The 4 H's of Biomarkers: Help, Harm, Hype & Hope

By Gilles Boire, Dunlop-Dottridge Lecturer

It was an honour to present the 2019 Dunlop-Dottridge Lecture in Montréal. I am an academic adult rheumatologist (also treating kids with rheumatic conditions) and a researcher in Sherbrooke, Québec. Mentors André Lussier and Henri H. Ménard in Sherbrooke, and Joe Craft and John Hardin at Yale University, introduced me to scientific rheumatology. My research has evolved from fundamental work on autoantigen/antibody systems to translational work on prognostic biomarkers in recent-onset inflammatory polyarthritis.

The ABC's of Biomarkers

Biomarkers are variables that can be objectively measured from fluids, such as blood or urine, from cells or tissues, from imaging, and even from your smart watch. They are used for diagnostic, prognostic or pathogenic purposes, or to monitor disease activity, treatment response or toxicity. Variables indicative of patients' feelings, well-being or functional status are NOT biomarkers. A biomarker may consist of a single variable or summarize multiple variables (then called a composite). The ideal biomarker informs clinical management, and is safe, easy to measure, sensitive, specific, reproducible, consistent across gender and race, and cost-efficient. Biomarkers are frequently correlated (*e.g.* C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]), and the information they generate may be redundant.

Current Biomarkers

Problems arise when the presence or absence of a biomarker takes precedence over the clinical characteristics. Healthy individuals may be labelled at risk for disease development, generating unnecessary anxiety and potential harm. Conversely, absent biomarkers may delay correct diagnosis. Sometimes biomarkers point in the wrong direction. It is thus critical to carefully consider all clinical findings when ordering and interpreting biomarkers, as the Choosing Wisely Canada campaign suggests.

Unrelated changes in practice may alter the course of disease and the pertinence of some biomarkers; similarly, a widely used biomarker may induce changes in care that may blunt its original impact. Finally, biomarkers do not holistically represent the actual patients; remember the importance of patient-derived variables.

Next-Generation Computational Biomarkers

Computational biomarkers originate from extremely rich data generated by ever more efficient molecular technologies, such as high throughput DNA sequencing, single cell gene expression, and microbiome and epigenetic studies. Making sense of such a large volume of data (big data) requires advanced statistical methods and techniques well beyond the typical clinician's understanding. Reliance on multiple parameters raises the potential for hidden correlations (*e.g.* microbiota and host genetics), complicating their use in combination with current or other next-generation biomarkers (MultiOmics), clinical parameters, and patient-related outcomes.

My presentation aimed at informing how much technology-driven biomarkers in development differ from the simple ones currently in use and how similar their evaluation should be.

The major difference is that computational biomarkers may inform beyond the crude tools of clinical evaluation, leading to a better understanding of the complex interaction of genes and environment that cause dysregulation of underlying disease. They help to classify patients into narrower, more homogeneous groups, paving the way to personalized medicine tailored to individuals rather than groups; prevention and cure then become potentially more accessible.

The similarity is that an incomplete evaluation of computational biomarkers may harm more than help. Lessons from the past tell us that biomarkers are subject to manipulation, leading to unfavourable outcomes despite increased costs. We will need to evaluate the proposed uses of candidate next-generation biomarkers in well characterized cohorts followed over a long period, to ensure that they are appropriate and result in improved outcomes.

For sure, the next generation of biomarkers based on big data heralds a new, exciting, yet controversial era for rheumatology.

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