Orofacial Pain and the Prospects of Precision Medicine

As major academic institutions are making huge financial investments to embrace the vision of precision medicine, it appears timely to reflect upon the prospects of aligning the range of disease conditions covered by this journal with the goal of a smarter, individualized medicine, yielding a greater chance of benefit to a particular patient while reducing the likelihood of encountering unwanted effects and complications. Delivering treatments in a way that is smarter than current practice holds the prospect of reducing health care cost in the long run. To best capture the operational framework of what is about to happen, Margaret Hamburg and Francis Collins have stated: "When the federal government created the national highway system, it did not tell people where to drive—it built the roads and set the standards for safety. Those investments supported a revolution in transportation, commerce, and personal mobility. We are now building a national highway system for personalized medicine, with substantial investments in infrastructure and standards. We look forward to doctors' and patients' navigating these roads to better outcomes and better health."[1]

The path to reach the point at which we will be able to offer an individualized treatment for "Mrs Jones" depends to a large degree on the type of condition experienced. For the rarest presentations, the genotype alone may yield useful information for the clinician in support of individualizing care. But for the more common diseases, the identification of valid biomarkers that support clinical decisions to define a "personalized/precise" approach for Mrs Jones represents a scientific challenge. The complex nature of their etiopathogenesis, including the multitude of mechanistic variations—not just two or three—producing an array of clinically similar symptoms, calls for the study of individual variations among cases and the degree to which specific variations contribute to the clinical picture. Elucidating this web may require sample sizes in excess of 20,000 subjects to reach reasonable confidence in the reported findings.

Today we have good reasons to group the common, persistent orofacial pain conditions in terms of their complex etiopathogenesis with chronic conditions such as obesity, diabetes, depression, hypertension, and many others. A personalized treatment strategy will need to consider genetics and environmental influences with effects that may even be inherited from one generation to the next but not associated with changes in the DNA sequence. It will also need to consider risk-conferring behaviors, varying in their individual effect among clinical cases. Unraveling this mechanistic complexity will be the scientific challenge ahead.

The perception of "bodily dysfunction" is a personal matter that shapes much of how and to what degree symptom severity is felt and reported. It is now established that common genetic variants are associated with variations in brain function, which in turn can be linked to personality traits, behavioral phenotypes, and emotional states. Each of the genetic and epigenetic variants, including their interactions, can either amplify or attenuate the expression of the perceived state of dysfunction reported and measured clinically. The path to precision and personalized medicine will have to identify and take into account those individually applicable genetic and epigenetic variants that amplify to a significant degree the perceived and observed state of disease and treatment response.

Precision medicine hinges on individual test results that promise a significantly better outcome for a given patient with a specific intervention when compared with other types of treatment. There is increasing awareness that the exploitation of perceptual profiles yields important clues, as genetic variants linked to the function of calcium channels, adrenaline, neurotrophic factors, dopamine, opiates, neuropeptide Y, and serotonin influence processes associated with the perception of symptoms and, to a lesser degree, the clinical manifestation of bodily dysfunction. While amazing results are attainable in the very near future for very rare diseases that are identifiable by the genetic code, acknowledging the complexity of the etiopathogenesis in effect in common diseases makes it clear that the roadway to precision medicine is in need of a "navigation tool" as inferred in the quote by Hamburg and Collins,[1] cited above. Navigating the scientific discovery for the field that is represented by this journal in order to mine the avenues of precision medicine will require the dissection of the high-level case definitions that are based on symptoms and clinically observable signs to the study of low-level, intermediate phenotypes, markers of vulnerability, and subclinical traits that may or may not result in clinic cases.

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Reference

1. Hamburg MA, Collins, FS. The path to personalized medicine. N Engl J Med 2010;363:301–304.

doi: 10.11607/ofph.2015.4.e