000 individuals identified 38 gene loci that are potentially connected with increased susceptibility to migraine. Among these, two gene loci are within ion channel genes (*KCNK5* and *TRPM8*), both of which are important for pain transmission. However, the other identified loci, *SLC24A3*, *REST*, *GJA1*, *YAP1*, *PRDM16*, *LRP1*, *MRVI1,* are located within genes for different metabolic or signaling functions, as well as transcription factors that are unrelated to ion channels, and have not been connected with persistent pain before (Gormley et al., 2016).

Apart from classical genetic biomarkers within coding regions for translatable proteins, several studies indicate a role for micro-RNAs as potential biomarkers for persistent pain states (Bali & Kuner, 2014). However, most of these studies use rodent pain models, thus making it difficult to translate the results to neuropathic pain patients. In a recent study, however, the authors were able to translate their observations on the involvement of a microRNA in neuropathic pain from rodent models to neuropathic pain patients. They identified a microRNA,

miR-30c-5p, that was elevated both in rodent tissue and plasma during nerve-injury-induced neuropathic pain, as well as in plasma and CSF of patients suffering from neuropathic pain (Tramullas et al., 2018).

Taken together, several SNPs and genes are known that could potentially be linked to altered susceptibility to a persistent or pain state or a neuropathic pain syndrome. However, further studies are needed to identify more reliable genetic biomarkers and to determine whether these biomarkers relate to the most suitable pharmacological treatment for the individual patient (Fig. 3, Table 2).

5. Quantitative sensory testing (QST)

Quantitative sensory testing is a standardized series of neurological tests to determine normal and aberrant sensory parameters, such as mechanical, cold or heat detection and pain thresholds in humans (Shy, et al., 2003). QST can be performed in neuropathic pain patients yielding a specific QST profile for each patient. These profiles can then be collected in databases to identify specific QST patterns and specific somatosensory changes for distinct neuropathic pain states in patients (Maier et al., 2010). In this way, the QST profile of a neuropathic pain patient may be used to predict the most effective pharmacological treatment. For example, if a patient with post-herpetic neuralgia has an altered heat pain threshold and the cellular and molecular mechanism for this sensory deviation is known, it could be targeted specifically with a medication. In this case, QST may serve as a biomarker for the prediction of the most effective drug therapy for neuropathic pain patients.

Indeed, several randomized clinical trials have revealed correlations between sensory parameters of neuropathic pain patients and the effectiveness of analgesic therapies. For example, in a randomized clinical trial involving 22 patients with postherpetic neuralgia or nerve-injury induced neuropathic pain, a correlation was seen between the intensity of mechanical allodynia and the effectiveness of lidocaine (Attal, Rouaud, Brasseur, Chauvin, & Bouhassira, 2004). Moreover, a correlation between basal heat pain threshold and the effectiveness of opioid therapy was observed in in a randomized clinical trial involving 64 patients suffering from postherpetic neuralgia (Edwards, Haythornthwaite, Tella, Max, & Raja, 2006). A recent study, in which 83 polyneuropathy patients were stratified into groups of “irritable” and “non-irritable nociceptor” based on QST measurements, demonstrated a correlation between the analgesic efficacy of oxcarbazepine and the “irritable nociceptor” phenotype (Demant et al., 2014).

In a further study, a large cohort of 902 neuropathic pain patients with different pain etiologies was subdivided into three main phenotypic groups based on clustering sensory profiles that had been assessed with QST. These three groups were named according to their phenotypes: “sensory loss”, “thermal hyperalgesia” and “mechanical hyperalgesia”.

Using this classification of neuropathic pain patients, a distinct QST profile can be observed for each subgroup. Moreover, when compared with previous results of clinical trials for the treatment of neuropathic pain, this phenotypic stratification of patients even suggested that the response of each subgroup to a specific pharmacotherapy to be predicted. For example, patients with a QST profile similar to the subgroup “heat hyperalgesia” showed stronger responses to oxcarbazepine in a randomized placebo-controlled trial, indicating that sodium channel blockers may be adequate pharmacotherapy for patients with a similar QST profile. Likewise, patients with a QST profile similar to the subgroup “mechanical hyperalgesia” showed stronger responses to pregabalin in retrospective analyses of placebo-controlled trials, indicating that calcium channel blockers may be particularly efficient in this phenotypic subgroup (Baron, et al., 2017). This study demonstrates how sensory profiles from neuropathic pain patients can be used to predict the most suitable pharmacological treatment.

Although these findings are promising, the mechanisms of cellular and molecular changes in neuropathic pain states are not fully understood at present, thus making it difficult to suggest a specific mechanism-based pharmacological treatment for each aberrant QST parameter. Moreover, only a few drugs are available clinically that target a specific mechanism in the peripheral nervous system to alleviate neuropathic pain (Table 3).

In summary, QST is a promising candidate for a sensory biomarker. However, although clinical data indicate that isolated parameters may act as prognostic markers for pharmacological therapy in patients, conclusive evidence for the use of a QST parameter as a clinical predictor for pharmacological treatment of pain is currently lacking (Grosen, Fischer, Olesen, & Drewes, 2013; Marcuzzi, Dean, Wrigley, Chakiath, & Hush, 2016). More research is required to link QST parameters with specific pharmacological treatments.

6. Towards Biomarker based pain therapy – future perspectives

In conclusion, the measurement of multiple biomarkers, including plasma and CSF small molecules, peptides and other signaling mediators, together with genetic biomarkers and QST may lead in the future to patient-specific recommendations for pharmacotherapy of individuals with persistent or neuropathic pain. Major disadvantages are the time, cost and effort required to screen and treat an individual patient. However, this is a general sociopolitical challenge to the future of precision medicine and not only restricted to biomarker-based pain therapy.

Several aspects need to be addressed and established for biomarker-based pain therapy. First, a clear correlation must be demonstrated between a biomarker readout and pharmacological therapy. For example, SNPs in genes encoding for voltage gated sodium channels that result in higher activity of these channels point to the use of sodium channel blockers, such as carbamazepine for pain therapy in these patients. This is an obvious correlation, but for other readouts and readout combinations, it may be more difficult to deduce the optimal pharmacological treatment. In this regard, companion diagnostic tools and the determination of threshold concentrations, such as for example determining the plasma levels of NGF before applying an NGF-blocking antibody, are important to inform therapeutic decisions. A helpful framework for drawing up evidence-based criteria for biomarkers use is provided by the Evidentiary Criteria Writing Group. This group proposes the use of a five-component system that defines need, context of use (COU) and assesses benefit and risk to evaluate whether the evidence for a particular biomarker is sufficient to justify its use (Leptak et al., 2017).

Second, a prioritization system is required to identify the readout parameters that are most likely connected to the patient’s pain syndrome and need to be addressed by a pharmacological therapy. In this regard, QST as a first physiological screening, may be of central importance to identify sensory alterations. Additional biomarker measurements that follow in a hierarchical order may then help to clarify which cellular and molecular factors are involved, as shown in Fig. 4. For migraine patients, for example, this hierarchical system can be very simple. The concentrations of CGRP in blood and CSF can be used to determine whether anti-CGRP therapy is potentially more beneficial for the patient than conventional triptane therapy. For other pain entities, more readout parameters may be necessary to suggest the optimal therapy.

Third, more analgesic substances are required to specifically address the cellular and molecular mechanisms of the individual pain syndrome. This is particularly difficult as it requires an initiative from the pharmaceutical industry to invest in the development of novel analgesics. Moreover, medications that are currently used for the therapy of persistent or neuropathic pain, such as amitriptyline, are rather promiscuous in their pharmacological actions and do not address a single mechanism.

Fourth, the complexity of pain and of the effects of analgesic drugs will undoubtedly require adequate reflection in data analysis strategies. Indeed, experimental and clinical data gathered in pain research are already “big data”, and contemporary methods of data science

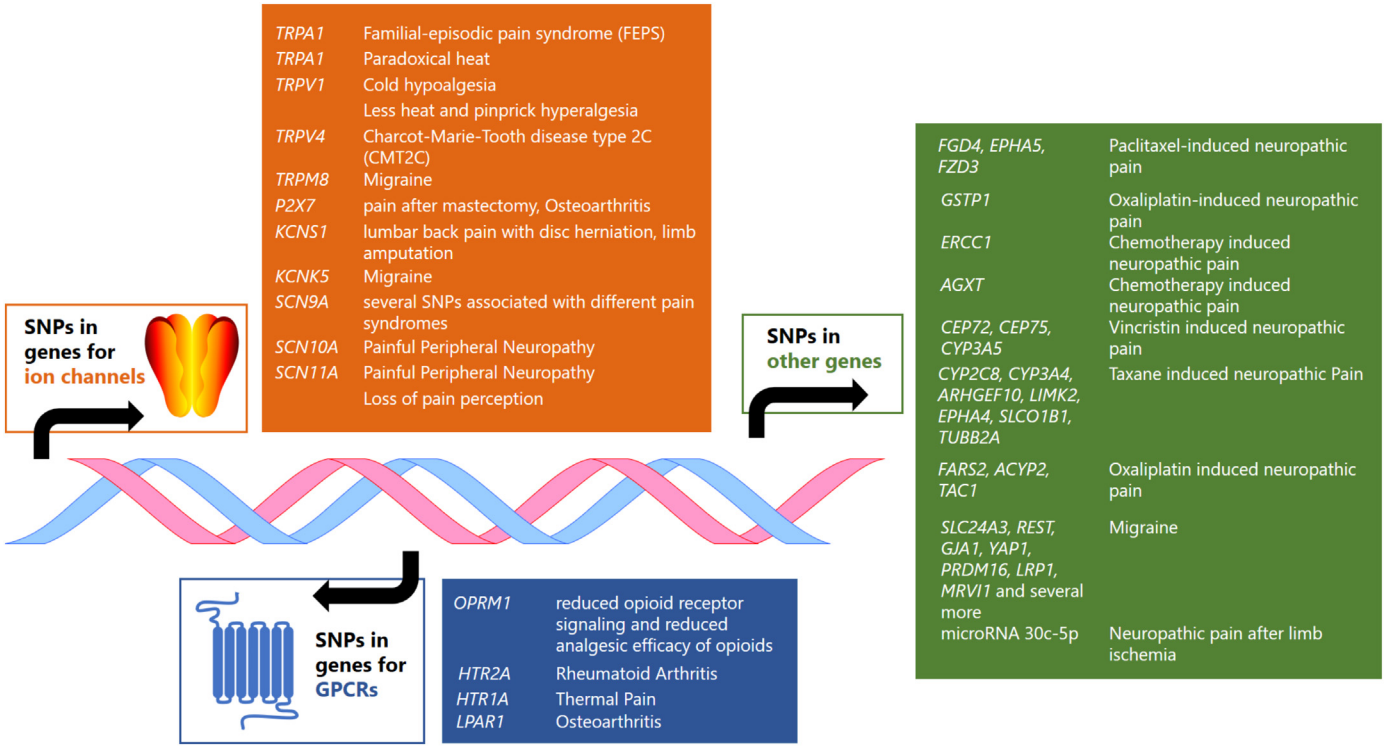

Fig. 3. Potential genetic biomarkers of pain. Single nucleotide polymorphisms (SNPs) in genes for ion channels (orange), genes for G-protein coupled receptors (GPCRs, blue) and other genes (green) and the associated clinical pathology. For schematic drawings Scientific Illustration Toolkits from Motifolio were used. Abbreviations: TRPA: transient receptor potential ankyrin; TRPV: transient receptor potential vanilloid; TRPM: transient receptor potential melastatin ; P2X: *Purine* gated ion channel; KCNS: Potassium Voltage-Gated Channel Modifier; KCNK: two-pore-domain potassium channel; SCN: Sodium Voltage-Gated Channel; OPRM: Opioid Receptor Mu; HTR: serotonin receptor; LPAR: Lysophosphatidic Acid Receptor; FGD: FYVE, RhoGEF And PH Domain Containing 4; EPHA: Ephrin Receptor A; FZD: Frizzled Receptor; GSTP: Glutathione S-transferase P; ERCC: Excision Repair Cross-Complementation; AGXT: Alanine-glyoxylate aminotransferase; CEP: Centrosomal protein; CYP: Cyotochrome-P_{450}-oxygenase; GST: Glutathione *S*-transferase; ARHGEF: Rho Guanine Nucleotide Exchange Factor; LIMK: LIM Domain Kinase; SLCO1B1: Solute Carrier Organic Anion Transporter Family Member 1B1; TUBB: Tubulin Beta; FARS: Phenylalanyl-tRNA Synthetase; ACYP: Acylphosphatase; TAC: Tachykinin Precursor; SLC: Plasma Membrane Sodium/Calcium Exchanger; REST: RE1-Silencing Transcription Factor; GJA1: Gap Junction Alpha-1 protein; PRDM: PR Domain; LRP: Low Density Lipoprotein Receptor-Related Protein; MRVI: Murine Retrovirus Integration.

(President's Information Technology Advisory, 2005) allow computation in data-driven approaches that exceed statistical analysis. Statistics is based on mathematics and concerned with hypothesis testing via analysis of the probability of an observation, given a known expected data distribution. Data-driven systems have developed from computer science and focus on hypothesis generation and on the prediction of phenotypes from acquired data, without the ubiquitous necessity of prior assumptions. This prediction involves artificial intelligence and the currently most popular implementation of machine-learning is a set of methods that can automatically detect patterns in data. The patterns uncovered are then used to predict or classify future data, to observe structures such as subgroups in the data or to extract information from the data to derive new knowledge (Dhar, 2013; Murphy, 2012) (so-called DIKW, data – information – knowledge – wisdom, approaches). Machine-learning is currently used increasingly in pain and analgesia (Lotsch & Ultsch, 2018) and, for example, led to identification of genetic biomarkers of pain sensitivity (Lötsch & Ultsch, 2013) or opioid effects (Kringel et al., 2017) that outperformed classical approaches. Collectively, the combination of sensory, molecular and genetic biomarkers with machine learning may indeed lead to more effective patient stratification in the future and may suggest individual therapeutic options for the treatment of persistent pain in patients.

6.1. Limitations

Although the identification of many potential biomarkers of persistent and neuropathic pain therapy is promising, several limitations to their clinical use and the reliability of biomarkers in persistent pain

Table 3
Potential sensory biomarkers of pain.

Sensory parameter	Pain state of patients	Observed link between sensory parameter and treatment	Reference(s)
Mechanical allodynia	Postherpetic neuralgia, nerve-injury induced neuropathic pain (n=22)	intensity of mechanical allodynia correlates with the effectiveness of lidocaine	Attal et al. (2004)
Basal heat pain threshold	Postherpetic neuralgia (n=64)	Opioid therapy was more effective in patients with higher basal heat pain threshold	Edwards et al. (2006)
Full QST followed by stratification	Peripheral neuropathic pain due to polyneuropathy, nerve injury or postherpetic neuralgia (n=83)	Stratifying patients in irritable nociceptor (IN) and non-irritable nociceptor (NIN) groups and readout of preservation of thermal sensation correlates with effectiveness of oxcarbazepine	Demant et al. (2014)
Full QST followed by stratification	polyneuropathy (n=512), radiculopathy (n=75), peripheral nerve injury (n=227), post herpetic neuralgia (n=88)	After collecting QST profiles, patients were subdivided into three main phenotypic subgroups: 1. “sensory loss”, 2. “thermal hyperalgesia”; 3. “mechanical hyperalgesia”. This stratification could be useful for future design and evaluation of clinical trials for neuropathic pain patients	Baron, et al. (2017)

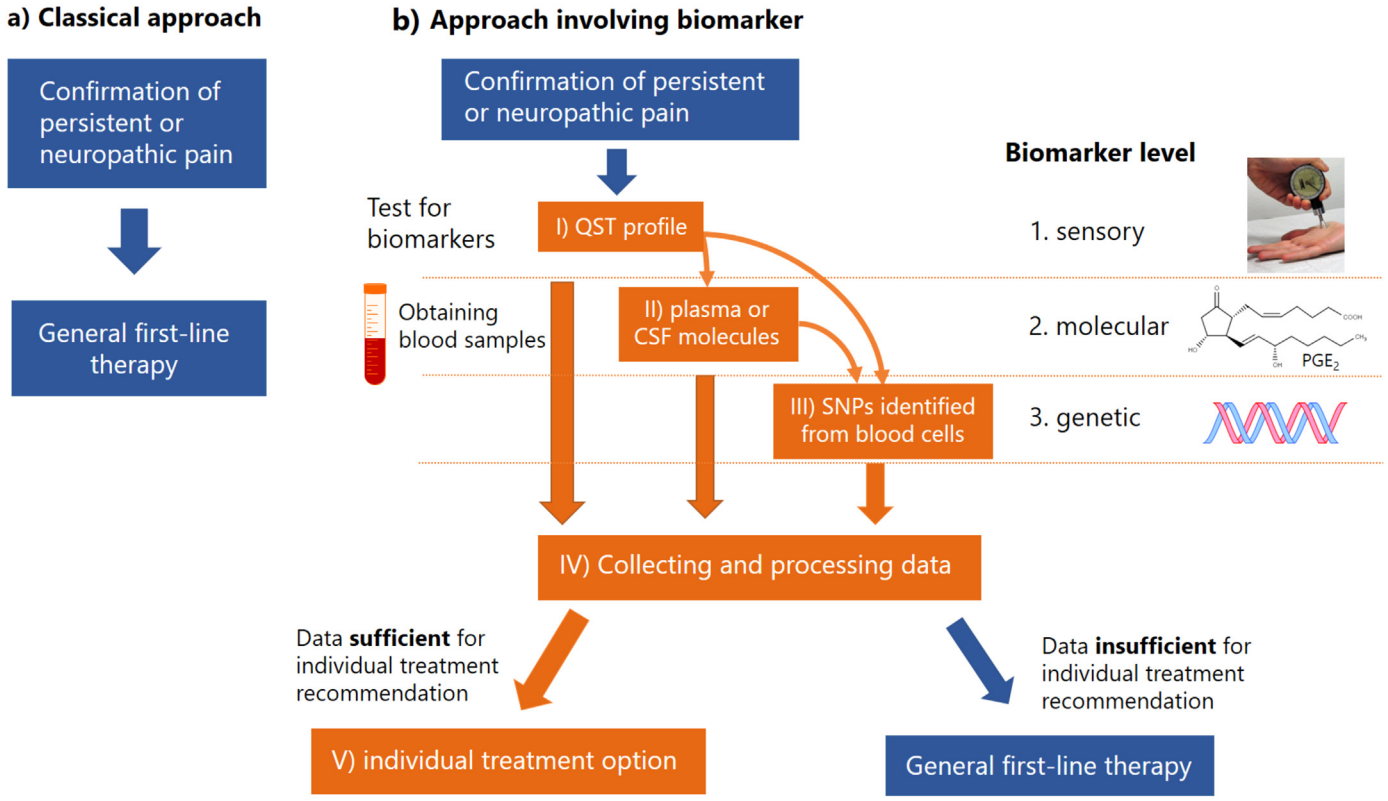

Fig. 4. Classical approach (a) vs. biomarker-based approach (b) for the therapy of persistent or neuropathic pain in patients. CSF: Cerebrospinal Fluid; SNP: Single Nucleotide Polymorphism; QST: Quantitative Sensory Testing; PGE_2: Prostaglandin E_2. Image obtained from DFNS (German Research Association Neuropathic Pain).

therapy need to be addressed. First, the concentration thresholds of biomarkers may vary profoundly in patients, due to adaptation to a chronic pain state, to comorbidities and related administration and combination of pharmacological agents that cause alterations in metabolic processes, due to age-related changes in metabolism, or simply due to biological variability. Specifically, biomarkers, such as CYP-epoxygenases, that are involved in the metabolism of various pharmacological agents and xenobiotics, may be markedly affected by these confounding factors.

Moreover, the timing of biomarker analysis is critical. If a biomarker can predict the severity of a pain state or of disease progression, it may only be useful as a reliable factor for a limited period. At later time points, it may no longer fulfil the criteria for a biomarker. Indeed, most biomarkers discussed above are status quo biomarkers, that may change during disease progression. To address this issue, the time-course of each potential biomarker would need to be determined within the respective pain state to identify the time point at which correlation with the pathophysiological state, or, in the case of a prognostic biomarker, with disease progression is greatest.

Technical difficulties may also arise. Should the biomarker be chemically unstable, restrictions may be needed in the handling and storage of patient samples, causing additional costs or requiring additional laboratory personnel and time which can be difficult in clinical practice.

There are also ethical and legal aspects that need to be addressed. Obtaining samples from patients requires their consent. This is generally high, when the procedure is short and can be incorporated in medical routine. However, obtaining CSF from patients is associated with a certain risk of injury. Therefore, a risk-benefit relationship should always be considered before analyzing CSF for potential biomarkers, including whether the information that can be generated from the sample justifies a risky sampling procedure.

The information generated by biomarkers for persistent or neuropathic pain can potentially be abused, for example by employers, who refuse to hire candidates when a certain biomarker threshold concentration is exceeded, or by health insurance companies. The broad spectrum of ethical and legal implications associated with biomarkers has recently been the subject of an excellent review in the context of brain-imaging-derived biomarkers for persistent pain states (Davis et al., 2017).

Conflict of interest

The authors declare that there are no conflicts of interest.

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