A biomarker by any other name...

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In the world of translational research, some poorly defined terms regularly creep into our conversations. Some of these, such as 'biomarker' and 'surrogate marker', are often used interchangeably, and another, 'validated', is used with little relationship to its scientific meaning. Words and definitions do matter, however, and we should aim for consistency.

Biomarkers are defined as objectively measured indicators of biological processes or response to a therapeutic intervention. How biomarkers are categorized, however, is not well established. For instance, a classification system suggested to the FDA would separate the various biomarkers under the categories of Exploration, Demonstration, Characterization, and Surrogacy; only biomarkers in the final category would be acceptable for drug-approval purposes. Examples of such surrogate markers include cholesterol level, HIV load, CD4 count, and blood pressure. Prevention of radiographic progression in rheumatoid arthritis has also been used as a surrogate for joint surgery in clinical trials.

Another system, described by Frank and Hargreaves, divides biomarkers into three types: type 0 biomarkers are measures of the natural history of disease and correlate with clinical outcomes; type 1 biomarkers usually determine the biological effect of a therapeutic intervention; and type 2 biomarkers are the equivalent of 'Surrogacy' markers mentioned previously (Frank R and Hargreaves R [2003] *Nat Rev Drug Discov* 2: 566–580).

For a biomarker measurement to be useful, the assay or test must be 'validated'—a term that is often used rather loosely. Several characteristics should be carefully documented for validation (US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: bioanalytical method validation. [<http://www.fda.gov/CDER/GUIDANCE/4252fnl.htm>]). Most of these goals are appropriate for assays that measure specific analytes, such as messenger RNA, small molecules, or proteins.

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Validation of other types of assays, such as imaging, can be problematic because of the lack of 'gold standards' or methods of anatomic confirmation. The main criteria include: calibration, including external standards when possible; precision, generally with a coefficient of variability of approximately 15–20%; accuracy compared to a 'gold standard'; specificity; recovery of an analyte from a 'spiked' sample; assay stability over time; and a standard operating procedure.

This presents a problem in the world of clinical research. For instance, has anyone truly validated microarrays, proteomic assays, or 'quantitative' immunohistochemistry? These and many other assays are casually referred to as validated or as surrogate markers, but we are far from where we need to be.

Technical validation of an assay is only the start of discovering a clinically useful, validated biomarker or imaging end point. The simplest situation is when a biomarker can be correlated directly to the mechanism of action of an agent, as hemoglobin A1c can be correlated to the mechanism of a drug that improves glucose tolerance. The more novel the biomarker, the more difficult validation can become. For instance, demonstrating a change in messenger-RNA signatures in a disease after a therapeutic intervention would require extensive evaluation of treated and untreated patients. Only over time and after assessing the effect of several interventions can one be confident that a biomarker has biological relevance. In cases where this is not practical, validation can sometimes be accomplished using meta-analysis.

Some might quibble with these particular definitions. It is probably more important, however, that we differentiate a true surrogate marker from all other types of biomarkers in our communications and be clear about the meaning of validation. Only then can we begin studying how biomarkers can be used for both early, proof-of-concept clinical trials and studies for drug registration.

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Competing interests

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