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Review

Perspectives on next steps in classification of oro-facial pain – Part 3: biomarkers of chronic oro-facial pain – from research to clinic

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SUMMARY **The purpose of this study was to review the current status of biomarkers used in oro-facial pain conditions. Specifically, we critically appraise their relative strengths and weaknesses for assessing mechanisms associated with the oro-facial pain conditions and interpret that information in the light of their current value for use in diagnosis. In the third section, we explore biomarkers through the perspective of ontological realism. We discuss ontological problems of biomarkers as currently widely conceptualised and implemented. This leads to recommendations for research practice aimed to a better understanding of the potential contribution that biomarkers might make to oro-facial pain diagnosis and thereby fulfil our goal for an expanded multidimensional framework for oro-facial pain conditions that would include a third axis.**

KEYWORDS: **chronic oro-facial pain, temporomandibular disorders, pain, biomarkers, ontology, classification**

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Introduction

The Institute of Medicine (IOM) defines biomarkers as '... characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes or responses to an intervention'. (1) Biomarkers whose relationship to disease is not clearly established are termed 'investigative' (2). Investigative biomarkers can be developed to differentiate between being diseased and non-diseased (diagnostic), to assess the severity or extent of disease (burden of disease), to predict future onset of disease (prognostic) and/or to provide information about treatment effectiveness (efficacy of intervention) (2). Biomarkers are often used as surrogate endpoints, that is as a substitute for a clinical endpoint. For example, in blood pressure trials of antihypertensive drugs, drug-related decreased blood pressure (the biomarker) is associated with the decreased risk of serious cardiovascular events.

The criteria for evaluation of potential biomarkers include these three key aspects and their respective parameters:

1 Analytical validation (sensitivity, specificity, reproducibility, ease of administration)
2 Qualification (evidence for association, study designs, for example case–control or prospective)
3 Utilisation (specific proposed use)

Blood glucose is a classic example of a biomarker used to diagnose and monitor diabetes. Glucose is easily and reliably measured, and well-defined normal

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and pathological ranges for blood glucose exist for the population. Blood glucose levels are used to monitor the effectiveness of therapy with insulin and oral hypoglycaemic agents. The degree to which glucose concentrations are controlled in diabetic patients can be used to predict long-term consequences of disease progression.

The authors of this study were invited by the International RDC/TMD Consortium Network for a symposium, held at the 2013 IADR General Session in Seattle, in order to review biomarkers related to the development of an oro-facial pain classification system. The other two studies are focused on general principles of ontology (3) and psychosocial considerations related to an oro-facial pain taxonomy (4). This study will first discuss biomarkers, in the context of usage in an oro-facial pain diagnostic and classification system, and then, it will critically assess the various problems that affect such potential usage.

Biomarker candidates for oro-facial pain

Biomarkers for oro-facial pain discussed in this study can be categorised by the method used to measure them: (i) physiological (e.g. reflex responses, pressure pain thresholds, quantitative sensory testing); (ii) psychological or behavioural characteristics (e.g. dynamic pain psychophysical testing); (iii) radiological [computed tomography (CT), magnetic resonance imaging (MRI), functional MRI (fMRI), positron emission tomography (PET)]; and (iv) molecular [small molecules (amino acids, prostaglandins, leukotrienes) and proteins (e.g. cytokines, COX, etc.)]. Increasingly investigated biomarkers are genomic and transcriptomic in nature, but this is beyond the scope of this study. The following sections discuss the use and potential application of some of these biomarker candidates and applicable tests.

We have grouped potential craniofacial biomarkers into three categories, based on their method of acquisition as follows: direct physiological measures, biosamples and imaging (5). Direct physiological measures require the use of a stimulus that is typically nociceptive (e.g. pressure, thermal) but it may also be non-nociceptive (e.g. pressure, movement), and such measures assess the impact of the stimulus on a physiological (reflex) or behavioural response as the measurement. Molecules (metabolites, proteins, nucleic acids, etc.) are assessed via a biosample (e.g. blood, saliva, cerebrospinal fluid, tissue biopsy), and the process of acquiring a sample may include a stimulus (for example, nociceptive) or sample acquisition may be with the organism at rest, and while a behavioural response by the individual may accompany the process of collecting the sample, such a response is not necessary nor is the response part of the measurement. Imaging includes magnetic resonance imaging (MRI)-based techniques (diffusion tensor imaging, spectroscopy, volumetric MRI, functional MRI), X-rays including computed tomography scans, positron emission tomography, which reveal structural changes and can also provide information about local metabolic activity.

Direct physiological measures

Pressure pain threshold (PPT) is the minimum load required to cause a painful sensation from a specific tissue (e.g. skin, muscle, joint) and forms part of the compliment of tests employed in quantitative sensory testing (QST; discussed below). Pressure pain threshold can be easily measured in an office with an algometer. Pressure pain threshold can be used for diagnosis and to determine treatment efficacy, for example, by assessing pain sensitivity in the masticatory muscles and the temporomandibular joint of individuals with symptoms compatible with temporomandibular disorders (TMD). It has been suggested that PPT in the masseter muscle may be as good as palpation to recognise TMD-related pain (6). One advantage of PPT measurement data is that they are usually found to have good to excellent interexaminer reliability (7). However, to use PPTs in this way would require that there be standardised, accepted instrumentation for measuring them, standardised units for reporting the load, specific criteria for PPT application (loading area, rate of stimulus application, sites to be tested, number of trials) and perhaps a determination of what other factors might significantly affect the PPT (menstrual cycles, diurnal cycle). Also to be determined are what constitute normal values in healthy individuals, and what values fall outside of the range of 'normality' (8). Although substantially lower masticatory muscle PPT values have been found in large cohorts of TMD patients when compared with healthy controls (7), these differences have not always been detected in small group studies due to the variability inherent in PPT

values (9, 10), reducing the diagnostic utility of this biomarker. It is unclear whether analgesic interventions alter both PPT and TMD symptoms in a related manner, and this question warrants further investigation.

The jaw-stretch reflex is a monosynaptic stretch reflex that can be evoked by rapid depression of the mandible. Jaw-stretch reflexes can be measured in an office, but accurate measurement requires relatively complex equipment. Because some factors (e.g. EMG activity and jaw displacement) influence the amplitude of the reflex itself, while other factors (e.g. recording site) influence the amplitude of the registered measurement, standardised parameters for measuring jaw-stretch reflexes would need to be developed. While it is clear that experimental muscle pain alters the amplitude of the stretch reflex (11–14), it is not clear whether clinical pain, such as masticatory muscle pain associated with TMD, reliably modulates this reflex. In TMD patients with joint pain, injection of lidocaine into the joint reduces the jaw-stretch reflex and ongoing pain (15). On the other hand, skeletal muscle relaxants have very little effect on enhancement of the reflex that can be produced by experimental masseter muscle pain (16). Thus, the jaw-stretch reflex may be more useful in assessing the integrity of the trigeminal sensory system, rather than as a biomarker of disease for TMD (15, 17–19).

Traditional quantitative sensory testing (QST) provides a powerful method of assessment for sensory functioning and for the effectiveness of different treatments (20). In this method, standardised non-invasive stimuli of different modalities are applied to measure the functionality of different nerve fibre populations. As an indication of response, the method relies on subjective verbal or non-verbal report (20), and the assessment of functioning is made through evaluation of sensory thresholds (detection and pain thresholds, pain tolerance, pain summation thresholds), suprathreshold intensity ratings (response–magnitude and stimulus–response relationships) and sensory mapping (20). The assumption is that the responses to various stimuli provide information about the functionality of the peripheral and central nervous systems.

Standardisation is difficult to achieve with QST, as data from one assessment system cannot be easily compared to another. This discrepancy can be somewhat reduced by routinely using the same methods and devices, and using the patient's contralateral side as a reference when possible (21). To maximise accuracy, QST analysis should assess sensitivity at a number of locations: the painful (affected area), contralateral and neighbouring sites, and non-related sites. All tested locations should be methodically mapped and sensory alterations beyond the primary affected site may indicate systemic disease or centrally mediated conditions that will require further evaluation. A major limitation to standardisation that is more difficult to overcome is that the test's accuracy relies on patient responses. The patient's response can be biased, influenced either by a time gap between experiencing the sensation and providing the response, or by a range of expectations specific to the patient. These biases can generally be controlled by more sophisticated but time-consuming psychophysical methods (staircase, etc.).

Quantitative sensory testing alone has no diagnostic power; however, it can add an additional dimension to pain evaluation. Various clinical conditions and pathological processes may have a different, characteristic sensory signature. For example, severe nerve injury (partial or complete nerve transection) is typically characterised by immediate myelinated and unmyelinated nerve fibre hyposensitivity that will be represented by elevated detection thresholds of sensitivity to all modalities (22). Partial damage may be followed by either hyposensitivity or hypersensitivity accompanied by ongoing neuropathic pain (23, 24). Another example is that early perineural inflammation may produce short-lasting large myelinated nerve fibre hypersensitivity that is revealed clinically by reduced detection threshold in those fibres (25–30).

Employing QST can enable the practitioner to distinguish between allodynic conditions (i.e. where pain is caused due to a stimulus that normally would not evoke pain). In allodynia conditions, the pain threshold is reduced whereas the detection threshold can increase, decrease or remain unchanged. The interval between detection and pain thresholds, for example, has been shown to have clinical significance in the assessment of centrally mediated pain conditions (31). Similarly, several types of hyperalgesic conditions can be defined as well. Heat hyperalgesia, for example, is related to thin unmyelinated nerve fibres, while tactile hyperalgesia may suggest involvement of myelinated fibres.

A significant attempt to standardise QST was made by The German Research Network on Neuropathic

Pain (32). The Network employed a systematic sequence of thermal and mechanical QST on patients suffering from various neuropathic pain conditions. The findings were categorised as gain and loss of sensation. Ninety-two per cent of the patients presented with at least one sensory abnormality, and a sensory profile was suggested for each neurological syndrome. However, combinations of gain and loss of sensations were found to exist across all the evaluated pain syndromes, thereby reducing diagnostic specificity. Nevertheless, there is preliminary evidence for alterations in the QST profiles of some patients with TMD compared to healthy controls and chronic widespread (fibromyalgia) patients (33), suggesting that QST may be able to provide specific pain signatures that could be used to assist in the diagnosis of oro-facial pain conditions. However, as mentioned earlier, this method alone has no diagnostic power. Guidelines for the assessment of oro-facial somatosensory function in the clinical setting exist (20), but they are not yet standardised or validated; consequently, there is an ongoing effort to develop consistent approaches for assessment (34). These will be required for this technique to be evaluated as a potential biomarker of TMD and other oro-facial pain conditions.

Dynamic pain psychophysical testing is part of a new generation of psychophysical testing that allows for the evaluation of modulatory processes. This method comes in addition to recognising the pain perception obtained by static pain psychophysics of thresholds or supra-threshold magnitude evaluation, described above under QST. The technique relies on the fact that pain perception is the result of generated data from the periphery, which is transmitted centrally, and then modulated in the CNS before its arrival in the cortex for conscious perception. Therefore, the same type of external stimulus may evoke perceptions of different sorts among different people, depending on their central modulation processes and the situation they are in.

Two modulatory mechanisms are commonly tested in the laboratory or clinic. One is temporal summation (TS), the psychophysical correlate of 'wind-up', a process whereby repeated noxious stimulation results in progressively larger neuronal responses and reflects central sensitisation; note that TS is often subsumed within the QST rubric. Temporal summation is thought to result from increased activation of N-methyl-D-aspartate (NMDA) receptors in response to sustained nociceptive input. The clinical manifestation of TS may be allodynia and hyperalgesia (35–37). TS is tested by application of a number of repeated nociceptive stimuli at a fixed interval. The increase in pain score is assessed at the end of the final stimulus. The second mechanism is conditioned pain modulation (CPM), which is thought to be the human psychophysical equivalent of diffuse noxious inhibitory control (DNIC). Conditioned pain modulation represents the endogenous analgesia system, where descending pathways induce modulatory effects on incoming painful stimuli. This phenomenon, at least partially, is opioid-mediated (38). Animal studies demonstrated the role of spinal noradrenaline (NA) and serotonin (5-HT) in mediation of pain inhibition and CPM (39–44). Conditioned pain modulation is tested in the laboratory using two remote noxious stimuli, where the first 'conditioning pain' inhibits the second 'test pain'.

In recent years, many reports used TS or CPM to demonstrate altered pain modulation in chronic pain patients. Enhanced TS was found in chronic pain patients such as fibromyalgia (45–48), tension headache and musculoskeletal pain (49, 50), migraine (51), chronic low back pain (52), and temporomandibular disorders (TMD) (53–57). Similarly, a less-efficient CPM response was found in many of the idiopathic pain syndromes such as TMD (58), fibromyalgia (48, 59–61), tension headache (62) and irritable bowel syndrome (63). Among healthy subjects, reduced pain modulatory capacity was demonstrated in older subjects (64) and among females when compared with males (65). Less-efficient CPM was found among patients with chronic post-endodontic treatment pain as well (C. Nasri-Heir, J. Khan, B. Benoliel, C. Feng, D. Yarnitsky, F. Kuo, C. Hirschberg, G. Hartwell, C.-Y. Huang, G. Heir, O. Korczeniewska, S.R. Diehl & E. Eliav, unpublished data).

It has been suggested that dysregulation of the pain modulatory system can lead to the development of chronic pain disorders (66–69). Patients with altered pain modulation are more prone to develop post-operative (thoracotomy) chronic pain (70). Moreover, a recent study has shown that painful diabetic neuropathy patients with less-efficient CPM benefit more from treatment with duloxetine (71) that has the potential to enhance the descending pain inhibition

by inhibiting reuptake of spinal noradrenalin (NA) and serotonin (71–73).

The pain modulatory system can be activated by stimuli other than pain; isometric contraction and exercise have been shown to be strong descending pain inhibitory system motivators (74). A recent study demonstrated that subjects with high CPM induced by painful heat stimulus also exhibited high CPM induced by isometric contraction (D.A. Alnaas, C. Nasri-Heir & E. Eliav, unpublished data). This may suggest common mechanisms or pathways for pain-induced and isometric muscle contraction-induced CPM.

Biosamples

Biomarkers from blood have been identified for many diseases, including the example of diabetes given earlier. There are reasonably good biomarkers of inflammation, but as yet it has been difficult to find a molecular biomarker of pain, let alone for a specific type of pain such as oro-facial pain related to TMD. This is compounded by the finding of little evidence of gross pathological changes to the masticatory muscle tissues of TMD patients with myalgia (75). Despite the lack of gross pathology, microdialysis studies have recently found that interstitial glutamate concentrations are 2–4 times greater in the masseter muscle of myofascial patients with TMD than in healthy controls (9). In an animal model, a similar 2–3 times elevation of interstitial glutamate concentrations over baseline in the masseter muscle is associated with excitation and mechanical sensitisation of masseter muscle nociceptors (76). These findings could indicate that glutamate concentration in the masseter muscle reflects ongoing disease and therefore could serve as a diagnostic biomarker. In addition to glutamate, studies employing microdialysis have demonstrated elevated levels of serotonin, leukotriene B4, lactate and pyruvate in localised myalgias; however, most of these results have come from studies on muscles other than masticatory muscle in patients who had chronic myofascial pain that was not diagnosed as a TMD (77).

Other molecular biomarkers of disease have been identified in the TMJ, including tumour necrosis factor (TNF)α, an inflammatory cytokine which is found at significantly higher concentrations in the TMJ synovial fluid of patients with evidence of joint damage (78, 79), although there is no correlation between pain and TNFα concentrations (80). Recently, blood levels of three other cytokines, monocyte chemotactic protein-1 (MCP-1), interleukin (IL) 1ra and IL-8, have been shown to be expressed at higher levels in patients with TMD compared to healthy controls, and their pattern of expression appears to differentiate patients with widespread pain from those with pain localised to the oro-facial region (81). Specifically, MCP-1 and IL-1ra are selectively elevated in TMD patients with localised pain, while IL-8 is selectively elevated in TMD patients with widespread pain. Monocyte chemotactic protein-1 is a pro-inflammatory cytokine released upon local inflammation and promotes the release of CGRP. IL1ra is anti-inflammatory and blocks IL1 pathway mediating pain. IL-8 is pro-inflammatory and may also be elevated in fibromyalgia.

Imaging

Imaging techniques that have been employed to investigate central nervous system function in oro-facial pain research include computed tomography scans, magnetic resonance imaging (MRI), functional MRI (fMRI) and positron emission tomography (PET) scans (82–85). Other magnetic resonance-based measures include diffusion tensor imaging, spectroscopy and volumetric imaging (86). In terms of central nervous system function, fMRI has been employed to identify cortical and subcortical regions that appear to be activated during painful experiences, although none of the structures activated are uniquely activated by pain (86). Thus, while no specific pattern of brain activation has yet been identified in individuals suffering from pain, several lines of evidence suggest that the insular cortex may be a critical site of pain integration (86). There is some evidence that cortical activation induced by innocuous stimulation differs under conditions of ongoing oro-facial pain. Through the use of fMRI, it has been found that experimental pain from the facial skin or masseter muscles causes bilateral activation of the ventroposterior thalamus (VPM), whereas innocuous stimulation (brushing the face) results only in the activation of the contralateral VPM. This suggests that fMRI signals from the thalamus may prove useful as a means to differentiate between noxious and innocuous pain input from the face (84). Cortical activation in response to low frequency vibration of the index finger in patients with TMD appeared to be increased in several key regions when compared to healthy controls, but no major dif-

ference in the pattern of activation was identified (83). At present, fMRI patterns cannot be used as a biological marker of oro-facial pain.

For imaging of masticatory muscles or TMJ, there are comparatively fewer options (87–89). One very interesting technique that has been recently applied to study patients with TMD is MRI diffusion tensor imaging/fractional anisotropy to assess white matter in the central roots of the trigeminal nerve (90). This technique employed fractional anisotropy, a measure of relative diffusion in three dimensions. It is thought that decreases in fractional anisotropy reflect nerve pathology such as decreased fibre density, axonal diameter or myelination. Patients with TMD had significantly lower levels of fractional anisotropy in the central root of the trigeminal nerve, which may indicate that this technique has identified a pathological change in the trigeminal nerve associated with TMD-related pain. The degree of fractional anisotropy is associated with disease duration, making this potential biomarker a candidate for both diagnosis and disease burden, if these findings can be replicated in larger patient cohorts. Unfortunately, MRI is expensive and the availability of MRI machines varies greatly in different countries (78, 88, 91).

Ontological perspectives on biomarkers and diagnostic classifications for oro-facial pain disorders

The standard definition for 'biomarker' violates ontological principles

For the notion of a biomarker to play a prominent role in diagnostic classifications, for instance in the formulation of diagnostic criteria, there must be a uniform understanding among developers of such classifications about what biomarkers precisely are and whether all entities to which the term 'biomarker' is assigned form a uniform group. For a group of entities to be uniform, all and only its members must exhibit a certain combination of characteristics and this is so irrespective of whether science has advanced enough to discover this unique combination of characteristics and whether an appropriate terminology has been developed to report on these characteristics adequately. This understanding must thus also include in what way biomarkers are distinct from other entities on the side of the patient such as signs, symptoms and diagnostic tests that are applied to them – all entities which are already standardly referred to in the formulation of diagnostic classes and corresponding criteria. And finally, a similar understanding must be established for each of the various sorts of biomarkers as, for instance, suggested by terms used in previous sections such as 'investigative biomarkers', 'prognostic biomarkers', 'radiologic biomarkers' and so forth.

Unfortunately, the IOM has not provided a definition for 'biomarker' which is such as to denote all and only entities from some uniform group. The definition exhibits, for example, the conflation often encountered in medical discourse between entities on the side of the organism – in the case of health care: human beings – and the *evidence* for the existence of such entities (92). This and other conflations are widespread, and it is thus no surprise to find examples thereof in the IOM's report on biomarkers, for instance in '*Cholesterol and blood sugar levels are biomarkers, as are blood pressure, enzyme levels, measurements of tumour size from MRI or CT, and the biochemical and genetic variations observed in age-related macular degeneration.*' (1)[p2] where characteristics on the side of the patient are conflated with measurements of these characteristics. Moreover, it is even unclear whether by 'measurements' is meant either (a) the processes of measuring an entity on the side of the patient or (b) the data – usually expressed as values of some sort – obtained through such a process of measuring. In (1)[p18], the need is expressed '*. . .to develop a transparent process for creating well-defined consensus standards and guidelines for biomarker development, validation, qualification, and use* [bold emphasis added] *to reduce the uncertainty in the process of development and adoption.*' This would restrict biomarkers to be measuring processes and/or devices to assist in such processes as it is hard to fathom that what is proposed to be developed here are blood sugar levels and tumour sizes. But that then, in turn, cannot be lined up with the IOM's definition for biomarker which is stated to be something that is (i) objectively measured – surely, the idea is not that what is measured would be the measuring process of, for instance, blood glucose itself – and (ii) an indicator for normal, pathological or response to treatment processes – clearly, the mere performance of some test is itself not an indication at all of what is going on in the patient, rather an indication of what is going on in the mind of the clinician as he is trying to find out what is going on in the patient.

That the terminology around biomarkers is inconsistent – a problem the IOM recognises in its own report (1)[p22] but unfortunately is contributing to rather than solving it – does not mean that the ideas behind it do not have value. But it does mean that the terminology needs to be rendered unambiguous and anchored in an ontology which recognises all types of entities to be referred to in standards and guidelines for biomarker development, validation, qualification and use.

Biomarkers under the perspective of the Ontology of General Medical Science (OGMS)

Ceusters and Smith have recently proposed an ontological realism-based account for biomarkers (93). This account renders IOM's view of biomarkers coherent under the following assumptions: (i) that the IOM intended biomarkers to be entities on the side of the patient, and not (for example) processes on the part of the clinician or data obtained through such processes including what can be seen or measured, for example in radiographic images; (ii) that in requiring that biomarkers be 'objectively measured and evaluated' the IOM had in mind not that an entity becomes a biomarker after and because it has been measured and evaluated, but rather that it was a biomarker already prior to observation because of certain properties it has intrinsically; and (iii) that the logical disjunction expressed by the 'or' in the list of processes for which the IOM definition asserts biomarkers to be an indicator has to be interpreted as an exclusive or (XOR). Thus, they assume that the IOM would not accept as biomarker some entity 'e' from which it cannot be determined whether 'e' is the result of a normal process or of a pathological process, and so forth. Under these assumptions, it is possible to interpret the vague term 'characteristic' in the IOM definition as denoting that what is intended by the OGMS term 'bodily feature' (92).

Entities that qualify as bodily features are instances of one or other of the following three disjoint types: (i) physical bodily components (nerve cells, nociceptors, neurotransmitters, etc.) and components in the interior or on the surface of the body (pathogens, toxins, microbiome, ...); (ii) bodily qualities such as cytokine concentrations; and (iii) bodily processes in which physical components participate, irrespective of them being normal (e.g. neurotransmission and concordant pain sensation), pathological (e.g. phantom pain) or induced through interventions.

Conclusion

Uses of biomarkers for oro-facial pain

Biomarkers are needed to serve as diagnostic, burden of disease, prognostic or efficacy of intervention tools for temporomandibular disorders and other oro-facial disorders causing pain. At present, however, there are no validated biomarkers of oro-facial pain. An ideal biomarker needs to be easily and reliably measured either by a trained clinician in the office or by a laboratory. Methodologies that provide or could provide fingerprint or signature type information, such as genetic or molecular profiling, QST- or MRI-based techniques or combinations of various techniques may define the unique pathology associated with oro-facial conditions. However, these techniques are, at the moment, still time-consuming, complicated and expensive, and consequently, their value as biomarkers will require the development of standardised and feasible clinical protocols as well as strong evidence for their diagnostic utility before they will be accepted into the mainstream of clinical assessment of oro-facial pain. Given these constraints, there is a need to continue to evaluate the simple biomarkers of oro-facial pain such as physiological and molecular biomarkers.

Recommendations for ontology-based representation of biomarkers in diagnostic classifications and related criteria for oro-facial pain

Both researches aiming at the discovery of suitable biomarkers for oro-facial pain and the adequate use thereof to build diagnostic classifications will benefit from the advantages ontology has to offer. An initial goal will be to clean up the terminology around biomarkers, the scope of which is much broader than only the domain of pain research. If this is not immediately feasible for biomedicine in general, then at least pain researchers could get a competitive advantage by implementing a few simple steps.

A good start would be to develop on the basis of the literature an inventory of biomarker candidates relevant for pain research and subsequent application for diagnostics. This inventory should include, for each biomarker, a number of essential information

elements. One element is the type of bodily feature the biomarker is an instance of; the most generic and minimum allowed types, in terms of the OGMS, are physical component, bodily process, and bodily quality. If the biomarker is determined to be a physical component, then further subtyping should be documented using ontologies accepted in the Open Biomedical Ontologies Foundry (94) or candidate ontologies thereof; examples are the Foundational Model of Anatomy (95) for any bodily component down to individual cells, the Cellular Component taxonomy of the Gene Ontology (96), the Protein Ontology (97) and so forth.

If the biomarker is a bodily process, good candidate ontologies for clarifying the terminologies are the Biological Process and Molecular Function taxonomies of the Gene Ontology. As bodily processes always depend on at least one bodily component, it should for such a biomarker also be indicated which bodily components it depends on, using one of the ontologies just mentioned. If that is not documented in the ontology used to type the biomarker, it should be added to the inventory of biomarker candidates.

If the biomarker is a bodily quality, a good ontology for further subtyping is the Phenotypic Quality Ontology (PATO) (98). As with processes, the biomarker candidate inventory should further contain information about what bodily component this biomarker is a quality of.

The second sort of information the inventory should contain is the type of investigation used in the cited literature source to determine the biomarker being documented. A candidate ontology for this is the Ontology of Biomedical Investigations (OBI) (99). As various types of assays can be used to measure the same biomarker, each biomarker might need several distinct measurement-related entries.

The third piece of information is, in case of an inventory aimed towards diagnostic classification development, where the biomarker is believed to be an indicator of the underlying pathology. This information is typically available as a diagnosis.

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