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Towards a holistic understanding of pain in the biomarker age

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Pain biomarkers cannot prove or disprove another person's pain, but they need not be rejected as futile or reductionist. When developed within a bio-psycho-social framework and guided by epistemic humility and ethical safeguards, they can complement and enrich the voices of those living with pain rather than replace them.

Recent work by Vollert and colleagues[1] offers a timely and important warning about the promises and perils of pain biomarkers. Their central message — that no biological test can prove or disprove another person's pain — echoes an important position articulated in earlier work[2]. What has been less clearly suggested until now, though, is that attempts to replace patients' own reports with biological measures are not merely ethically risky, but conceptually flawed. The experience of pain is, by definition, subjective and personal; for this reason, all pain-related data, including language, can only ever be expressions or representations of pain, not pain itself.

From this perspective, the claim that no pain biomarker can prove or disprove someone's pain is necessarily true. As is commonly said, all pain is real, yet each pain is unique, shaped by an individual's history, context and internal bodily and brain states. As a result, assessing pain inevitably involves a fundamental gap between first-person experience and third-person inference based on partial representations of pain. This gap can never be eliminated. What can be done, however, is to approach this gap responsibly by listening to suffering through as many complementary channels as possible. The role of biomarkers, in this view, is not to replace or diminish existing forms of communication, but to add complementary channels through which pain can be more fully expressed and heard.

Thus, our nuanced disagreement with Vollert et al. lies not in the fundamental limits of biomarkers but in the conclusions drawn from them. That pain cannot be reduced to any biological measure does not render biomarker development futile or conceptually flawed. Rather, it suggests that biomarkers should be understood as partial, imperfect and necessarily incomplete models that might still be useful in some contexts.

All models are wrong, but some are useful

When read from this perspective, the argument by Vollert and colleagues invites a more careful interpretation. The authors have correctly identified several reasons why diagnostic and monitoring pain biomarkers face fundamental challenges: (1) the highly individual and context-dependent nature of pain; (2) core principles of brain organization, including degeneracy, pleiotropy and dynamical systems properties; and (3) the technical and analytical limitations inherent in functional neuroimaging methods. This set of fundamental issues, however, is not unique to pain biomarker research and underscores why various fields, including psychology, cognitive and systems neuroscience, and even genetics, are intrinsically challenging, yet remain at the frontiers of scientific endeavor.

George Box's aphorism, "all models are wrong, but some are useful," captures the epistemic status of this endeavor[3]. Any attempt to model pain, like any attempt to model complex biological, psychological or social phenomena, necessarily involves abstraction, reduction and systematic bias. It is neither possible nor desirable to construct models that fully capture the richness, individuality and complexity of lived experience. Instead, the goal is to develop simplified and imperfect models that nevertheless provide insight or utility in specific contexts. In this sense, pain biomarker research can be understood as an effort to construct models of pain that are inevitably wrong, yet potentially useful. It follows that no single biomarker, nor any small set of biomarkers, can represent pain in its entirety. This recognition motivates a rejection of reductionism and a turn toward a pluralistic approach, in which multiple imperfect measures are valued for what they can contribute.

For example, in drug development and clinical trials, studies typically rely heavily on self-report, which is vulnerable to expectancy and contextual influences and may contribute to high failure rates despite substantial investment[4]. If we had supplementary biological measures that could help to disentangle pharmacological target engagement from non-specific treatment effects, we might be able to demonstrate drug effects more effectively, ultimately accelerating the development of better analgesics for patients. In this sense, pain biomarker research should not be equated with an attempt to simplify or diminish the complexity of pain. Rather, it is better understood as an effort of addition and enrichment: increasing the number of channels through which patients' pain and its underlying mechanisms can be inferred, interpreted and taken seriously. The appropriate question, then, is not whether pain can be reduced to biological measures — it cannot — but how much additional, context-sensitive information biomarkers can provide, and in which settings. That, ultimately, remains an empirical question.

Half-empty or half-full?

Vollert and colleagues rightly delineate a pessimistic scenario: biomarkers could be misused to invalidate patients, deny care or erode trust in subjective pain reports. This risk is real and must be taken seriously[2]. However, an alternative, more optimistic scenario deserves equal consideration. For many people living with chronic pain, the central challenge is not that their pain is over-measured, but that a lack of appropriate diagnostic and assessment tools leaves their pain unseen, doubted or invalidated. This is particularly true for marginalized individuals and groups, who often face systematic disbelief and

under-treatment. In these contexts, language and self-report often fail not because these individuals lack the words to express their pain, but because their reports are interpreted, and often discounted, within broader social, cultural and institutional frameworks[5]. Power structures, stereotypes and stigma shape whose suffering is acknowledged and whose is questioned. In some cases, individuals even refrain from reporting their pain or seeking help in anticipation that their suffering will not be accepted or taken seriously[6,7].

In such cases, additional sources of evidence, if developed and used carefully and ethically, could support rather than undermine patients. This view is consistent with prior work showing that many people living with chronic pain are open to, and often actively seek, new diagnostic tests and assessment tools that could provide more accurate, credible and communicable information about their condition[8,9]. From an optimistic perspective, the future of pain assessment may involve multiple complementary tools that integrate biological, psychological and social dimensions of pain, enabling more holistic and person-centered evaluations[10]. The same technologies that could, if misused, exclude or invalidate patients could also, if governed responsibly, contribute to more integrative assessments and render otherwise invisible pain more visible.

Seen in this way, the glass is neither simply half-empty nor half-full. Which of these futures ultimately materializes depends less on the mere existence of pain biomarkers than on how they are embedded within clinical practice, legal systems and social norms. Importantly, pain assessment was already flawed well before the advent of the 'biomarker age', with well-documented disparities and biases[11]. Biomarkers do not create these problems, nor will they solve them on their own; however, in principle, they may become part of a more just and evidence-rich system if developed, interpreted and governed wisely.

Towards a truly bio-psycho-social view of pain

Underlying Vollert and colleagues' argument is a deeper concern: that the growing emphasis on biomarkers may push pain research back towards a narrow form of biological reductionism. However, from the perspective of someone who has long worked on pain biomarkers, I would argue that the opposite is actually true: empirical evidence suggests that biomarker research, rather than reinforcing a reductionist biological account, is increasingly exposing its limits. For example, prefrontal cortex regions such as the ventromedial prefrontal cortex — an area involved in autobiographical memory and the integration of internal and external contextual information[12] — have emerged as important predictors of pain while exhibiting substantial individual variability[13]. Moreover, individual differences in pain sensitivity are better explained when sociodemographic and psychological variables are taken into account[14], and personalized fMRI-based models that successfully predict spontaneous pain in one individual with chronic pain fail to generalize to another individual[15]. Collectively, these findings reveal how strongly pain-related brain responses are shaped by idiosyncratic psychological and social factors. Therefore, it is unlikely that this line of research will collapse pain into biology. The limits of measurement will be discovered not by declaring them in advance, but by pushing measurement until it fails and by learning from the systematic patterns of those failures. From this perspective, identifying when pain biomarkers fail is not a fundamental conceptual issue but an empirical one.

The risks emphasized by Vollert and colleagues are real and important, but they do not imply that the endeavor itself is misguided or futile. The appropriate response is not to abandon measurement, but to pursue it with epistemic humility and ethical clarity. Many of the problems discussed — disbelief, stigma and disparities in pain care — will not disappear if we avoid new technologies, nor will they be solved by technology alone. Addressing them requires far broader efforts, including shifts in social norms, reforms in education and training, and changes in health policy that more deeply reflect an integrated bio-psycho-social perspective of pain. In this sense, the field may not yet have gone far enough. A clearer understanding of the limitations of pain biomarkers will emerge only through sustained empirical engagement. Ultimately, a holistic understanding of pain will arise not from a single decisive test but from a pluralistic framework in which multiple imperfect models — biological, psychological and social — are used to complement, rather than replace, the voices of those living with pain.

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